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Impact of pre-stenting antiplatelet therapy regimens on clinical outcomes following carotid artery stenting: a retrospective analysis

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ABSTRACT

Objectives: This study investigates the influence of various antiplatelet regimens before carotid artery stenting (CAS) on short-term and long-term clinical outcomes. Effective antiplatelet therapy is vital for enhancing the success and safety of CAS. Determining the best approach remains a priority.

Methods: This retrospective cohort analysis involved 235 patients who underwent CAS at a single institution between October 2020 and October 2024. Participants were divided into three groups based on the antiplatelet regimen administered before the procedure: dual antiplatelet therapy (DAPT), aspirin monotherapy (SAPT-A), and clopidogrel monotherapy (SAPT-C). The main outcomes evaluated were stroke, transient ischemic attack (TIA), and bleeding complications. Secondary outcomes included restenosis, stent thrombosis, and death. Statistical methods were applied to compare outcomes across the groups.

Results: Stroke (0.8%) and TIA (2.5%) were notably less frequent in the DAPT group compared to the SAPT-A (7.1% and 12.5%, respectively) and SAPT-C (6.9% and 8.6%, respectively) groups ($P < 0.05$). Rates of stent thrombosis (1.7%-1.8%) and mortality (0.8%-3.4%) at six months showed no significant differences among the groups ($P > 0.05$).

Conclusions: Pre-procedural DAPT reduces short-term ischemic complications in CAS. However, long-term outcomes were comparable across regimens. These findings suggest that antiplatelet strategies should be individualized. Larger studies with longer follow-ups are needed.

Keywords: Carotid artery stenting, dual antiplatelet therapy, aspirin, clopidogrel, ischemic complications, restenosis, transient ischemic attack

Carotid artery stenosis is a major risk factor for ischemic stroke, significantly contributing to cerebrovascular morbidity and mortality [1]. The annual risk of stroke in asymptomatic individuals with $\geq 50\%$ carotid artery stenosis ranges from less than 1% to approximately 4.3% [2-5]. Carotid artery

stenting (CAS) was introduced in the early 1990s as a less invasive option for revascularization, particularly suited for patients at high surgical risk or with challenging anatomical considerations [6, 7]. Although CAS has demonstrated efficacy and an acceptable safety profile, ischemic complications due to distal

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embolization and atherothrombosis still pose significant challenges, requiring optimization of pre- and post-procedural management strategies. Antiplatelet therapy plays a critical role in CAS by reducing the risk of thrombotic events. Aspirin is still a key anti-thrombotic agent, but its variable efficacy among patients has highlighted the complementary benefits of Adenosine diphosphate (ADP) receptor antagonists such as clopidogrel and ticlopidine, which have shown improved outcomes when combined with aspirin in stent procedures [8, 9]. Studies have specifically demonstrated that dual antiplatelet therapy with clopidogrel and aspirin effectively reduces complications following CAS [10-12]. Dual antiplatelet therapy with clopidogrel and aspirin has been linked to a low rate of ischemic complications after CAS. Additionally, clopidogrel has shown superior efficacy compared to ticlopidine [13]. In a study investigating late stent thrombosis due to delayed endothelialization for the importance of long-term antiplatelet therapy, early discontinuation of antiplatelet therapy within the first 9 months after the procedure in patients with drug-eluting stents emerged as an important risk factor [14]. CAS is a minimally invasive option for revascularization in high-risk surgical patients, and additional antiplatelet therapy is crucial to manage ischemic complications, reduce distal embolization and prevent both early and late atherothrombotic events, thus improving the long-term success of the procedure [15].

With the growing use of CAS, understanding the influence of various antiplatelet regimens on procedural and long-term outcomes is crucial. This study aimed to assess the effects of pre-procedural antiplatelet therapy on ischemic and hemorrhagic outcomes in patients undergoing CAS and to offer insights for optimizing treatment strategies to enhance procedural safety and efficacy.

METHODS

Study Design and Population

This study was conducted at a tertiary hospital between October 2020 and October 2024. It adhered to the 2008 Declaration of Helsinki and was approved by the Clinical Research Ethics Committee (Approval No: 2024/22-1). Patient data were anonymized to maintain confidentiality.

The inclusion criteria encompassed patients aged 18 years or older with significant carotid artery stenosis, defined as $\geq 50\%$ stenosis for symptomatic patients and $\geq 70\%$ for asymptomatic patients. The diagnosis was confirmed using imaging modalities, including Doppler ultrasound, CT angiography, or MR angiography, which were used primarily to assess the degree of stenosis. Plaque composition and morphology were not routinely evaluated in this study. However, restenosis and stent thrombosis were assessed using follow-up imaging. Comprehensive medical records documenting clinical, procedural, and follow-up data at 24 hours, 1 month, and 6 months postoperatively were mandatory.

A total of 312 carotid artery stenting (CAS) procedures were performed at our institution between October 2020 and October 2024. After applying the study's inclusion and exclusion criteria, 77 patients were excluded for the following reasons:

- Previous carotid intervention (n=21) (stenting or endarterectomy)
- Non-atherosclerotic carotid stenosis (n=18) (e.g., arterial dissection, vasculitis)
- Contraindications to antiplatelet therapy (n=13) (e.g., active bleeding, severe allergic reactions)
- Incomplete medical records (n=15) (e.g., missing procedural or follow-up data)
- Non-adherence to pre- or post-procedural antiplatelet therapy (n=10)
- After these exclusions, 235 patients were included in the final analysis.

Procedure Details

CAS was performed under local anesthesia with mild sedation to enable patient feedback during the procedure. Access was achieved via the femoral artery, and a guiding catheter was advanced to the stenotic segment of the carotid artery. A distal embolic protection device was used to reduce the risk of embolization. Balloon angioplasty was employed for pre-dilatation of the stenosis, followed by the deployment of a self-expanding stent to maintain vessel patency. Upon stent placement, the embolic protection device was retrieved, and completion angiography was performed to confirm successful revascularization. Postoperative follow-up included regular assessments, with specific evaluations of headache conducted as per the study's follow-up protocol.

CAS was performed by experts with extensive experience and adhered to standardized institutional protocols to maintain consistency across cases.

Antiplatelet Therapy

Patients were categorized into three groups based on their antiplatelet regimen prior to carotid artery stenting: (1) Dual Antiplatelet Therapy (DAPT): Combination of clopidogrel and aspirin; (2) Single Antiplatelet Therapy - Aspirin (SAPT-A): Aspirin alone; and (3) Single Antiplatelet Therapy - Clopidogrel (SAPT-C): Clopidogrel alone.

As this is a retrospective study, the allocation to antiplatelet regimens was determined by treating physicians at the time of care, based on clinical judgment and patient-specific factors. Eligibility criteria required patients to have been on antiplatelet therapy for at least one month before the procedure to ensure sufficient platelet inhibition. After CAS, all patients were prescribed dual antiplatelet therapy (DAPT) with aspirin and clopidogrel for six months to minimize the risk of ischemic events and stent thrombosis. Following this period, the regimen was transitioned to aspirin monotherapy for long-term secondary stroke prevention. Compliance with the antiplatelet regimen was

monitored during follow-up visits at one and six months.

Outcome Measures

The primary outcomes were the incidence of ischemic events, including stroke and transient ischemic attacks (TIA), and hemorrhagic complications, such as intracranial and extracranial bleeding, within 30 days and during the 6-month follow-up. Secondary outcomes included stent thrombosis, restenosis identified through follow-up imaging, and all-cause mortality at 6 months. Procedural success was defined as achieving residual stenosis of <30% without peri-procedural complications.

Data Collection

Demographic, clinical, and procedural data were systematically retrieved from electronic medical records. Collected variables included patient age, gender, comorbidities (e.g., hypertension, diabetes mellitus, and coronary artery disease), stenosis grade, pre-procedural antiplatelet regimen, and procedural details. Follow-up data were collected at 24 hours, 1 month, and 6 months post-procedure. These included imaging findings to evaluate restenosis, detailed records of is-

Table 1. Distribution of demographic data of patients according to antiplatelet use

Variables		Anticoagulant usage			P value
		DAPT (n=121)	SAPT-A (n=56)	SAPT-C (n=58)	
Gender	Male	89	40	35	0.188 [†]
	Female	32	16	23	
Hypertension	No	19	10	18	0.051 [†]
	Yes	102	46	40	
Diabetes mellitus	No	60	26	32	0.634 [†]
	Yes	61	30	26	
Symptomatic stenosis	No	46	21	27	0.501 [†]
	Yes	75	35	31	
Mean±SD					
Age		62.3±2.8	62.7±2.8	63.2±3.2	0.151 [‡]
Stenosis degree (%)		77.5±6	74.0±7.2	75.2±7.1	0.069 [‡]

DAPT=Dual Antiplatelet Therapy, SAPT-A=Single Antiplatelet Therapy-Aspirin, SAPT-C=Single Antiplatelet Therapy-Clopidogrel, SD=standard deviation

[†]Chi-Square Test, [‡]One Way ANOVA Test

chemic and hemorrhagic events, and adherence to prescribed antiplatelet therapy.

Statistical Analysis

Statistical analyses were conducted using IBM® SPSS® Statistics version 25 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to evaluate the normality of numerical data. Qualitative variables were expressed as frequencies and percentages, while continuous variables were presented as mean±standard deviation. Categorical variables were compared using the Chi-square test, and relationships between numerical variables and anticoagulant treatment groups were analyzed using the One-Way ANOVA test. P-value of <0.05 was considered statistically significant.

RESULTS

This study assessed the outcomes of pre-procedural antiplatelet regimens in CAS. Of 235 patients, 51.4% (n=121) received dual antiplatelet therapy (DAPT), 23.8% (n=56) received aspirin alone (SAPT-A), and 24.6% (n=58) received clopidogrel alone (SAPT-C). The mean age was 62.3±2.8 years for DAPT, 62.7±2.8 years for SAPT-A, and 63.2±3.2 years for SAPT-C

(P=0.151). The average stenosis grade was 77.5±6.0% in DAPT, 74.0±7.2% in SAPT-A, and 75.2±7.1% in SAPT-C (P=0.069) (Table 1).

Primary Outcomes

At 30 days, stroke occurred in 0.8% of the DAPT group, significantly lower than 7.1% in SAPT-A and 6.9% in SAPT-C (P=0.047) (Table 2). TIA rates were also lower in DAPT (2.5%) compared to SAPT-A (12.5%) and SAPT-C (8.6%) (P=0.029). Myocardial infarction and 30-day mortality showed no significant group differences (P>0.05) (Fig. 1).

Secondary Outcomes

At six months, stent thrombosis rates were similar: 1.7% in DAPT, 1.8% in SAPT-A, and 1.7% in SAPT-C (P=0.998) (Table 3). Restenosis was seen in 4.1% of DAPT, 7.1% of SAPT-A, and 5.2% of SAPT-C patients (P=0.699). Stroke rates were 2.5% in DAPT, 8.9% in SAPT-A, and 8.6% in SAPT-C (P=0.108). Mortality rates did not differ significantly (P=0.446) (Fig. 2).

DISCUSSION

Atherosclerosis, characterized by arterial narrowing due to plaque buildup within vessel walls, is a major

Table 2. Month 1 results of patients according to antiplatelet use (Primary outcomes)

Variables		Antiplatelet usage			P value
		DAPT (n=121)	SAPT-A (n=56)	SAPT-C (n=58)	
Stroke 1 st month	No	120	52	54	0.047 [†]
	Yes	1	4	4	
TIA 1 st month	No	118	49	53	0.029 [†]
	Yes	3	7	5	
MI 1 st month	No	120	55	56	0.446 [†]
	Yes	1	1	2	
Bleeding	No	116	53	56	0.876 [†]
	Yes	5	3	2	
Mortality 1 st month	No	121	56	57	0.216 [†]
	Yes	0	0	1	

DAPT=Dual Antiplatelet Therapy, SAPT-A=Single Antiplatelet Therapy-Aspirin, SAPT-C=Single Antiplatelet Therapy-Clopidogrel, TIA=Transient Ischemic Attack, MI=Myocardial Infarction

[†]Chi-Square Test

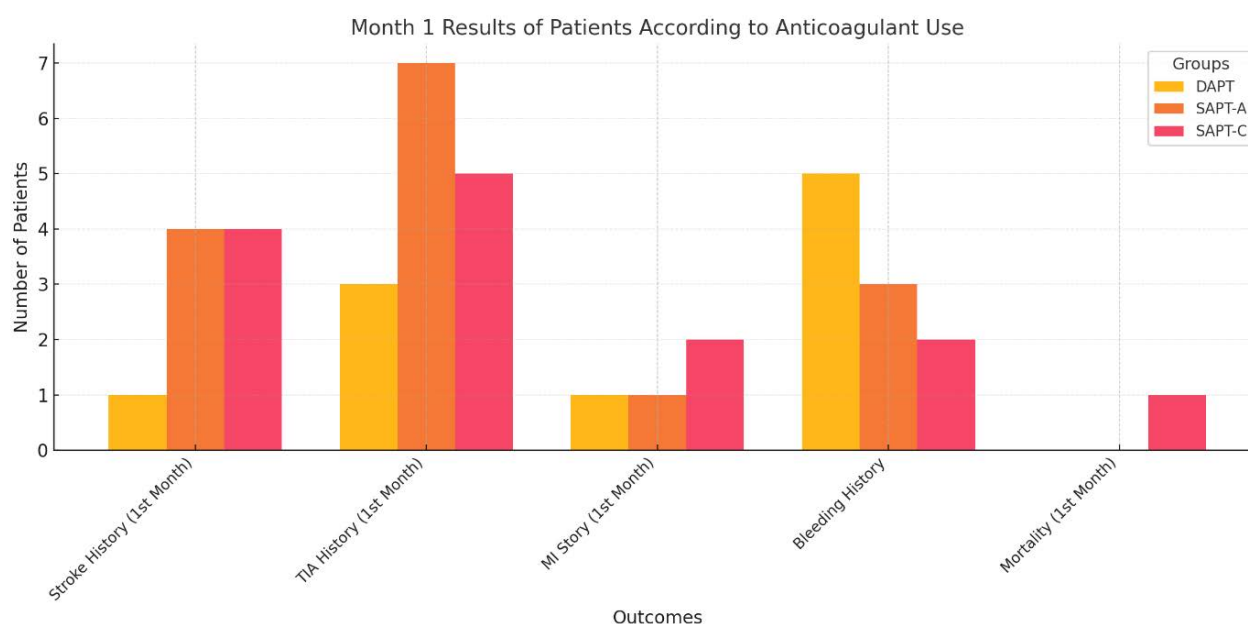


Fig. 1. Month 1 results of patients according to anticoagulant use.

contributor to cardiovascular disease [16], including carotid artery stenosis and its associated risks of ischemic events. Systemic atherosclerosis can lead to arterial occlusion, and advancements in treatment have

shifted from surgical interventions to minimally invasive endovascular methods, which offer faster recovery and reduced complications [17, 18]. This study evaluated the effects of pre-procedural antiplatelet reg-

Table 3. Outcomes of patients at 6th month according to antiplatelet use (Secondary outcomes)

Variables		Antiplatelet usage			P value
		DAPT (n=121)	SAPT-A (n=56)	SAPT-C (n=58)	
Stent thrombosis	No	119	55	57	0.998 [†]
	Yes	2	1	1	
Restenosis	No	116	52	55	0.699 [†]
	Yes	5	4	3	
Stroke 6 th month	No	118	51	53	0.108 [†]
	Yes	3	5	5	
TIA 6 th month	No	114	47	52	0.088 [†]
	Yes	7	9	6	
MI 6 th month	No	120	54	54	0.079 [†]
	Yes	1	2	4	
Mortality 6 th month	No	120	55	56	0.446 [†]
	Yes	1	1	2	

DAPT=Dual Antiplatelet Therapy, SAPT-A=Single Antiplatelet Therapy-Aspirin, SAPT-C=Single Antiplatelet Therapy-Clopidogrel, TIA=Transient Ischemic Attack, MI=Myocardial Infarction

[†]Chi-Square Test

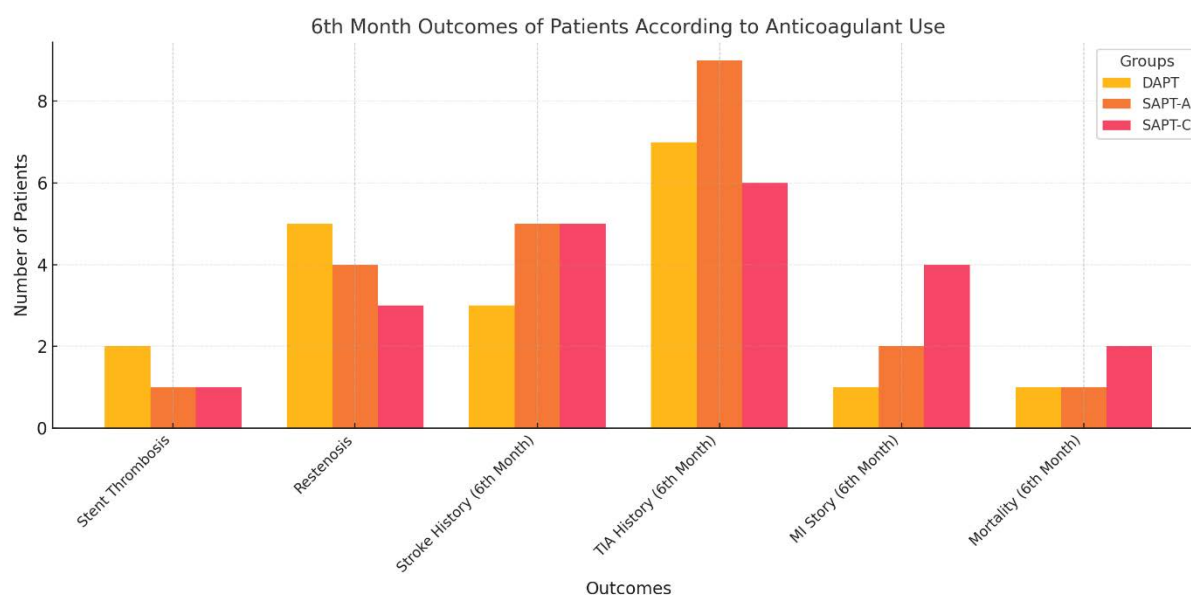


Fig. 2. 6th month outcomes of patients according to anticoagulant use.

imens on short- and long-term outcomes after CAS. The findings indicated that DAPT significantly reduced ischemic event risk while maintaining a favorable short-term safety profile. However, long-term outcomes did not differ between groups, likely due to the standard post-procedure DAPT regimen. Previous research supports the effectiveness of DAPT in preventing thrombotic events. The combination of aspirin and clopidogrel, in particular, has shown greater efficacy than single-agent therapies in reducing neurological complications [10, 11, 19]. The CARESS study demonstrated that dual antiplatelet therapy with clopidogrel and aspirin significantly lowered asymptomatic embolization rates, as detected by transcranial Doppler, in patients with recent symptomatic carotid stenosis. This finding highlights its superiority over aspirin monotherapy in high-risk patients [12]. Conversely, adding aspirin to clopidogrel in high-risk patients with ischemic events did not significantly improve vascular outcomes but notably increased the risk of major and life-threatening bleeding [20]. The MATCH study revealed that combining clopidogrel with aspirin provided no significant advantage over clopidogrel monotherapy in high-risk patients with recent ischemic events. However, the combination significantly elevated bleeding risk, limiting its use in this population [21]. Our study demonstrated that pre-procedural DAPT effectively reduced stroke and transient ischemic attack (TIA) rates in the short term. A signif-

icant reduction in these complications was observed in the DAPT group within the first month. No significant differences were observed among the groups regarding long-term outcomes. This homogeneity in long-term results may be attributed to the routine post-procedural administration of DAPT across all groups. On the other hand, differences in bleeding complications have been found depending on pre-procedural treatment, suggesting the need for individualization of the treatment regimen.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) showed a two-year stroke incidence of 22% in patients with moderate carotid stenosis and 26% in those with severe stenosis [22].

The CREST study demonstrated that CEA and CAS had comparable clinical outcomes, with similar post-procedural complication rates (CAS: 7.6% vs. CEA: 6.4%, $P=0.25$) [23]. These findings confirm that CAS is a safe option for patients who are not suitable for surgery for anatomical or clinical reasons.

Our study aligns with these findings, highlighting the critical role of DAPT, particularly in preventing short-term ischemic events. In conclusion, this study underscores the need to optimize antiplatelet strategies for CAS. Dual antiplatelet therapy appears to be an effective approach for reducing short-term ischemic complications. However, larger prospective studies are necessary to refine individualized treatment regimens and assess their impact on long-term outcomes. These

results emphasize the importance of tailoring antiplatelet therapy to each patient and pave the way for developing new strategies to enhance the efficacy and safety of CAS.

Limitations

This study has several limitations. First, its retrospective design restricts the ability to establish causation, as data were collected from records, increasing the potential for missing or inaccurate information. Second, the study was conducted at a single center, limiting the findings' generalizability. Multi-center studies may yield results that are more representative of broader populations.

CONCLUSION

This study evaluated the impact of different antiplatelet regimens administered before CAS on short- and long-term clinical outcomes. The findings showed that DAPT significantly reduced short-term ischemic complications without compromising procedural safety. However, no notable differences were observed in long-term outcomes between the groups, likely due to the uniform post-procedural administration of DAPT.

These results underscore the importance of tailoring antiplatelet strategies for CAS. DAPT emerges as a beneficial approach for reducing short-term ischemic events in carefully selected patients. However, treatment plans should consider the potential risks, such as bleeding. Future research involving larger and more diverse populations with longer follow-up periods is necessary to further clarify the long-term effects of antiplatelet regimens. Such studies would strengthen the evidence base for optimizing the safety and efficacy of CAS.

Ethical Statement

This study was conducted in accordance with the ethical principles outlined in the 2008 Declaration of Helsinki. Ethical approval was obtained from the Zonguldak Bülent Ecevit University Clinical Research Ethics Committee (Approval No: 2024/22-1). All patient data were anonymized to ensure confidentiality and privacy.

Authors' Contribution

Study Conception: OA, MSG, EK; Study Design: OA, EK; Supervision: OA, EK; Funding: N/A; Materials: MSG, EK; Data Collection and/or Processing: OA, EK; Statistical Analysis and/or Data Interpretation: OA, EK; Literature Review: OA, MSG, EK; Manuscript Preparation: OA, MSG, EK and Critical Review: OA, MSG, EK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The effect of sertraline-selenium combination on cardiac contractile strength

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ABSTRACT

Objectives: Individuals with myocardial infarction (MI) frequently exhibit a heightened prevalence of depression, which elevates the likelihood of negative cardiovascular outcomes. This study aimed to assess the potential synergistic effects of sertraline, an antidepressant utilised for the prevention and treatment of depression commonly associated with cardiac disorders, and selenium, an antioxidant trace element, on atrial contraction force.

Methods: Thirty-two adult male Wistar albino rats were randomly allocated into four groups. Atrial strips were positioned in the organ bath, and the tension was calibrated to 2 g. In the control group, isometric contractions were elicited using 10⁻³ M adrenaline, and the contractions were documented. Sertraline (S) was incrementally administered to the S group in dosages of 0.01 mM, 0.1 mM, 1 mM, and 2 mM. In the Selenium (Se) Group, selenium was incrementally administered at concentrations of 0.1, 1, 2, and 4 mmol/L. S+Se group, S cumulative (0.01 mM, 0.1 mM, 1 mM, 2 mM) and Se cumulative (0.1, 1, 2, 4) mmol/L were administered at fifteen-minute intervals.

Results: The S group had a statistically significant reduction in contraction compared to the control group. Statistically substantial inhibition was noted in the Se group relative to the control group. Statistically significant contraction inhibition was noted in the S+Se group relative to the S group and Se group (P=0.035 and P=0.02, respectively).

Conclusions: According to the results of our study, sertraline-selenium combination showed an effect by inhibition of cardiac Ca²⁺ channels in rat atrium. Additional research is needed to elucidate the mechanism of action of sertraline, which is used in the treatment of depression that often accompanies cardiac disorders, and selenium, an effective trace element with antioxidant properties.

Keywords: Sertraline, selenium, rat atrium, contraction, relaxation

The onset of early depression is a prevalent issue among individuals undergoing heart surgery [1]. Approximately 50% of individuals with coronary heart disease exhibit concomitant depression [2, 3]. About two-thirds of patients hospi-

talised following myocardial infarction (MI) exhibit mild depression symptoms, whereas 15% of individuals with cardiovascular illness manifest more severe depressed symptoms. Depression correlates with heightened vulnerability to cardiovascular illness,

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along with an elevated occurrence of eventual mortality and other cardiovascular events [4-6]. The incidence of depression fluctuates according on the classification and severity of cardiovascular disease. The incidence of depression is thrice greater in myocardial infarction patients compared to the general population [7].

Sertraline (S) is the predominant selective serotonin reuptake inhibitor (SSRI) employed in the management of depression, anxiety, and obsessive-compulsive disorder. S inhibits the reuptake of 5-HT from the synaptic cleft in the central nervous system, facilitating the accumulation of 5-HT in the synaptic cleft. Consequently, sertraline exerts its impact via elevating the 5-HT levels in the central nervous system [8]. Despite the fact that selective serotonin reuptake inhibitors (SSRIs) exhibit safer cardiotoxicity profiles compared to tricyclic antidepressants, literature indicates that SSRIs may induce mild bradycardia, negligible QT interval prolongation, dysrhythmic syncope, and orthostatic hypotension [9]. Certain clinical investigations indicate that SSRIs may diminish the occurrence of cardiac events in individuals with myocardial infarction by inhibiting platelet aggregation [10].

Social stress can induce oxidative damage. Distressed personality (Type D), characterised by a propensity for negative feelings and the suppression of emotional expression in social settings, has been demonstrated to forecast a bad prognosis for coronary artery disease, independent of other biological and psychosocial risk factors [11]. MI is marked by damage to myocardial cells and, in serious cases, permanent necrosis. Rapid haemoperfusion (reperfusion) is a critical salvage therapy for myocardial infarction patients, essential for preserving cardiac tissue from irreversible necrosis. Reperfusion of ischaemic myocardium may exacerbate myocardial ischaemic injury, known as myocardial ischaemia-reperfusion injury (MIRI), resulting in cardiomyocyte death [12]. Oxidative stress denotes the disparity between reactive oxygen species (ROS) activity and antioxidant defences, and is associated with the development of chronic heart failure (CHF). Xanthine oxidase (XO) generates reactive oxygen species (ROS), which contribute to the pathophysiology of both experimental and clinical heart failure by influencing several characteristics of the failing heart, including contractile

performance, interstitial fibrosis, endothelial dysfunction, and myocyte hypertrophy. Xanthine oxidase expression is elevated in ischemia-induced heart failure, and its inhibition enhances cardiac contractility in patients with congestive heart failure. Antioxidant defence systems involve the activation of heat shock proteins. Inducible heat shock protein (Hsp) 70 synthesis escalates when cardiomyocytes encounter acute hypoxia or ischaemia. Inducible Hsp70 plays a protective effect following ischaemia and diminishes the risk of coronary artery disease progression. Reduced Hsp70 levels and elevated XO levels result in heightened oxidative damage, augmented myocardial oxidative stress, and raised tumour necrosis factor (TNF) levels, hence negatively impacting cardiac prognosis [11].

Cardiac surgery is linked to oxidative stress generated by ischaemia-reperfusion. Oxidative stress induces an inflammatory response marked by endothelial dysfunction and damage to vital organ systems. Strategies to mitigate oxidative stress-induced inflammation have garnered significant interest in recent years. Selenium, a vital trace element, facilitates host-specific anti-inflammatory and antioxidant mechanisms [13]. Heart cells in mice were safeguarded against damage from cancer treatments that can induce cardiac injury by minimising cellular harm and inhibiting necrosis. Se safeguards cells from apoptosis by diminishing oxidative stress, modulating inflammation, inhibiting endothelial dysfunction, and providing cellular protection against apoptosis [14].

Major surgical procedures elevate the risk of depression in postoperative patients. Numerous scheduled surgeries have been linked to depression, with cardiovascular procedures being the most extensively studied in relation to postoperative depression. This study aimed to assess the potential synergistic effects of sertraline, an antidepressant utilised for the prevention and treatment of depression commonly associated with heart disorders, and selenium, an antioxidant trace element, on atrial contraction strength.

METHODS

All experimental protocols conducted in this study received approval from the Necmettin Erbakan University Animal Experiments Local Ethics Committee (HADYEK, protocol number 047/2021). Adult Wistar

Albino rats, weighing between 230 and 260 grammes, were utilised for this study.

Atrium excision from all subjects in the experimental groups was conducted between 08:00 and 09:00 hours in the morning. Cervical dislocation was performed on the animals under ketamine/xylazine anaesthesia (75 mg/kg - 10 mg/kg), and the atria were then immersed in Krebs solution. Following the excision of tissue and blood remnants, 3-4 millimetre strips obtained from the atria were affixed to hooks in the transverse orientation within an isolated organ bath containing Krebs solution, which was continuously aerated with 95% O₂ and 5% CO₂ at 37°C, with a tension set to 2 g. The tissues were cleaned for one hour at 15-minute intervals post-hanging to mitigate the influence of anaesthetic drugs. Adrenaline (0.001 M) was administered to the tissue chambers to elicit isometric contractions.

Control Group (n=8): Contractions were recorded in the recording system. Contraction amplitude values were determined as contraction parameter.

Sertraline Group (S) (n=8): After the plateau of contractions was observed (approximately 30 minutes), S (0.01 mM, 0.1 mM, 1 mM, 2 mM) dissolved in crepe was added cumulatively at fifteen minutes intervals. Contraction amplitude values were determined as contraction parameter [15].

Selenium Group (Se) (n=8): After the observation of the plateau where contractions occurred (approximately 30 minutes), (0.1, 1, 2, 4) mmol/L selenium

was added cumulatively at ten minutes intervals, respectively. Contraction amplitude values were determined as contraction parameters.

Sertraline+Selenium (S+Se) (n=8): After the observation of the plateau where contractions occurred (approximately 30 minutes), S (0.01 mM, 0.1 mM, 1 mM, 2 mM) and Se cumulatively (0.1, 1, 2, 4) mmol/L were added at fifteen minutes intervals and sequentially.

Statistical Analysis

All tests were two-tailed, and findings were deemed statistically significant at $P < 0.05$. The variation in tension values over time and within groups was examined using a mixed-effects two-way repeated measures ANOVA model incorporating interaction variables (group $\times$ time). The tension values of the groups at different time intervals were analysed using the Tukey-Kramer post-hoc test. The outcomes of the post-hoc analysis are represented by Mean Difference and Standard Error (SE). The analyses were conducted using JASP Team (2019). JASP (version 0.11.1).

RESULTS

In groups 2 and 3, adrenaline 10⁻³ was applied in isolated organ bath and cumulative sertraline and selenium were administered every 15 minutes. There was a statistically significant decrease in group 2 compared

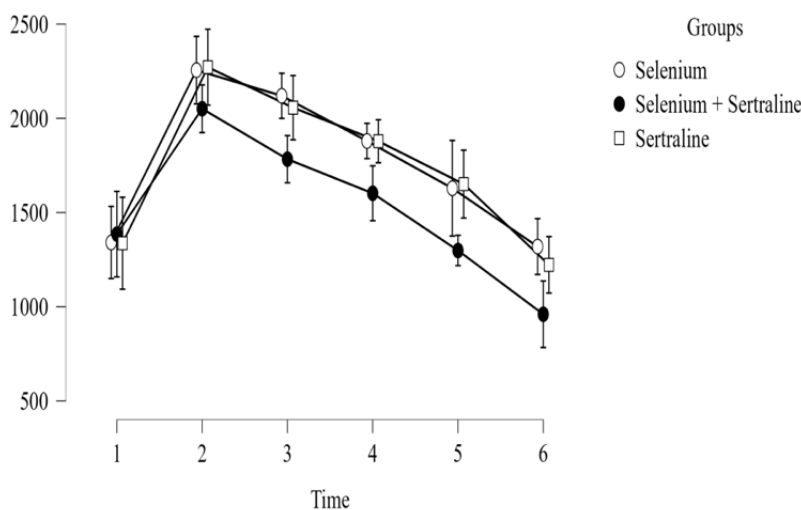


Fig. 1. No significant difference was observed between groups 2 and 3. Group 4 Isometric tension relationship between groups 2 and 3 Significant inhibition was observed after administration of sertraline 0.01 mM dose (n=8 for each group).

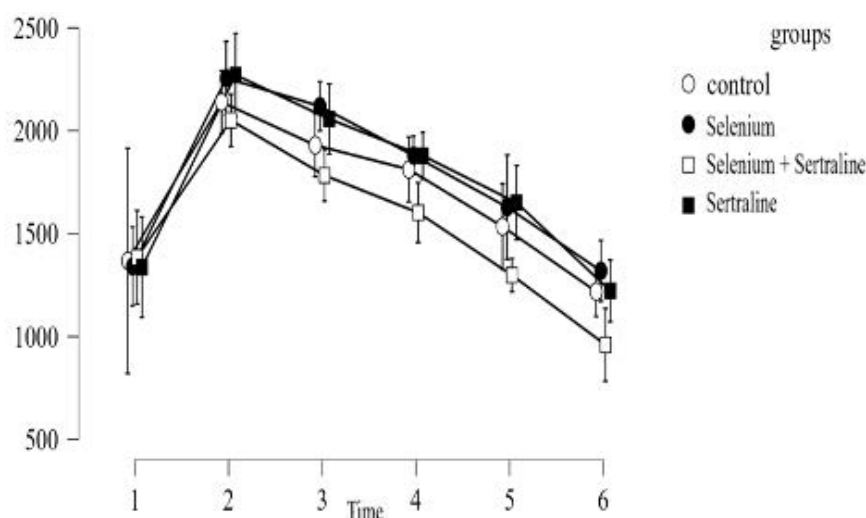


Fig. 2. The time intervals in groups 2, 3, and 4 show 15 minute intervals after adrenaline administration. Group 1 shows the 30-minute period after adrenaline administration. Contraction inhibition was observed in rats in the control group after 60 minutes (n=8 for each group).

to the control group ($P < 0.05$). There was a statistically significant decrease in group 3 compared to the control group ($P < 0.05$), (Fig. 1).

Group 4 showed a statistically significant contraction inhibition in muscle tension compared to groups 2 and 3 ($P < 0.05$). There was no significant difference in group 2 and group 3 ($P > 0.05$). The time intervals in groups 2, 3, 4 show intervals of 15 minutes after adrenaline administration. Group 1 shows the 30-minute period after adrenaline administration. In the control group, contraction inhibition was observed after 60 minutes (Fig. 2), (Table 1).

DISCUSSION

To the best of our knowledge, this is the first study investigating the possible synergistic effects of sertraline and selenium on the contractile force of the heart. Ac-

cording to our study findings, sertraline decreased the contraction power of the heart depending on the cumulative dose. In combination with selenium, it increased the negative inotropic effect depending on the cumulative dose.

A prospective cohort research was done to examine the correlation between depression and the occurrence of significant adverse cardiac events in individuals with acute myocardial infarction (AMI). The trial included 3,568 participants and featured a 2-year follow-up period to assess the incidence of significant adverse cardiac events. The study indicated an elevated occurrence of the major adverse cardiac event (MACE) rate (cardiac death, recurrent non-fatal myocardial infarction, revascularization, and stroke) in persons experiencing both anxiety and depression [16]. A meta-analysis published in 2011 examined the correlation between depression and mortality rates in individuals with MI. This thorough study encom-

Table 1. Results of sertraline-selenium administration in rat atrium

Comparison	Mean Difference	SE	t	P value
Selenium vs. (Selenium + Sertraline)	243.977	82.940	2.942	0.020
Selenium vs. Sertraline	21.197	82.940	0.256	0.965
(Selenium + Sertraline) vs. Sertraline	-222.781	82.940	-2.686	0.035

Post Hoc Comparisons (Tukey)

passed 29 trials with a cumulative total of 16,889 subjects. Research indicated that patients exhibiting depressive symptoms faced a 2.25-fold heightened risk of all-cause mortality and a 2.71-fold elevated risk of cardiovascular mortality. Additionally, the likelihood of negative cardiac events escalated by 59% in these patients [17]. Consequently, SSRIs have been employed in the management of depression associated with cardiovascular illnesses since the 2000s [18].

Research indicates that SSRIs possess effects beyond the inhibition of neuronal 5-HT reuptake; for instance, fluoxetine has been documented to obstruct sodium, calcium, and potassium channels in cardiac and vascular tissues [19]. Short-term administration of sertraline in healthy individuals results in the attenuation of sympathetic nervous system activity, evidenced by a reduction in heart rate. Sertraline acutely diminishes sympathetic nervous system activity by agonist action at 5-HT_{1A} receptors [20]. It should also be noted that sertraline may influence QT variability independently of treatment effects. When we look at the studies with fluoxetine, another antidepressant of the SSRI group. Fluoxetine suppresses the activities of 5-HT_{2C}, 5-HT₃, and nicotinic receptors, which are primarily implicated in the control of vasomotor tone, as well as voltage-dependent Na, Cl, and K channels. Consequently, fluoxetine may directly influence cardiac contractility and heart rate due to its negative inotropic action. It has been suggested that similar processes prolong the QT interval and may cause tachycardia [21]. Research by Akıncı *et al.* [22] on human saphenous vein grafts demonstrated that the arterial relaxation effects of fluoxetine are not reliant on endothelium-derived dilator factors or potassium channel activation. Fluoxetine is believed to induce endothelium-independent relaxation by disrupting calcium signalling pathways responsible for contraction in vascular smooth muscle [22]. A separate study has demonstrated that acutely given selenium influences ventricular cardiac contractility in two distinct periods. A preliminary transient rise in developed force was succeeded by a decline in contractility, which coincided with an elevation in the resting tension of this force. This phenomenon was linked to a disturbance in Ca²⁺ homeostasis and an alteration in contractility. The findings from isolated myocytes suggest that the transient positive inotropy is partially attributable to selenium's direct influence on myofilaments, while the

reduction in developing force and the elevation in resting tension stem from diminished Ca²⁺ transients [23]. In a separate study, Ayaz *et al.* [24] showed that chronic administration of sodium selenite at micromolar concentrations for 4 weeks led to significant changes in the kinetics of both Ca²⁺ and K⁺ currents, although there were no significant changes in the mechanical and electrical activities of the heart, although there were marked prolongation trends in the repolarisation phase of action potentials. The authors showed that the small prolongation in the repolarisation phase of action potentials was mostly attributable to changes in the kinetics of these currents [24]. Another study shown that selenium deficiency or excess does not directly influence the contraction mechanism; rather, it impacts the signalling pathway of β -adrenoreceptors, which includes adrenoreceptors, G-proteins, adenylyl cyclase (AC), protein kinase A (PKA), and calcium channels in cardiac tissue. Their study detailed an alteration in the signalling pathway of β -adrenoreceptors in rats low in selenium. The total quantity of β -adrenoreceptors in the cardiac membranes of these animals was found to be roughly 30% lower than that in control rats [25]. Similar to other SSRIs, instances of significant bradycardia have been documented with sertraline [26, 27].

A study by Pousti *et al.* [28] involving guinea pig atrium demonstrated that sertraline (2-16 μ g/mL) treatment resulted in a dose-dependent reduction in contraction rate (17-46%) and contraction force (26-48%). According to these findings, it was elucidated that sertraline has direct cardiac effects likely due to the blockage of cardiac Na⁺ and Ca²⁺ channels [28]. A separate investigation demonstrated that the cumulative injection of sertraline at concentrations ranging from 10⁻⁹ to 10⁻⁴ M in rat atrial resulted in a dose-dependent reduction in cardiac contractile force [29]. The effects of sertraline may result from the suppression of Ca²⁺ currents [30]. In our investigation, cumulative treatment of sertraline led to a dose-dependent reduction in cardiac contraction rate and force. These findings elucidate our data indicating that sertraline exerts a direct cardiac effect, maybe attributable to the blockage of cardiac Ca²⁺ channels in rat atria.

Selenium is a crucial trace element that exhibits significant antioxidant properties by inhibiting the generation of reactive metabolites induced by several toxicants in humans and animals [31]. Selenium is es-

sential for numerous biological activities, encompassing thyroid hormone metabolism, the body's antioxidant defence mechanisms, the adaptive and acquired immune systems, and the prevention of specific malignancies [32]. Research indicates that low serum or plasma selenium concentrations may correlate with several illnesses, including acute myocardial infarction, chronic ischaemic heart disease, congestive heart failure, cardiomyopathy, and hypertension [33, 34]. Gunes *et al.* [32] demonstrated a significant reduction in elevated heart damage biomarker enzymes induced by cyclophosphamide due to selenium application during cyclophosphamide treatment.

A further study demonstrated that selenium shortage in rat cardiac tissue resulted in elevated reactive oxygen species levels and reduced total antioxidant levels, leading to oxidative damage in cardiomyocytes. At the conclusion of the trial, an elevation in antioxidant enzyme levels was seen following selenium supplementation [35]. This outcome can be ascribed to the inhibitory influence of Se on lipid peroxidation, a factor in the pathogenesis of cardiovascular disease [36]. A further study demonstrated that pretreatment with Se reduced the expression of inflammatory genes, including TNF- α and NF- κ B, in an animal model of myocardial infarction. Consequently, Se may be seen as safeguarding cellular activities through the modulation of the inflammatory response [37]. In our investigation, the cumulative administration of selenium to atrial tissue adversely affected the heart's inotropic response following a 2 mM selenium dose. Se may adversely impact the inotropic action of the heart by blocking Ca²⁺ ion channels, contingent upon the dosage.

Limitations

The first limitation of the study is that it is an *in vitro* study. Optimum conditions were tried to be provided in the isolated organ bath. However, the next stage of the study is also planned as *in vivo*. Secondly, the prophylactic effect of selenium was not investigated. The prophylactic effect will also be analysed in the *in vivo* study.

CONCLUSION

In conclusion, both the independent and combined

treatment of sertraline and selenium adversely affected cardiac contractile strength. Observational studies indicate an inverse correlation between selenium levels and the occurrence of coronary heart disease; however, the reliability of this information remains questionable. Further investigation is necessary to elucidate the specific mechanism by which selenium influences cell survival, particularly its cardioprotective properties.

Ethical statement

The study was approved by Necmettin Erbakan University Animal Experiments Local Ethics Committee (HADYEK, protocol number: 047/2021).

Consent to Participate

Not applicable.

Data Availability

Datasets that support the conclusions of this article are included in the article. However, data are available from the authors upon reasonable request and with the permission of (Third party name).

Authors' Contribution

Study Conception: ZISG, HS, RÖK; Study Design: ZISG, HS, RÖK; Supervision: ZISG, NG; Funding: NG, ZISG, HS, RÖK, MA; Materials: : ZISG, HS, RÖK; Data Collection and/or Processing: HS, RÖK, MA; Statistical Analysis and/or Data Interpretation: HS, MA; Literature Review: HS; Manuscript Preparation: HS and Critical Review: ZISG, NG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Maternal heart disease and pregnancy complications: a tertiary hospital experience from Türkiye

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ABSTRACT

Objectives: Maternal heart disease is a leading cause of non-obstetric maternal mortality and morbidity, complicating the necessary physiological changes during pregnancy. This study aimed to evaluate maternal and perinatal outcomes in pregnancies complicated by maternal heart disease.

Methods: A retrospective analysis was conducted from November 2022 to November 2023 at a tertiary care hospital. Ninety-three pregnant women with maternal heart disease were included and categorized into congenital heart disease, rheumatic heart disease, and other cardiac conditions. Data on demographics, obstetric complications, and perinatal outcomes were analyzed.

Results: Among the participants, 47.3% had rheumatic heart disease, 37.6% had other cardiac conditions, and 15.1% had congenital heart disease. Maternal outcomes included a 29% incidence of preterm delivery, and an 8.6% occurrence of fetal growth restriction, and 7.5% of mothers requiring postpartum intensive care. However, no maternal mortality was observed. Neonatal outcomes included a 30.3% admission rate to the neonatal intensive care unit and a 12.9% incidence of respiratory distress syndrome, with no recorded fetal mortality. Outcomes were consistent across the three cardiac disease groups, demonstrating the effectiveness of multidisciplinary care approaches.

Conclusions: Early diagnosis, individualized care, and multidisciplinary management are essential for improving outcomes in pregnancies with maternal heart disease. Despite no observed maternal or fetal mortality, high rates of preterm births and neonatal complications emphasize the need for targeted interventions. Addressing modifiable risk factors like hypertension and obesity is critical. Multicenter studies with larger cohorts are recommended to enhance management strategies.

Keywords: Maternal heart disease, pregnancy outcomes, rheumatic heart disease, neonatal complications, high-risk pregnancies

Maternal heart disease affects 1% to 4% of all pregnancies and is the leading cause of non-obstetric maternal mortality [1-3]. Pregnancies complicated by maternal heart disease are linked

to increased maternal morbidity due to obstetric complications including preterm birth, postpartum hemorrhage, placental abruption, miscarriage, heart failure, preeclampsia, eclampsia, higher intensive care unit ad-

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mission rates, and an elevated risk of thromboembolism [4]. Furthermore, prematurity and fetal growth restriction (FGR) are significant factors that elevate fetal morbidity in these cases. Especially in low- and middle-income countries, inadequate prenatal care and delayed diagnosis further increase this risk [5].

To meet the increased metabolic demands of pregnancy and childbirth, significant cardiovascular changes take place [6]. Starting around the fifth week of pregnancy, systemic vasodilation begins, leading to a decrease in systemic vascular resistance [7]. During pregnancy and childbirth, systemic blood volume and stroke volume increase by 30-50%, whereas pulmonary vascular resistance decreases [6, 8]. Healthy pregnant women generally adapt well to these physiological changes. However, the presence of pre-existing or newly diagnosed cardiac dysfunction may impair with these natural physiological adaptations during pregnancy, increasing the risk of adverse maternal, obstetric, fetal, and neonatal outcomes [9]. An inability to adapt to these changes may also serve as an early indicator of previously undiagnosed heart disease [10].

Maternal heart disease has multiple causes, and the prevalence of rheumatic and ischemic heart disease among pregnant women is rising due to hypertension, diabetes, obesity, advanced maternal age, and prior Coronavirus disease 2019 (COVID-19) infection. At the same time, patients with congenital heart disease are surviving longer due to advances in medical treatment [11-16].

Early diagnosis and appropriate management of cardiac conditions during pregnancy, along with increased awareness among both patients and healthcare providers and adherence to established treatment guidelines, can help reduce maternal-fetal morbidity and mortality. This study aimed to present our findings about pregnant women with maternal cardiac disease and their perinatal outcomes. The study focused on patients who were tracked at a tertiary care hospital.

METHODS

This retrospective analysis was conducted in the Perinatology Clinic of Ankara Etlik City Hospital between November 2022 and November 2023. The annual birth rate at our clinic is approximately 12,800. The

study included ninety-three patients diagnosed with maternal cardiac disease before, during, or after pregnancy who received medical care at our clinic during the study period. The patients were categorized into three groups: congenital heart disease (e.g., tetralogy of Fallot, patent ductus arteriosus, atrial septal defect), rheumatic heart disease (including mitral valve stenosis, mitral valve regurgitation, aortic valve regurgitation) and other heart diseases (e.g., Brugada syndrome, cardiomyopathy, and arrhythmias).

The study included patients aged 18 to 45, but excluded those who did not continue treatment at our hospital or whose medical data were inaccessible. Demographic data, including age, gravida, parity, and body mass index (BMI), were collected for all patients. The gestational age was determined using the patient's last menstrual period (LMP) as a reference and subsequently verified through ultrasound examination. Parameters such as obstetric complications (premature birth, placental abruption, premature rupture of membranes, gestational diabetes, high blood pressure during pregnancy, miscarriage, etc.), newborn birth weight, gender, APGAR scores at 1 and 5 minutes, need for neonatal intensive care and neonatal sepsis, were all recorded. The patients' cardiac follow-up data, including electrocardiographic and echocardiographic findings, were also evaluated. Patient data were obtained from electronic health records and the hospital's data management system.

The study was conducted under the principles specified in the Declaration of Helsinki. The Ankara Etlik City Hospital's Ethics Committee gave its permission to the study protocol (approval number: 2023-474).

Statistical Analysis

Statistical analysis was conducted using the IBM Corporation SPSS version 22.0 (IBM Corporation, Armonk, NY, USA). The Kolmogorov-Smirnov test was employed to assess adherence to a normal distribution. The descriptive statistics of continuous variables are presented as the "mean±standard deviation" for variables that follow a normal distribution and as the "median (min-max value)" for variables that do not. The chi-squared test or Fisher's exact test was used to compare categorical variables. The independent sample t-test was used to compare continuous variables that were normally distributed, while the Mann-Whitney U test was used to compare continuous variables that

were not normally distributed. A P-value of less than 0.05 was used as the threshold for statistical significance in all tests.

RESULTS

In our study, forty-four of ninety-three patients (47.3%) had rheumatic heart disease, fourteen (15.1%) had congenital heart disease, and thirty-five (37.6%) had other heart diseases that could not be categorized into these two groups (Fig. 1). Maternal heart disease was diagnosed in eighty (86%) patients before pregnancy, in nine (9.7%) patients during pregnancy, and in four (4.3%) patients after pregnancy. The median gestational age at diagnosis was 31 weeks (range: 8–36 weeks).

Table 1 displays the demographic features of pregnant women who have maternal heart disease. The mean age of our patients was 30.05 ± 5.6 years and their body mass index (BMI) was 30.57 ± 4.4 kg/m². Out of the patients enrolled in the study, four (4.3%) were smokers, four (4.3%) conceived through in vitro fertilization, thirty-two (34.4%) adhered to regular medication and forty-two (45.2%) had never given birth before. The mean gestational age at delivery was 38 ± 2 weeks (range: 23 ± 0 to 41 ± 2 weeks). Of these patients,

five (11.4%) patients with rheumatic heart disease and two (14.3%) patients with congenital heart disease, a total of seven (7.5%) patients required intensive care. A total of four (4.3%) patients required a postpartum blood transfusion. Out of the patients involved in the study, 67% underwent a cesarean section for childbirth, while 33% had a normal vaginal delivery. The average hospital stay of our patients was two (0-13) days.

Seventy-nine (84.9%) of ninety-three patients did not have hypertension. Four (4.3%) patients had chronic hypertension before pregnancy. Gestational hypertension occurred in six (6.5%) patients and preeclampsia in four (4.3%) patients during pregnancy. Of the ninety-three patients, two (2.2%) had pregestational diabetes and eight (8.6%) had gestational diabetes. FGR was observed in eight (8.6%) of ninety-three pregnant women with maternal cardiac disease, and intrahepatic cholestasis of pregnancy occurred in one (1.1%) patient. The pregnancies of two (2.2%) patients ended in miscarriage. While polyhydramnios was observed in five (5.4%) patients, oligohydramnios was observed in eight (8.6%) patients.

Table 2 displays the laboratory parameters of pregnant women who have maternal heart disease. The mean prenatal hemoglobin of the patients enrolled in the study was 11.8 ± 1.4 g/dL, while the mean postnatal hemoglobin was 10.5 ± 1.4 g/dL. The mean platelet

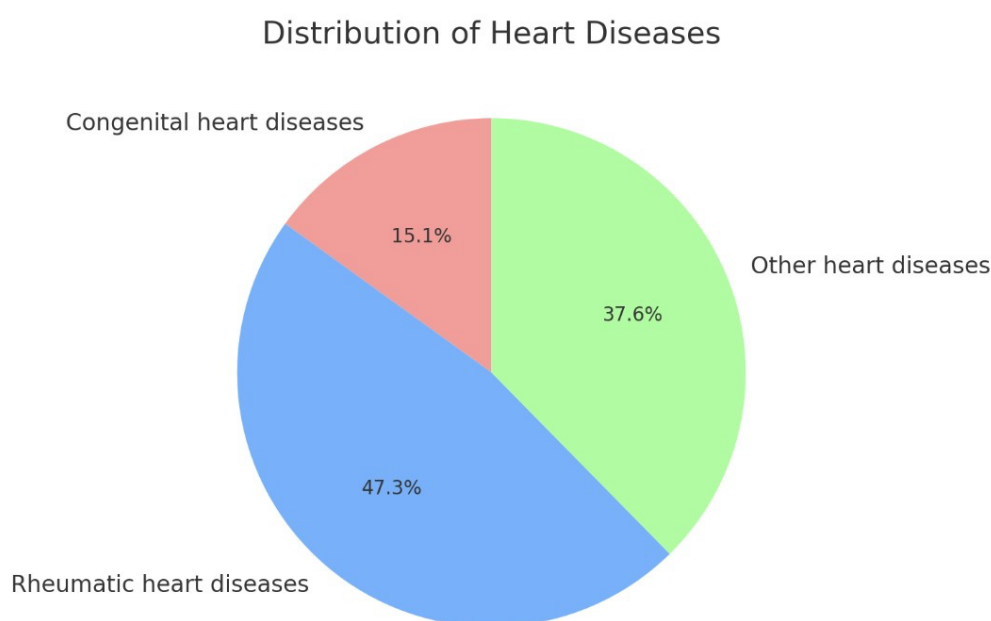


Fig. 1. Distribution of maternal heart diseases included in the study.

Table 1. Demographic characteristics of pregnant women with maternal heart disease

Parameter	Patient group n=93 (100%)	Congenital heart disease n=14 (15.1%)	Rheumatic heart disease n=44 (47.3%)	Others n=35 (37.6%)
Age (years)	30.05±5.6	28.64±5.9	30.18±.8	30.46±5.4
Body mass index (kg/m ²)	30.57±4.4	32.51±5.5	30.51±6.4	29.88±3.78
Weight gain during pregnancy (kg)	10 (0-34)	10 (4-24)	11.5 (0-34)	10 (1-32)
Gravida	2 (1-11)	1.5 (1-6)	2 (1-11)	2 (1-6)
Parity	1 (0-4)	0.5 (0-2)	1 (0-4)	1 (0-4)
Nulliparous	42 (45.2)	8 (57.1%)	22 (50)	22 (50)
In vitro fertilization	4 (4.3)	1 (7.1%)	1 (2.3)	1 (2.3)
Smoking	4 (4.3)	1 (7.1%)	1 (2.3)	1 (2.3)
Chronic medication use	32 (34.4)	4 (28.6%)	16 (36.5)	16 (36.5)
Gestational weeks at delivery	38+2 (23+0–41+2)	38+3 (33+6–41+0)	38+2 (23+0–41+1)	37+3 (23+5–41+2)
Hospitalization duration (day)	2 (0-13)	2 (1-6)	2 (0-6)	2 (0-13)
Admission to intensive care unit	7 (7.5)	2 (14.3)	5 (11.4)	0 (0)
Need for blood transfusion	4 (4.3)	0 (0)	3 (6.8)	1 (2.9)
Birth method				
Cesarean section	61 (67)	10 (71.4)	28 (65.1)	23 (67.6)
Normal spontaneous vaginal birth	30 (33)	4 (28.6)	15 (34.9)	11 (32.4)

Data are expressed as mean±standard deviation, median (min-max) or n (%) where appropriate.

count of the patients was 224 (10-502) ×10⁹/L, the mean fibrinogen level was 468.5 (270-844) mg/dL, the thyroid-stimulating hormone level was 2 (0.34-9.43) mIU/L and the albumin level was 36 (25-49) g/L.

An echocardiography was performed in seventy-eight (83.9%) of ninety-three patients, while an electrocardiography (ECG) was performed in all patients.

Table 2. Laboratory parameters of pregnant women with maternal heart disease

Hemoglobin level before birth (g/dL)	11.8±1.4
Hemoglobin level after birth (g/dL)	10.5±1.4
Platelet count (×10 ⁹ /L)	224 (10-502)
Fibrinogen count (mg/dL)	468.5 (270-844)
Thyroid stimulating hormone (mIU/L)	2 (0.34-9.43)
Albumin (g/L)	36 (25-49)

Data are expressed as mean±standard deviation or median (min-max) where appropriate.

No changes were detected in the ECGs of eighty (86%) patients. The pathological changes detected in the ECG are listed in Table 3. Incomplete right bundle branch block was present in five (5.4%) patients participating in the study, negative T wave in four (4.3%) patients, ventricular extrasystole in one (1.1%) patient, precordial ST depression in one (1.1%) patient, inter-ventricular conduction delay in one (1.1%) patient, supraventricular extrasystole in one (1.1%) patient, atrial fibrillation in one patient and ventricular fibrillation in one (1.1%) patient. A simultaneous occurrence of ventricular fibrillation and a negative T wave was observed in one patient's ECG, while a partial right bundle branch block and a negative T wave were observed concurrently in another patient's ECG.

Also, Table 3 shows the symptoms seen in pregnant women with maternal heart disease. Thirteen (14%) of the patients had dyspnea, ten (10.8%) had palpitations, seven (7.5%) had chest pain, six (6.5%) had cardiac arrhythmia and four (4.3%) had lower extremity edema.

Table 3. Pathological changes detected on ECG and symptoms seen in pregnant women with maternal heart disease

	Patient group (n=93)
ECG changes	
Incomplete right bundle branch block	5 (5.4%)
Negative T wave	4 (4.3%)
Ventricular extrasystole	1 (1.1%)
Precordial ST segment depression	1 (1.1%)
Interventricular conduction delay	1 (1.1%)
Supraventricular extrasystole	1 (1.1%)
Atrial fibrillation	1 (1.1%)
Ventricular fibrillation	1 (1.1%)
Symptom	
Dyspnea	13 (14%)
Palpitation	10 (10.8%)
Chest Pain	7 (7.5%)
Arrhythmia	6 (6.5%)
Lower extremity edema	4 (4.3%)
Pulmonary edema	0 (0%)

Data are expressed as n (%). ECG=Electrocardiography

Two (2.2%) out of ninety-three pregnant women with maternal heart disease resulted in miscarriage and not a live birth. There are a total of ninety-three newborns since two (2.2%) of the remaining ninety-one patients were twin pregnancies. Table 4 displays the perinatal results of expectant mothers with maternal heart disease. Out of the infants born to expectant mothers with maternal cardiac disease, fifty-one (54.8%) were female and forty-two (45.2%) were male. The average weight of the newborns was 3 060 (550-4 350) g and their APGAR scores were 9 (3-9) in the first minute and 10 (4-10) in the 5th minute. Twelve (12.9%) of the newborns had respiratory distress syndrome (RDS). Of these, two (14.2%) were in the congenital heart disease group, six (13.6%) in the rheumatic heart disease group, and four (11.4%) in the other heart disease group. Thirty (30.3%) newborns required intensive care. Of these, six (42.9%) belonged to the congenital heart disease group, thirteen (30.2%) to the rheumatic heart disease group, and eleven (32.4%) to the other heart disease group. In

four (4.4%) patients, fetal distress developed during delivery. Of these, one (7.1%) belonged to the congenital heart disease group, two (4.7%) to the rheumatic heart disease group and one (2.9%) to the other heart disease group. Preterm birth occurred in twenty-seven (29%) pregnancies. Of these, four (28.6%) belonged to the congenital heart disease group, ten (23.3%) to the rheumatic heart disease group, and thirteen (38.2%) to the other heart disease group. Neonatal sepsis developed in two (2.2%) of the newborns. One (2.9%) of the neonates who developed neonatal sepsis was the child of a mother with rheumatic heart disease, while one (2.9%) belonged to the other heart disease group. Fourteen (15%) neonates received phototherapy due to hyperbilirubinemia. Of these newborns, eight (57.1%) were in the congenital heart disease group, two (14.2%) in the rheumatic heart disease group, and four (28.5%) in the other heart disease group.

In Table 5, patients were divided into two groups: rheumatic and non-rheumatic heart disease, and their demographic data were compared. 44 (47.3%) patients had rheumatic heart disease, while 49 (52.7%) patients belonged to the non-rheumatic heart disease group. maternal age, BMI, weight gain during pregnancy, gravida, parity, and nulliparity were similar in both groups ($P=0.838$, $P=0.912$, $P=0.344$, $P=0.565$, $P=0.971$, and $P=0.374$, respectively). One (2.3%) of the pregnant women with rheumatic heart disease and three (6.1%) of the pregnant women with non-rheumatic heart disease were in vitro fertilization pregnant women, and there was a similarity between the groups ($P=0.619$). Smoking and postpartum blood transfusion requirements were also similar between groups ($P=0.619$ and $P=0.341$, respectively). Gestational weeks at delivery, length of postnatal hospital stay, admission to the neonatal intensive care unit (NICU) and birth method were similar in both groups ($P=0.814$, $P=0.227$, $P=0.219$ and $P=0.713$, respectively).

Table 6 compares the perinatal outcomes of patients with rheumatic heart disease and non-rheumatic heart disease. Fetal gender, fetal weight, APGAR score at the first minute, and APGAR score at the fifth minute were similar between the two groups ($P=0.435$, $P=0.853$, $P=0.837$ and $P=0.849$, respectively). RDS, NICU admission, fetal distress, and preterm birth rates were also similar between the two groups ($P=0.989$, $P=0.599$, $P=1$, and $P=0.205$, respectively).

Table 7 shows the laboratory values of patients

Table 4. Perinatal outcomes of pregnant women with maternal heart disease

Parameter	Patient group n=93 (100%)	Congenital Heart disease n=14 (15.1%)	Rheumatic heart disease n=44 (47.3%)	Others n=35 (37.6%)
Gender				
Female	51 (54.8%)	7 (50%)	26 (59.1%)	18 (51.4%)
Male	42 (45.2%)	7 (50%)	18 (40.9%)	17 (48.6%)
Fetal weight (gr)	3060 (550-4350)	3210 (1890-3820)	3000 (550-4350)	3000 (850-3880)
1st min. APGAR	9 (3-9)	9 (5-9)	9 (3-9)	9 (5-9)
5th min. APGAR	10 (4-10)	10 (6-10)	10 (4-10)	10 (7-10)
Respiratory distress syndrome	12 (12.9%)	2 (14.2%)	6 (13.6%)	4 (11.4%)
Admission to neonatal intensive care unit	30 (30.3%)	6 (42.9%)	13 (30.2%)	11 (32.4%)
Fetal distress	4 (4.4%)	1 (7.1%)	2 (4.7%)	1 (2.9%)
Preterm birth	27 (29%)	4 (28.6%)	10 (23.3%)	13 (38.2%)
Neonatal sepsis	2 (2.2%)	0	1 (2.9%)	1 (2.9%)
Need for phototherapy	14 (15%)	8 (57.1%)	2 (14.2%)	4 (28.5%)

Data are expressed as median (min-max) or n (%) where appropriate.

Table 5. Comparison of demographic characteristics according to patients with rheumatic or non-rheumatic heart disease

	Rheumatic heart disease n=44 (47.3%)	Non-rheumatic heart disease n=49 (52.7%)	P value
Age (years)	30.18±5.8	29.94±5.59	0.838 ^a
Body mass index (kg/m²)	30.51±6.5	30.64±4.5	0.912 ^a
Weight gain during pregnancy (kg)	11.5 (0-34)	10 (1-32)	0.344 ^b
Gravida	2 (1-11)	2 (1-6)	0.565 ^b
Parity	1 (0-4)	1 (0-4)	0.971 ^b
Nulliparous	22 (50%)	20 (40.8%)	0.374 ^c
In vitro fertilization	1 (2.3%)	3 (6.1%)	0.619 ^d
Smoking	1 (2.3%)	3 (6.1%)	0.619 ^d
Gestational weeks at delivery	38+2 (23+0-41+1)	38 (23+5-41+2)	0.814 ^b
Hospitalization duration (day)	2 (0-6)	2 (0-13)	0.227 ^b
Admission to the intensive care unit	5 (11.4%)	2 (4.1%)	0.219 ^d
Need for blood transfusion	3 (6.8%)	1 (2%)	0.341 ^d
Birth method			0.713 ^c
Cesarean section	28 (65.1%)	33 (68.8%)	
Normal spontaneous vaginal birth	15 (34.9%)	15 (31.3%)	

Data are expressed as mean±standard deviation, median (min-max) or n (%) where appropriate.

^aStudent t-test, ^bMann Withney-U, ^cPearson chi square, ^dFisher's exact test

Table 6. Perinatal outcomes of pregnant women according to rheumatic or non-rheumatic heart disease

Parameters	Rheumatic heart disease n=44 (47.3%)	Non-Rheumatic heart disease n=49 (52.7%)	P value
Gender			0.435 ^a
Female	26 (59.1%)	25 (51%)	
Male	18 (40.9%)	24 (49%)	
Fetal weight (gr)	3000 (550-4350)	3080 (850-3880)	0.853 ^b
1st min. APGAR	9 (3-9)	9 (5-9)	0.837 ^b
5th min. APGAR	10 (4-10)	10 (6-10)	0.849 ^b
Respiratory morbidity	6 (13.6%)	6 (12.2%)	0.989 ^a
Admission to neonatal intensive care unit	13 (30.2%)	17 (35.4%)	0.599 ^a
Fetal distress	2 (4.7%)	2 (4.2%)	1 ^c
Preterm birth	10 (23.3%)	17 (35.4%)	0.205 ^a

Data are expressed as median (min-max) or n (%) where appropriate.

^aPearson chi square, ^bMann Withney-U, ^cFisher's exact test

with rheumatic and non-rheumatic heart disease. Hemoglobin levels before birth, hemoglobin levels after birth, platelets, fibrinogen, and albumin were similar between the groups (P=0.156, P=0.827, P=0.080, P=0.587, and P=0.656, respectively).

DISCUSSION

Our study provides a current evaluation of maternal and neonatal complications in pregnant women with maternal heart disease. Rheumatic heart disease was

the most common, affecting 47.3% of the patients. Additionally, hypertensive disorders were the most frequently observed comorbidity, present in 15.1% of pregnant women with maternal heart disease. In our study, the mean age of pregnant women with heart disease was below 35 years and 86% of them were diagnosed before getting pregnant. Seven patients (7.5%) required postpartum intensive care and no maternal mortality was observed. Preterm birth occurred in twenty-seven (29%) of the cases. Among the neonates, thirty (30.3%) required NICU, twelve (12.9%) developed RDS, two (2.2%) developed neonatal sepsis, and

Table 7. Comparison of laboratory parameters of pregnant women according to rheumatic or non-rheumatic heart disease

Parameters	Rheumatic heart disease n=44 (47.3%)	Non-rheumatic heart disease n=49 (52.7%)	P value
Hemoglobin level before birth (g/dL)	12.06±1.32	11.65±1.44	0.156 ^a
Hemoglobin level after birth (g/dL)	10.55±1.57	10.61±1.27	0.827 ^a
Platelet count (×10⁹/L)	229 (11-502)	215 (99-373)	0.080 ^b
Fibrinogen count (mg/dL)	468 (270-844)	469 (346-739)	0.587 ^b
Albumin (g/L)	36 (25-46)	35 (26-49)	0.656 ^b

Data are expressed as mean±standard deviation, median (min-max).

^aStudent t-test, ^bMann Withney-U,

fourteen (15%) required phototherapy. No fetal mortality was observed.

The etiology of maternal heart disease is multifactorial, with rheumatic heart disease being the predominant condition observed during pregnancy [15, 17]. In a study by Subbaiah *et al.* [18] which examined the outcomes of pregnant women with maternal heart disease, rheumatic heart disease was predominant, affecting 64% of the patients. That study included one hundred patients with maternal heart disease and reported an 18% rate of fetal complications. In addition, twelve patients had gestational diabetes mellitus and nine had hypertensive pregnancy disorders [18]. In a study by Madazli *et al.* [19], the outcomes of 144 pregnant women with maternal heart disease were analyzed, with 87.5% of these patients having rheumatic heart disease. Maternal morbidity was observed in sixteen cases (11.1%) and perinatal mortality in six cases (4.2%) [19]. In their review, Drenthen *et al.* [20] examined the pregnancy outcomes of patients with congenital heart defects. While most of them experienced a healthy pregnancy, maternal morbidity was observed in 11% of patients, with heart failure developing most frequently in these patients [20]. In our study, 47.3% of patients had rheumatic heart disease and 15.1% had congenital heart disease, with rheumatic heart disease being the predominant group. The most common concomitant disease in maternal heart disease was hypertension, followed by diabetes mellitus patients. There was no maternal mortality among our patients. When looking at patients with and without rheumatic heart disease, maternal and perinatal morbidity rates were similar. These findings underscore the need for early detection, risk stratification, and implementation of personalized care plans, especially in areas where rheumatic heart disease is common.

Prematurity and fetal growth restriction are prevalent factors that contribute to increased fetal morbidity in pregnant women with maternal cardiac disease [5]. In a prospective study by Beaton *et al.* [21] conducted at three centers, the prevalence of maternal heart disease and perinatal outcomes were assessed. Out of fifty-four patients with maternal heart disease, fifty-one (87.9%) had rheumatic heart disease. This study reported one maternal death and three cases of fetal morbidity, with all three pregnancies resulting in preterm labor [21]. In their meta-analysis of rheumatic

heart disease, Liaw *et al.* [22] evaluated a total of 11 studies and found a high rate of premature births (9.35%-42.97%), FGR (6.76%-22.40%) and perinatal deaths (0.00%-9.41%) in rheumatic heart disease [22]. Nyugen Manh *et al.* [5] conducted a study to examine the connection between maternal heart illness and FGR. They discovered that FGR occurred in 9.15% of the cases, indicating a notable correlation with maternal heart disease [5]. Similarly, Khanna *et al.* [23] included 80 pregnant women in their descriptive study. 4 (5%) of the pregnant women with rheumatic heart disease had FGR and 19 (23.7%) had preterm delivery. A further investigation conducted by Rezk *et al.* [24] analyzed the rates of maternal and fetal mortality and morbidity in a sample of 192 pregnant women diagnosed with rheumatic heart disease. The study revealed elevated rates of maternal illness in both cohorts, accompanied by heightened rates of preterm birth and hospitalizations to the neonatal critical care unit [24]. In our study, there was no significant difference in perinatal mortality and morbidity between the groups with and without rheumatic heart disease. As indicated, no fetal mortality was observed in our study, while preterm birth was the most significant factor contributing to fetal morbidity, occurring in twenty-seven cases (29%). The rate of FGR among our patients was 8.6%, with eight patients affected. The fact that no fetal mortality was observed demonstrates the effectiveness of the multidisciplinary treatment approaches implemented in a tertiary health center. However, these complication rates in high-risk pregnancies highlight once again the need for more effective strategies for the management of maternal heart disease.

Limitations

This study has some limitations. First, the generalizability of the results and the assessment of cause-effect relationships is limited due to the single-center and retrospective study design. The small sample size can reduce statistical power, especially when comparing subgroups. In addition, the lack of detailed information on the specific treatment protocols applied to the patients makes it difficult to assess the impact of treatment approaches on outcomes. Future multicentre and prospective studies can be planned to improve the generalizability of the results and data quality.

CONCLUSION

This study comprehensively evaluates maternal and neonatal outcomes in pregnancies complicated by maternal heart disease and emphasizes the critical importance of early diagnosis, regular follow-up, and multidisciplinary management. The fact that there was no maternal mortality in our study demonstrates the potential benefits of effective prenatal care, individualized treatment plans, and coordinated efforts by healthcare teams. However, the high rates of preterm births (29%), the need for NICU (30.3%), and RDS (12.9%) highlight the ongoing challenges in dealing with these high-risk pregnancies. It also emphasizes the importance of interventions targeting modifiable risk factors such as hypertension, diabetes, and obesity, which are common in this patient group. Public health strategies to reduce these risk factors, raise awareness, and provide pre-conception counseling can be effective in reducing the risks associated with maternal heart disease. Multicenter studies with larger sample groups can contribute to the development of management strategies by providing more comprehensive information on the impact of maternal heart disease on pregnancy.

Ethical Statement

The study was conducted under the principles specified in the Declaration of Helsinki. The Ankara Etlik City Hospital's Ethics Committee gave its permission to the study protocol (approval number: 2023-474 and date 16.08.2023).

Authors' Contribution

Study Conception: GK; Study Design: GK; Supervision: ATÇ; Funding: N/A; Materials: HA, Sİ; Data Collection and/or Processing: ZS, AAF, UK; Statistical Analysis and/or Data Interpretation: UK, AAF; Literature Review: GK; Manuscript Preparation: GK; and Critical Review: GK, ATÇ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Improvements in functional exercise performance at 6 months following bariatric surgery: A prospective cohort study

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ABSTRACT

Objectives: Successful weight loss after bariatric surgery has been associated with a variety of improvements in health status. Delayed heart rate recovery after the six-minute walking test (6MWT) is associated with morbidity and mortality in various cardiac and respiratory diseases. We aimed to evaluate the effect of bariatric surgery on functional exercise performance and autonomic dysfunction in patients who had undergone laparoscopic sleeve gastrectomy.

Methods: Pre-operative and post-operative (6 months) demographics, comorbidities, weight, and height of the patients undergoing laparoscopic sleeve gastrectomy were recorded. All patients underwent a 6MWT. 6MWT was performed according to the American Thoracic Society standards. Additionally, heart rate (HR) and oxygen saturation were assessed at rest, at the end of the test, and in the first minute following testing. Autonomic dysfunction was assessed by heart rate recovery (HRR), which was calculated as the difference between the maximum HR reached during the 6MWT and the HR at the first minute after the test. Patients were classified depending on whether their HRR was slow (HRR<12 beats, “delayed recovery”) or more rapid (HRR≥12 beats, “non-delayed recovery”).

Results: A total of 62 patients were prospectively enrolled. The mean age of the patients was 36.8±9.1 years and 74% were female. Pre-operative and post-operative body mass indices were 48.5±5.2 kg/m² and 34.4±3.5 kg/m², respectively (P<0.001). Excess weight loss was 52.7±12.7%. Post-operative six-minute walking distance significantly improved compared to pre-operative period (406±48 meters vs. 443±52 meters, P<0.001). Compared with pre-operative period, perceived breathlessness and fatigue at the end of the 6MWT decreased from 1.3±1.5 to 0.4±0.9 Borg units (P<0.001), and 3.2±2.1 to 0.8±1.4 Borg units (P<0.001), respectively. We observed a remarkable, but statistically non-significant increase in the number of patients in the delayed HRR group from 21% (n=13) to 42% (n=26) in the postoperative period, compared to the preoperative assessment (P=0.12).

Conclusions: Laparoscopic sleeve gastrectomy is associated with rapid weight loss and improvements in perceived exertional dyspnea, fatigue and six-minute walking distance at 6 months after surgery. Failure of the heart rate to fall after cessation of exertion, a delayed HRR, has previously been found to be associated with increased mortality in cardiac failure. Further investigation is required to examine the physiological mechanisms involved in autonomic dysfunction, and consequences of delayed HRR after rapid weight loss by bariatric surgery.

Keywords: Exercise performance, six-minute walking test, heart recovery rate, bariatric surgery

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Obesity is linked to various health conditions, early mortality, reduced functional capacity, and diminished quality of life [1-4]. Bariatric surgery is a well-established intervention for the treatment of severe obesity, resulting in substantial weight loss and improvements in obesity-related comorbidities such as type 2 diabetes, hypertension, and obstructive sleep apnea [5, 6]. Beyond its metabolic benefits, bariatric surgery also has profound effects on physical function, a key determinant of quality of life and long-term health outcomes [7]. Improvements in functional exercise performance following bariatric surgery have gained attention as they reflect enhanced mobility, reduced biomechanical limitations, and better overall health [8, 9].

The six-minute walk test (6MWT) is a practical, reliable, and widely used tool for evaluating functional exercise capacity in clinical and research settings [10]. As a submaximal exercise test, it measures the distance an individual can walk on a flat surface in six minutes, providing an integrated assessment of cardiorespiratory, musculoskeletal, and metabolic function [11]. Its simplicity, safety, and minimal equipment requirements make it particularly suitable for bariatric surgery patients, who often experience significant functional limitations prior to surgery [12]. Moreover, the 6MWT has been shown to be sensitive to detecting changes in functional capacity over time, making it an ideal metric for evaluating the impact of bariatric surgery on physical function [8, 9].

Patients with severe obesity frequently demonstrate reduced 6MWT performance due to the combined effects of excess body weight, joint pain, and reduced cardiorespiratory fitness [13]. Postoperatively, the substantial weight loss associated with bariatric surgery alleviates biomechanical strain and enhances physical activity levels, contributing to measurable improvements in walking capacity [14]. The 6MWT can therefore serve as a valuable tool to quantify these improvements and track the recovery of functional mobility over time. Additionally, better functional performance, as captured by the 6MWT, is strongly associated with increased physical activity participation, which supports long-term weight maintenance and overall health [15].

This study focuses on the changes in 6MWT performance at 6 months following bariatric surgery,

highlighting its role as a reliable and clinically relevant measure of functional recovery in this population.

METHODS

Study Design and Population

We prospectively enrolled patients willing to participate and were diagnosed with obesity (body mass index [BMI] over 35 kg/m²) meeting national institutes of health criteria admitted for bariatric surgery operation consecutively between 01 August 2015 to 15 December 2017. Patients were evaluated for weight loss, functional exercise performance, and autonomic function at baseline and at a 6-month follow-up visit. The study was approved by the institutional ethics committee (2014/10/08), and all participants provided written informed consent before enrollment. Patients with a follow-up of 6 months were included in the final study population. Patients with loss in follow-up were excluded from the study. Patients with previous history of bariatric operation such as gastric band, gastric sleeve or all other types of laparoscopic, open, primary, or revision procedures were excluded from the study. After exclusions the patients with sleeve gastrectomy, were selected for further analysis. After pre-operative preparations and obtaining the patients dietary habits, the patients that were operated with sleeve gastrectomy, selected as the best suitable option for those patients. Pre-operative and post-operative (6 months) demographics, weight, and height of the study participants were recorded. Comorbid conditions, including diabetes mellitus, hypertension, musculoskeletal complaints, and OSAS, were assessed before and after surgery. Improvement or resolution of these conditions was determined through clinical evaluation and medical records review at the 6-month follow-up visit. All patients underwent a six-minute walking test at baseline and at the 6-months follow-up visit.

Weight Loss and Body Composition Measurements

Body weight and BMI were recorded preoperatively and at the 6-month follow-up visit. The percentage of excess weight loss (EWL%) was calculated using the formula:

$$\text{EWL (\%)} = \frac{\text{preoperative weight} - \text{postoperative weight}}{\text{preoperative weight} - \text{ideal body weight}} \times 100$$

weight) / (preoperative weight-ideal weight) $\times$ 100, where ideal weight corresponds to a BMI of 25 kg/m².

Excess BMI loss (EBMIL) was also calculated as the percentage reduction in excess BMI over the follow-up period.

The 6-Minute Walking Test

The 6MWT was conducted in accordance with the American Thoracic Society (ATS) guidelines to assess functional exercise capacity [10]. The test was performed on a flat, straight, indoor corridor measuring 30 meters in length, marked at regular intervals. Participants were instructed to walk as far as possible within six minutes at their own pace while being allowed to slow down or rest if needed. A trained evaluator provided standardized verbal encouragement at specific time intervals (every minute), following ATS recommendations [10].

Participants were advised to avoid vigorous exercise before testing. Dyspnea and fatigue were measured using the Borg scale both before and immediately after the test. Oxygen saturation (SpO₂) and blood pressure were documented before and after the test. Total walking distance (6MWD) in meters was recorded as the primary outcome. Heart rate (HR) was recorded before the test, at the end of six minutes, and one-minute post-test to assess heart rate recovery (HRR). Any adverse symptoms, such as dizziness, chest pain, or excessive fatigue, were closely monitored, and the test was stopped if necessary for safety reasons [10].

Autonomic dysfunction was assessed by HRR, which was calculated as the difference between the maximum HR reached during the 6MWT and the HR at the first minute after the test. Patients were classified depending on whether their HRR was slow (HRR < 12 beats, “delayed recovery”) or more rapid (HRR > 12 beats, “non-delayed recovery”) [16].

The primary endpoint of the study was change in the six-minute walking distance, whereas the secondary endpoint was the diagnosis of the failure of heart rate recovery.

Statistical Analysis

Data were analyzed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). The data were analyzed for normal distribution of continuous variables by using histograms and the Kolmogorov–Smirnov

and the Shapiro–Wilk tests. Continuous variables with normal distribution were reported as mean $\pm$ standard deviation (SD) and the ones with abnormal distribution were reported as medians and interquartile ranges (IQR). Categorical variables were reported as frequencies and percentages. The paired t-test was used for within-group comparisons, while categorical variables were analyzed using the chi-square test or Fisher’s exact test, as appropriate. A P value < 0.05 was considered statistically significant.

To explore factors influencing changes in six-minute walking distance (Δ 6MWD) and HRR, generalized linear regression models were utilized. A generalized linear regression model examined relationships between Δ 6MWD and patient characteristics, including gender, age, EWL%, hypertension, diabetes, musculoskeletal complaints, smoking status, and pre-test oxygen saturation. A second generalized linear regression model evaluated the association between HRR and patient characteristics, including gender, age, and EWL%, to determine factors influencing changes in autonomic function after surgery. Lastly, a multiple linear regression model was used to identify factors associated with HRR failure postoperatively, defined as HRR < 12 beats. Independent variables included gender, age, EWL%, smoking status, postoperative hypertension, and postoperative diabetes. Results were presented as odds ratios (Exp(B)) with 95% confidence intervals (CI).

RESULTS

Study Population

A total of 62 patients were included in the study, with a mean age of 36.8 ± 9.1 years. The majority of participants were female (74.2%). Baseline comorbidities were common, with 22.6% of patients diagnosed with hypertension, 16.1% with diabetes mellitus, 59.7% reporting musculoskeletal complaints, and 8.1% diagnosed with obstructive sleep apnea syndrome (OSAS). Tobacco use was reported by 14.5% of participants (Table 1).

Weight Loss and Body Composition Changes

At 6 months following laparoscopic sleeve gastrectomy, patients demonstrated significant weight loss. The mean preoperative weight of 131.2 ± 18.7 kg

Table 1. Baseline characteristics of the study participants (n=62)

Characteristics	Data
Age (years)	36.8±9.1
Gender (female), n (%)	46 (74.2)
Co-morbidities, n (%)	
Smoking	9 (14.5)
OSAS	5 (8.1)
HT	14 (22.6)
DM	10 (16.1)
Musculoskeletal complaints	37 (59.7)
Smoking status, n (%)	
Never smoker	34 (54.8)
Ex-smoker	19 (30.6)
Current smoker	9 (14.5)
Smoking history (pack years ⁻¹)	0.0 [IQR 25-75: 0.0-12.0]

Data are shown as numbers (%) or mean±standard deviations or medians [interquartile range 25 -75]. DM=diabetes mellitus, HT=hypertension, OSAS= obstructive sleep apnea syndrome

decreased to 93.0±12.0 kg ($P<0.001$), and BMI declined from 48.5±5.2 kg/m² to 34.4±3.5 kg/m² ($P<0.001$). EWL was 52.7±12.7%, while EBMI was 60.1±12.8%. Additionally, the percentage reduction in total weight and BMI was 28.8±6.6% and 29.1±6.7%, respectively (Table 2).

Resolution of Comorbidities

Substantial improvements in obesity-related comorbidities were observed in the postoperative follow up visit at 6 months (Table 3). The prevalence of diabetes mellitus decreased significantly from 16.1% preoperatively to 6.5% postoperatively ($P=0.031$). Hypertension showed a similar trend, with its preva-

lence dropping from 22.6% to 8.1% ($P=0.004$). Musculoskeletal complaints were notably reduced, with prevalence decreasing from 59.7% preoperatively to 22.6% postoperatively ($P<0.001$). While the proportion of patients with OSAS decreased from 8.1% to 1.6% ($P=0.125$).

Functional Exercise Performance

Functional exercise performance improved significantly after surgery. The 6MWD increased from 406±48 meters preoperatively to 443±52 meters postoperatively ($P<0.001$), representing a marked enhancement in mobility and physical capacity (Fig. 1). Patients also reported substantial reductions in per-

Table 2. Changes in weight and body mass index following bariatric surgery

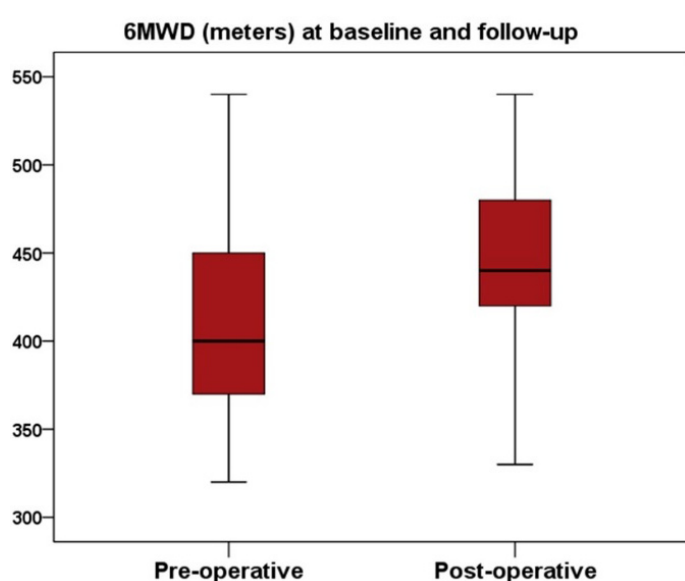
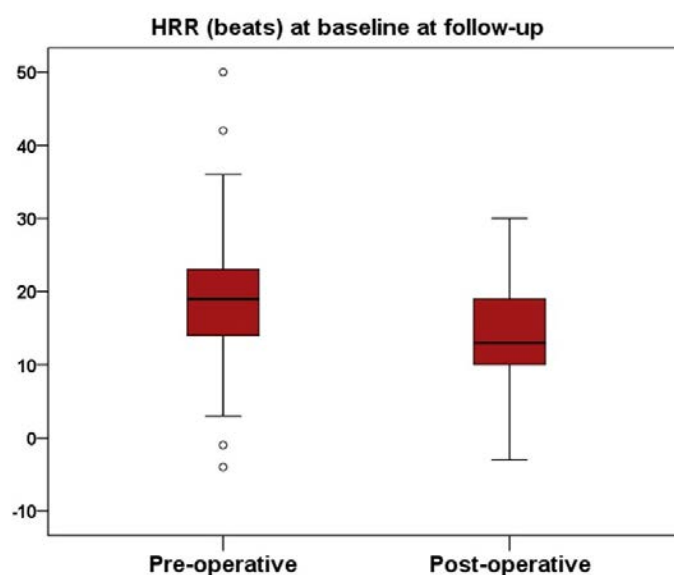
	Preoperative	Postoperative	P value
Weight	131.2±18.7	93.0±12.0	<0.0001
BMI	48.5±5.2	34.4±3.5	<0.0001
Weight loss %	28.8±6.6		
BMI loss %	29.1±6.7		
EBMI loss %	60.1±12.8		
EWL %	52.7±12.7		

Data are shown as mean±standard deviation. BMI=body mass index, EBMI=excess BMI, EWL=excess weight loss

Table 3. Resolution of comorbidities in the postoperative follow-up

Comorbidities	Preoperative	Postoperative	P value
	10 (16.1)	4 (6.5)	0.031
HT	14 (22.6)	5 (8.1)	0.004
OSAS	5 (8.1)	1 (1.6)	0.125
Musculoskeletal complaints	37 (57.7)	14 (22.6)	<0.0001

Data are shown as numbers and (%). DM=diabetes mellitus, HT=hypertension, OSAS= obstructive sleep apnea syndrome

**Fig. 1.** Comparison of six-minute walk distance (6MWD) at baseline and six-month Follow-up.**Fig. 2.** Comparison of heart rate recovery (HRR) at baseline and six-month follow-up.**Table 4. Change in dyspnea, fatigue scores assessed by the Borg scale and oxygen saturation and heart rate before and after bariatric surgery**

	Preoperative		Postoperative		P value*
	Pre-test	Post-test*	Pre-test	Post-test*	
Dyspnea	0.3±0.6	1.3±1.5	0.2±0.6	0.4±0.9	<0.0001
Fatigue	0.6±0.8	3.2±2.1	0.4±0.9	0.8±1.4	<0.0001
SpO ₂	96.8±1.2	95.7±2.0	97.4±1.5	96.9±1.2	0.145
HR	81.8±10.4	125.8±9.3	81.5±10.8	114.3±13.4	0.523

Data are shown as mean±standard deviation. SpO₂=oxygen saturation, HR=heart rate.

Dyspnea and fatigue were evaluated on Borg scale ranging from 0 to 10.

*represents paired t-test comparisons between preoperative post-test measurements and postoperative post-test measurements

ceived exertional dyspnea and fatigue during the 6MWT. Breathlessness, measured using the Borg scale, decreased from 1.3 ± 1.5 preoperatively to 0.4 ± 0.9 postoperatively ($P < 0.001$). Similarly, fatigue scores decreased from 3.2 ± 2.1 to 0.8 ± 1.4 ($P < 0.001$). These findings reflect the improved functional status and reduced effort associated with physical activity following significant weight loss.

Dyspnea and fatigue were assessed using the Borg scale before and after bariatric surgery (Table 4). Preoperatively, dyspnea scores increased from 0.35 ± 0.63 at rest to 1.26 ± 1.46 post-exercise, while fatigue scores increased from 0.58 ± 0.78 to 3.21 ± 2.09 . Following surgery, significant reductions were observed in both dyspnea and fatigue levels. Postoperatively, dyspnea increased only slightly from 0.24 ± 0.59 at rest to 0.37 ± 0.89 post-exercise, while fatigue scores rose from 0.45 ± 0.93 pre-test to 0.77 ± 1.44 post-test. Both

reductions were statistically significant ($P < 0.0001$). These findings indicate that bariatric surgery led to a substantial improvement in perceived exertional dyspnea and fatigue during physical activity.

Heart Rate Recovery and Autonomic Function
HRR, an indicator of autonomic function, was evaluated during the 6MWT. HRR was significantly reduced from 18.9 ± 9.8 beats to 13.7 ± 7.5 beats at follow-up compared to baseline tests ($P = 0.001$) (see Fig. 2). Patients were classified into two groups based on HRR: delayed recovery ($HRR < 12$ beats) and non-delayed recovery ($HRR \geq 12$ beats). Preoperatively, 21% ($n = 13$) of patients were in the delayed recovery group. Postoperatively, this proportion increased to 42% ($n = 26$), indicating a trend toward delayed recovery at 6 months; however, this change was not statistically significant ($P = 0.12$).

Table 5. General linear regression model for predictors of $\Delta 6MWD$

	B	Exp (B), CI (95%)	P value
Gender			
Male	ref	-	-
Female	-0.09	8.82 (1.00-1.02)	0.907
Age	-0.15	0.86 (0.46-1.59)	0.627
Smoking status			
Current smoking	ref	-	-
Ex-smoking	13.46	700.29 (0.00-1.02)	0.162
Never smoking	10.85	516.49 (0.00-1.74)	0.220
EWL%	0.24	1.89 (1.18-3.01)	0.007
Hypertension	2.05	7.81 (9.03-6750.07)	0.768
Diabetes mellitus	-11.49	1.02 (1.45-2292.17)	0.241
Joint pain	-7.69	0.00 (1.98-1050.49)	0.303
SpO₂ at baseline	-0.53	0.59 (0.00-70.16)	0.827

Factors Influencing the Change in Six-Minute Walking Distance (Δ 6MWD)

A generalized linear regression model was used to examine the relationship between patient characteristics and Δ 6MWD following weight loss (Table 5). The model included gender, age, EWL%, hypertension, diabetes, musculoskeletal complaints, smoking status, and pre-test oxygen saturation as independent variables. Importantly, we observed a significant association EWL% and Δ 6MWD ($B=0.637$, $P=0.007$), indicating that a greater reduction in excess weight was linked to a more pronounced improvement in six-minute walking distance. The odds ratio for EWL% ($\text{Exp}(B)=1.891$, 95% CI: 1.187-3.013) suggests that for each 1% increase in EWL, there was an approximately 89% greater likelihood of improving 6MWD by 1 meters postoperatively. Age and gender did not significantly influence Δ 6MWD ($P=0.627$, $P=0.907$, respectively). Hypertension ($P=0.768$), diabetes ($P=0.241$), and musculoskeletal complaints ($P=0.303$) showed no statistically significant effects on Δ 6MWD, indicating that these comorbidities did not independently predict postoperative improvements in exercise performance (Table 5). Smoking status was not significantly associated with Δ 6MWD ($P=0.220$ for non-smokers, $P=0.162$ for smokers). Moreover, pre-test oxygen saturation ($P=0.827$) was not a significant predictor of postoperative functional improvement.

Heart Rate Recovery (HRR) and Functional Improvement

Another generalized linear model was evaluated the association between HRR and patient characteristics, including gender, age, and EWL%, data not shown. We observed that there was no significant relationship between EWL and changes in HRR ($B= -0.016$, $P=0.872$). Age and gender were not significant predictors of HRR changes ($B=0.060$, $P=0.728$ and $B=-0.221$, $P=0.938$, respectively).

Last of we analyzed factors influencing the likelihood of HRR failure postoperatively, with variables including gender, age, percentage of EWL%, smoking status, postoperative hypertension, and postoperative diabetes in the following multiple linear regression model (data not shown). The model did not identify any significant predictors of postoperative HRR failure among the variables studied, including gender ($B=0.448$, $P=0.482$), age ($B= -0.017$, $P=0.598$),

EWL% ($B=0.027$, $P=0.258$), smoking status ($B=0.893$, $P=0.338$), and the presence of postoperative hypertension ($B= -1.150$, $p=0.368$) or diabetes ($B= -0.314$, $P=0.812$). These findings suggest that factors outside the scope of this model may play a more substantial role in determining HRR outcomes after surgery.

DISCUSSION

Our study demonstrates significant improvements in functional exercise capacity, weight loss, and resolution of obesity-related comorbidities six months after laparoscopic sleeve gastrectomy. Our findings highlight the benefits of bariatric surgery not only in metabolic outcomes but also in physical function, as reflected by changes in the six-minute walking distance and heart rate recovery.

Patients achieved substantial weight loss, with an average EWL of 52.7%. The reduction in BMI from 48.5 ± 5.2 to 34.4 ± 3.5 kg/m² aligns with previous studies demonstrating the efficacy of bariatric surgery in achieving significant weight reduction [17, 18]. In parallel, substantial improvements were observed in comorbidities such as hypertension, diabetes, and musculoskeletal complaints. These findings are consistent with previous research showing bariatric surgery's role in improving obesity-related comorbidities, particularly through weight loss and metabolic adaptations [18, 19].

The significant increase in 6MWD from 406 ± 48 meters to 443 ± 52 meters reflects enhanced functional exercise capacity and mobility after surgery. This improvement is likely due to reduced biomechanical strain, better cardiorespiratory fitness, and alleviation of joint pain associated with weight loss [9, 20, 21]. The reduction in dyspnea and fatigue, as measured by the Borg scale, further underscores the positive impact of weight loss on physical function. These results corroborate prior studies emphasizing the role of weight loss in improving physical performance and quality of life postoperatively [9, 20, 22, 23].

Generalized linear regression analysis identified EWL% as a significant predictor of improvement in 6MWD. For every 1% increase in EWL, there was an 89% greater likelihood of improving 6MWD by 1 meter postoperatively. These findings are in line with previous studies and emphasize the critical role of

weight loss in enhancing functional capacity, likely by reducing the biomechanical burden on joints and improving metabolic efficiency [21]. Other factors, including gender, age, comorbidities (e.g., hypertension, diabetes, musculoskeletal complaints), smoking status, and pre-test oxygen saturation, were not significant predictors. This suggests that the magnitude of weight loss is the primary driver of functional improvement, consistent with prior reports [21, 24].

Our findings demonstrated significant improvements in perceived exertional dyspnea and fatigue, as assessed by the Borg scale, following bariatric surgery. Our findings indicate that patients experienced reduced respiratory effort and muscle fatigue during physical activity six months postoperatively, highlighting the positive impact of weight loss on functional exercise performance. Dyspnea, or breathlessness, is a common symptom in individuals with obesity, attributed to multiple physiological mechanisms, including increased work of breathing, reduced lung volumes, and impaired respiratory muscle function [25]. Preoperatively, patients exhibited significantly higher dyspnea scores post-exercise, which aligns with previous studies indicating that individuals with obesity experience increased ventilatory demand during physical exertion. Postoperatively, the reduced dyspnea scores suggest improvements in pulmonary mechanics, including increased lung compliance and decreased respiratory resistance, which are known benefits of weight loss [26, 27].

Fatigue is another significant limiting factor in the physical performance of individuals with obesity. The excessive adipose tissue burden increases the metabolic cost of movement and contributes to musculoskeletal strain, leading to earlier onset of fatigue [28]. In our study, preoperative fatigue scores increased after exercise, suggesting that obesity is associated with reduced endurance and increased exertional effort. However, postoperatively, patients demonstrated a marked reduction in fatigue levels, suggesting enhanced exercise tolerance and efficiency of movement. This is likely due to reduced mechanical load, improved cardiovascular function, and better neuromuscular coordination following significant weight loss [28, 29]. These findings are in line with previous studies showing improvements in muscle function and reduced exertional effort after bariatric surgery [30].

The statistically significant reductions in both dyspnea and fatigue postoperatively indicate that bariatric surgery not only improves metabolic and cardiovascular health but also enhances perceived exertional effort during physical activity. These improvements can have substantial implications for increasing daily physical activity levels and long-term weight maintenance. Studies have shown that reduced perceived exertion encourages greater participation in physical activity, thereby reinforcing weight loss outcomes and improving overall quality of life [30].

Obesity is strongly linked to a heightened risk of cardiovascular mortality, which is partly attributed to increased sympathetic nervous system activity [31]. Bariatric surgery has been shown to improve long-term survival in individuals with severe obesity; however, the underlying mechanisms driving this benefit remain under investigation. HRR following exercise serves as an indicator of autonomic balance, reflecting the interplay between sympathetic and parasympathetic regulation [32]. Impaired HR recovery is a well-established predictor of elevated mortality risk, whereas improved HR recovery is associated with better overall prognosis [31, 32]. In our study, HRR decreased significantly postoperatively, from 18.9 ± 9.8 beats to 13.7 ± 7.5 beats. Despite this reduction in the rate recovery, there was an increased proportion of patients classified as having delayed recovery ($HRR < 12$ beats), rising from 21% to 42%. However, this trend was not statistically significant, indicating that other factors may contribute to postoperative HRR changes. The lack of significant predictors for HRR improvement or failure in our models, including EWL%, age, gender, and comorbidities, suggests that autonomic recovery may involve complex mechanisms beyond the variables analyzed in this study. Previous research has indicated that factors such as preoperative fitness levels and autonomic system remodeling may influence HRR outcomes [15]. Previous studies suggested that these changes are likely driven by an increase in cardiac vagal tone, accompanied by a reduction in resting sympathetic activity and a more rapid withdrawal of sympathetic stimulation following exercise [31]. Improvements in these physiological parameters appear to be independently associated with the extent of weight loss and improvement in metabolic features [31, 33].

Limitations

Our study has several limitations. The relatively small sample size and single-center design may restrict the generalizability of our findings. Additionally, the observational nature of the study prevents us from establishing causal relationships between the predictors and improvements in functional and autonomic recovery. Dyspnea and fatigue were assessed using the Borg scale, which, while useful for subjective evaluation, may introduce variability due to individual perception differences. Furthermore, we did not perform direct pulmonary function tests or muscle strength assessments, which could have provided more objective physiological insights into the observed reductions in dyspnea and fatigue. Future research should incorporate cardiopulmonary exercise testing and muscle strength measurements to better elucidate the mechanisms underlying these improvements.

Another limitation is the relatively short follow-up period of six months. Long-term follow-up is essential to assess the durability of functional gains and to further explore the factors influencing HRR outcomes after bariatric surgery. Despite these limitations, our study provides valuable insights into the determinants of functional improvement following weight loss. Unlike most prior studies that focus solely on postoperative changes, we employed a multiple linear regression model to identify EWL% as a significant predictor of 6MWD improvement, independent of age, gender, smoking status, and comorbidities. This robust statistical approach reinforces the critical role of weight loss in enhancing mobility and physical performance. Future studies with larger, multi-center cohorts and extended follow-up periods are warranted to validate these findings and further investigate the long-term effects of bariatric surgery on functional and autonomic outcomes.

CONCLUSION

In conclusion, our study highlights the significant benefits of laparoscopic sleeve gastrectomy on functional exercise capacity, weight loss, and the resolution of obesity-related comorbidities six months postoperatively. Patients experienced substantial weight reduction and improvements in comorbidities such as hypertension, diabetes, and musculoskeletal com-

plaints, aligning with prior evidence supporting bariatric surgery as an effective intervention for severe obesity. The increase in 6MWD reflects enhanced functional capacity and reduced effort associated with physical activity. Importantly, excess weight loss percentage emerged as a critical determinant of improvement in 6MWD, underscoring the role of weight loss in enhancing mobility and physical function. Conversely, other variables such as age, gender, smoking status, and comorbidities did not independently predict improvements in exercise capacity, emphasizing the primary influence of weight reduction. Although HRR, a marker of autonomic function, showed a significant postoperative reduction, no specific predictors of HRR changes were identified. This indicates the complexity of autonomic adaptations following bariatric surgery, warranting further investigation. Our findings underscore the importance of achieving substantial weight loss to enhance functional performance and quality of life in bariatric surgery patients. Future studies with larger sample sizes and extended follow-up periods are needed to explore long-term outcomes and elucidate the mechanisms underlying improvements in autonomic function.

Ethical Statement

The study was approved by the Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee (Decision no: 2014/10/08 and date: 14.05.2014), and all participants provided written informed consent before enrollment.

Authors' Contribution

Study Conception: AGD, ED; Study Design: AGD, ED; Supervision: AGD, ED, FC, MK; Funding: AGD, ED, FC, MK; Materials: AGD, ED, FC; Data Collection and/or Processing: AGD, ED; Statistical Analysis and/or Data Interpretation: AGD, ED; Literature Review: AGD, ED, MK; Manuscript Preparation: AGD; and Critical Review: AGD, ED, FC, MK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Impact of colchicine on inflammatory markers and pregnancy outcomes in familial Mediterranean fever patients

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ABSTRACT

Objectives: The aim of this study is to evaluate the effect of colchicine use on maternal inflammatory markers and pregnancy outcomes in pregnant women diagnosed with Familial Mediterranean Fever (FMF) and receiving colchicine therapy.

Methods: This retrospective analysis included 42 pregnant women diagnosed with FMF who underwent colchicine treatment and 126 healthy pregnant controls. Neutrophil/Lymphocyte Ratio (NLR), Platelet/Lymphocyte Ratio (PLR), and Monocyte/Lymphocyte Ratio (MLR) rates in the blood of the groups in the first trimester, obstetric morbidities and pregnancy outcomes were compared.

Results: The patient cohort had markedly reduced hemoglobin levels (12.15 ± 1.36 vs. 12.80 ± 1.02 g/dL, $P=0.001$), an elevated prevalence of anemia (19% vs. 3%, $P=0.002$), and diminished monocyte counts (0.55 vs. $0.61 \times 10^9/L$, $P=0.022$) as well as decreased MLR values (0.27 vs. 0.29 , $P=0.020$) in comparison to the control group. Other inflammatory markers, pregnancy complications, and neonatal outcomes were similar between the groups ($P>0.05$).

Conclusions: Colchicine seems to be useful in managing inflammation during FMF pregnancies without negatively affecting pregnancy or neonatal outcomes. Thorough prenatal care, encompassing anemia monitoring, is crucial for enhancing mother and fetal health.

Keywords: Familial Mediterranean fever, colchicine, inflammation, pregnancy

Familial Mediterranean Fever (FMF) is an autoinflammatory disorder characterized by autosomal recessive inheritance, predominantly observed in individuals of Mediterranean descent [1]. FMF is marked by repeated episodes of fever, abdominal pain, pleuritis, and arthritis [2]. Pregnancy may frequently occur during the condition, as women of reproductive age are impacted by it. The implications

and management of FMF during gestation can significantly impact both the mother and the fetus. FMF is recognized to elevate the risk of spontaneous abortion and preterm delivery [3, 4].

Colchicine is an efficacious anti-inflammatory agent that inhibits microtubule polymerization and modulates inflammatory pathways [5]. Colchicine is extensively utilized in autoinflammatory disorders

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since it alleviates aphthous ulcers, modulates inflammation, and diminishes the severity and frequency of relapses [6]. Colchicine is thought to be safe and effective during pregnancy to control and prevent flares in patients with FMF [7].

Although the inflammatory characteristics of FMF are well-documented, limited research has investigated the significance of hematologic markers in FMF pregnancies or their potential association with pregnancy outcomes [8]. Comprehending the correlation among FMF, systemic inflammation, and obstetric outcomes may enhance our capacity to anticipate and address issues in this high-risk population. In recent years, the utilization of straightforward and cost-effective biomarkers for quantitatively evaluating systemic inflammation has risen [9]. Blood-based markers of inflammation such as Neutrophil/Lymphocyte Ratio (NLR), Platelet/Lymphocyte Ratio (PLR), and Monocyte/Lymphocyte Ratio (MLR) are used as practical tools in the evaluation of different inflammatory conditions [10]. These markers are gaining increasing interest in predicting pregnancy-related complications and inflammatory diseases [11-13].

This study aims to evaluate NLR, PLR, and MLR values in pregnant women taking colchicine with FMF and investigate their association with pregnancy outcomes. Our secondary aim is to investigate pregnancy complications and neonatal outcomes in pregnant women with FMF taking colchicine. We hope to contribute to the understanding of inflammatory mechanisms in FMF pregnancies and their impact on maternal-fetal health.

METHODS

This retrospective study was conducted at the Perinatology clinic of Ankara Etlik City Hospital between October 2022 and November 2024. Approval was obtained from the hospital's ethics committee before starting the study (Decision no: AEŞH-BADEK-2025-0060, date: 08.01.2025). Due to the retrospective nature of the study, informed consent was not required, as approved by the ethics committee.

The study included pregnant women who had previously been diagnosed with FMF and were taking colchicine. Patients whose blood samples from the first trimester were not available and whose birth data

could not be accessed were excluded from the study. In addition, patients who had an abortion and patients with chronic diseases were excluded from the study.

After 42 individuals who met the inclusion and exclusion criteria were selected for the patient group, a control group was formed consisting of pregnant women of similar age and body mass index (BMI) in a 1:3 ratio. The following clinical and demographic data were obtained by reviewing the patient's medical records: Maternal age, body mass index, number of pregnancies, number of parities, and number of abortions. Laboratory data of the patients were obtained from the hospital data system. First-trimester complete blood parameters, including hemogram, complete blood count, lymphocyte level, neutrophil level, monocyte level, platelet count, as well as NLR, PLR, MLR rates, were calculated. Whether the patients had gestational hypertension, gestational diabetes, intrauterine growth retardation, abnormal amniotic fluid (polyhydramnios or oligohydramnios), preterm labor, preterm premature rupture of membranes diagnosis during pregnancy, and neonatal outcomes (neonatal weight, APGAR 1st and 5th-minute scores, need for neonatal intensive care or neonatal death) were recorded. Laboratory data and neonatal outcome differences between the groups were compared.

Statistical Analysis

The statistical analysis was conducted using IBM Corporation SPSS (version: 30.0.0.172). The adherence to the normal distribution was assessed utilizing the Kolmogorov-Smirnov test. For continuous variables with a normal distribution, descriptive statistics are presented as "mean±standard deviation"; for those without, they are presented as "median (interquartile range)". Fisher's exact test or the chi-squared test was employed to compare categorical variables. The Student T-test and the Mann-Whitney U test were employed to examine continuous variables with and without normal distribution.

RESULTS

Table 1 compares the demographic and obstetric characteristics of the patient (n=42) and control groups (n=126). No significant differences were observed in age, BMI, weight gain during pregnancy, or gravida

Table 1. Demographic data of the study population

Parameter	Patient group (n=42)	Control group (n=126)	P value
Age (years)	29 (24-32)	29 (26-34)	0.689 ^a
BMI (kg/m ²)	28.9 (25.3-32.8)	29.6 (26.9-33.7)	0.350 ^a
Weight gain during pregnancy (kg)	10 (8-12)	10 (8-15)	0.893 ^a
Gravida	2 (1-3)	2 (1-3)	0.565 ^a
Primipar	16 (35.7%)	22 (17.5%)	0.007^b
Two or more consecutive spontaneous abortions	2 (4.7%)	3 (2.3%)	0.367 ^c
IVF	2 (4%)	1 (0.7%)	0.155 ^c

Data are shown as median (Q1-Q3) or n (%) where appropriate. BMI=Body mass index, IVF= In vitro fertilization

^aMann-Whitney U Test, ^bChi-Square Test, ^cFisher Exact Test.

($P>0.05$). However, the patient group had a significantly higher proportion of primiparous individuals compared to the control group (35.7% vs. 17.5%, $P=0.007$). Other parameters, such as spontaneous abortion rates and in vitro fertilization (IVF) conception, were similar between the groups ($P>0.05$). However, there was a significant difference in the distribution of primiparous and multiparous participants between the groups.

The patient group had a higher proportion of primiparous individuals (35.7% vs. 17.5%, $P=0.007$). Other parameters, such as two or more consecutive spontaneous abortions (4.7% vs. 2.3%, $P=0.367$) and IVF conception rates (4% vs. 0.7%, $P=0.155$), did not show statistically significant differences. Table 2 presents the laboratory data of the patients. The blood sampling week was similar between the groups ($P=0.514$). Hemogram levels were significantly lower in the patient group (12.15 ± 1.36 g/dL) compared to the control group (12.80 ± 1.02 g/dL) ($P=0.001$). Anemia prevalence was higher in the patient group (19%) compared to the control group (3%) ($P=0.002$). Monocyte levels were also significantly lower in the patient group (0.55 vs. $0.61 \times 10^9/L$, $P=0.022$). Similarly, the MLR was significantly lower in the patient group (0.27 vs. 0.29, $P=0.020$). Other parameters, including whole blood cell count, lymphocyte, neutrophil, platelet levels, NLR, PLR, systemic immune-inflammation index (SII), pregnancy-associated plasma protein-A (PAPP-A) multiples of the median (MoM), beta human chorionic gonadotropin (beta-hCG) MoM, and nuchal

translucency (NT) MoM, did not show significant differences between the groups ($P>0.05$).

When the FMF and control groups were compared in terms of birth outcomes, no statistically significant differences were observed in gestational age at delivery, birth weight, preterm birth rates, primary cesarean section rates, 1st and 5th minute APGAR scores, neonatal intensive care unit admission rates, or composite adverse perinatal outcomes ($P>0.05$) (Table 3). Pregnancy outcomes showed no significant differences between the groups. Fetal growth restriction (16% vs. 7%, $P=0.069$), preterm labor (14% vs. 12%, $P=0.725$), and gestational diabetes (2.4% vs. 10%, $P=0.193$) were slightly more frequent in the patient group. Rates of polyhydramnios, oligohydramnios, and gestational hypertensive disease were comparable (Table 4).

DISCUSSION

In this study, we compared the first-trimester laboratory data and neonatal outcomes of pregnant women with FMF who used colchicine. We found no significant difference except for lower monocyte levels and MLR. In addition, pregnancy complications and neonatal outcomes in the FMF group were comparable to the general population. To our knowledge, this is the first study comparing the first-trimester blood analysis results of pregnant women using colchicine with those of normal pregnant women.

Table 2. Second trimester laboratory findings of the study population

Parameter	Patient group (n=42)	Control group (n=126)	P value
Blood sampling week	11 (8-12)	11 (9-12)	0.514 ^a
Hemogram (g/dL)	12.15±1.36	12.80±1.02	0.001^b
Anemia	8 (19%)	4 (3%)	0.002^c
Whole blood cells (×10 ⁹ /L),	8.68 (7.40-10.14)	8.55(7.44-9.75)	0.870 ^a
Lymphocyte (× 10 ⁹ / L)	2.09 (1.74-2.47)	1.94 (1.72-3.27)	0.486 ^a
Neutrophil (× 10 ⁹ / L)	5.94 (4.68-7.40)	5.60 (4.93-6.83)	0.737 ^a
Monocyte (× 10 ⁹ /L)	0.55 (0.42-0.62)	0.61 (0.52-0.71)	0.022^a
Platelet (× 10 ⁹ / L)	262 (206-303)	260 (231-311)	0.303 ^a
NLR	2.76 (2.02-3.65)	2.85 (2.23-3.66)	0.695 ^a
PLR	123 (98-156)	133 (109-163)	0.097 ^a
MLR	0.27 (0.23-0.31)	0.29 (0.25-0.37)	0.020
SII	721 (488-936)	770 (575-995)	0.354 ^a
PAPP-A MoM	0.97 (0.54-1.19)	1.00 (0.66-1.43)	0.262 ^a
bhCG MoM	0.85 (0.45-1.20)	0.84 (0.48-1.37)	0.861 ^a
NT MoM	0.77 (0.69-0.86)	0.74 (0.59-0.92)	0.760 ^a

Data are shown as mean±standard deviation or median (Q1-Q3) or n (%) where appropriate. bhCG=Beta-human chorionic gonadotropin, MoM=Multiple of the median, NLR=Neutrophil-to-lymphocyte ratio, NT=Nuchal translucency, PAPP-A=Pregnancy-associated plasma protein A, PLR=Platelet-to-lymphocyte ratio, SII=Systemic immune-inflammation index.

^aMann-Whitney U Test, ^bStudent-T Test, ^cFisher-Exact Test

Table 3. Comparison of birth outcomes between FMF and control groups

Parameter	Patient group (n=42)	Control group (n=126)	P value
Gestational age at delivery (week)	38 (37-39)	39 (37-40)	0.101 ^a
Birth weight (gram)	3145 (2720-3400)	3270 (2980-3480)	0.123 ^a
Preterm birth (<37 weeks)	5 (11%)	14 (11%)	0.888 ^b
Primary cesarean section	10 (23%)	27 (21%)	0.934 ^b
Fetal distress	4 (9%)	11 (8%)	0.544 ^c
APGAR score at 1st minute	9 (8-9)	9 (8-9)	0.056 ^a
APGAR score at 5th minute	1 (9-10)	10 (9-10)	0.164 ^a
NICU admission	5 (11%)	20 (15%)	0.566 ^b
Intrauterine ex	1 (2%)	0	0.250 ^c
CAPO	5 (11%)	20 (15%)	0.566 ^b

Data are shown as median (Q1-Q3) or n (%) where appropriate. CAPO=Composite adverse perinatal outcome, FMF=Familial Mediterranean fever, NICU=Neonatal intensive care unit.

^aMann-Whitney U Test; ^bChi-Square Test; ^cFisher-Exact Test

Table 4. Comparison of pregnancy complications in patients with FMF and control group

Parameters	Patient group (n=42)	Control group (n=126)	P value
Preterm labor	6 (14%)	15 (12%)	0.725 ^a
Preterm premature rupture of membranes	2 (4.9%)	0 (0%)	0.061 ^b
Gestational hypertensive disease	1 (2.4%)	2 (1.6%)	1 ^b
Gestational diabetes	1 (2.4)	13 (10%)	0.193 ^b
Fetal growth restriction	7 (16 %)	9 (7%)	0.069 ^a
Polyhydramnios	3 (7.3%)	4 (3.2%)	0.368 ^b
Oligohydramnios	3 (7.3%)	7 (5.6%)	0.712 ^b

FMF=Familial Mediterranean fever

^aChi-Square Test, ^bFisher-Exact Test

Individuals with FMF possess mutations in the Mediterranean fever gene, which encodes the pyrin protein involved in the synthesis of interleukin-1 β (IL-1 β) [14]. Colchicine, used to prevent acute attacks in FMF, suppresses inflammatory processes by inhibiting microtubule polymerization [15]. It is also thought that colchicine causes changes at the transcriptional level by altering gene expression in human umbilical vein endothelial cell line cells [16]. We analyzed systemic inflammatory markers, including NLR, MLR, and PLR, which are frequently utilized in cancer, rheumatic disorders, and numerous pregnancy issues, during the first-trimester complete blood study of pregnant women using this inflammatory medication [11, 17, 18]. Our findings show that colchicine treatment regulates the inflammatory response in pregnant women and keeps inflammatory levels at a level comparable to normal pregnant women. However, in our study, we observed that monocyte levels and MLR were lower in the patient group. It is known that colchicine reduces monocyte activation [19]. In addition, it is thought that the use of colchicine in Behçet's disease decreases the number of classical monocytes while increasing the number of non-classical monocytes [20]. In this context, our findings are consistent with the literature.

Anemia is common in FMF patients. This finding is also consistent with the study by Hirahara *et al.* [3], who reported an increased prevalence of anemia in FMF patients during pregnancy. In addition, in one study, anemia was detected in 63.4% of FMF patients [21]. Although the same study suggested that colchicine treatment improved anemia in FMF patients, our findings suggest that pregnant women with FMF who use colchicine should still be carefully mon-

itored for anemia.

Although there are older studies advocating routine amniocentesis in pregnant women using colchicine [22, 23], colchicine treatment during pregnancy in FMF patients is currently considered safe and amniocentesis is not routinely recommended [24].

Additionally, a study comparing pregnant women treated with colchicine during pregnancy and those not treated showed no significant difference in malformation rates [7]. In our study, the rate of chromosomal anomalies was not increased in the patient group, consistent with the literature. Furthermore, pregnancy-related biomarkers like PAPP-A MoM, β -hCG MoM, and NT MoM were similar among the groups, indicating that FMF does not substantially affect these first-trimester screening indicators. This discovery corroborates the findings of Sotskiy *et al.* [25], who similarly indicated no substantial disparities in biochemical markers between FMF patients and controls.

One of the main findings of our study is that the perinatal outcomes of FMF patients are similar to the general population. Although Ofir *et al.* [26] argued that FMF is a risk factor for preterm birth, they emphasized in their study that the perinatal outcomes were the same as those of pregnant women without FMF. However, unlike our study, only 66 percent of the patients in this study were using colchicine. In our study, there was no difference in pregnancy complications or birth outcomes between the pregnant women using colchicine and the control group. From this, it can be concluded that FMF pregnant women whose inflammatory pathways are regulated under colchicine treatment can be followed up similarly to the general population.

While our study offers significant insights, the

limited sample size may restrict the generalizability of the results. The other limitation of the study is the retrospective design of the study. Additionally, colchicine, which is frequently used in FMF patients, may influence immune mechanisms, blood parameters, and their functions, potentially affecting our findings. Subsequent research including larger cohorts and prospective methodologies is crucial to enhance our comprehension of FMF's effects on pregnancy and to corroborate our results.

CONCLUSION

In conclusion, our study highlights changes in monocyte levels in pregnant women with FMF who use colchicine, while pregnancy outcomes remain largely comparable to controls. These results highlight the importance of comprehensive prenatal care and continued use of colchicine to optimize maternal and fetal health in FMF patients. Attention should also be paid to the prevalence of anemia in pregnant women with FMF to optimize both maternal and fetal health in this population.

Ethical Statement

This study was approved by the Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee (Decision no: AEŞH-BADEK-2025-0060, and date: 08.01.2025).

Authors' Contribution

Study Conception: BTÇ; Study Design: BTÇ, GA; Supervision: ZŞ, NVT; Funding: N/A; Materials: BTÇ, FA, SNA; Data Collection and/or Processing: GA, GK, FA, SNA; Statistical Analysis and/or Data Interpretation: ZŞ, NVT; Literature Review: GA, GK; Manuscript Preparation: BTÇ, GA, ŞÇ; and Critical Review: BTÇ, ŞÇ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Predictors of major adverse events after stent implantation for atherosclerotic renal artery stenosis

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ABSTRACT

Objectives: Atherosclerotic renal artery stenosis (ARAS) is the most frequently seen cause of secondary hypertension (HT). ARAS associated with adverse cardiovascular events independently of other traditional cardiovascular risk factors, and increased mortality. Percutaneous transluminal renal arterial stenting (PTRS) is important methods in ARAS treatment. The aim of this study was to investigate major adverse events (MAE) and potential predictors in patients undergoing PTRS for ARAS by evaluating variables before and immediately after the procedure, including the SYNTAX score.

Methods: One hundred and five consecutive patients who underwent PTRS over a period of approximately 10 years were included in our study. Patients were divided into two groups, MAE negative (-) and MAE positive (+), according to the occurrence of MAE. After comparing both groups with difference tests, independent predictors were investigated with univariate and multivariate Cox regression analysis. Afterwards, Receiver Operating Characteristics (ROC) analysis was performed on independent predictors.

Results: The average age of the patients was 63.32 ± 11.62 years (range: 30-83 years) and 52 (49.5%) of them were male. Sixty-two patients constituted the MAE (-) and 43 the MAE (+) groups. In multivariate Cox regression analysis, chronic obstructive pulmonary disease (COPD), left ventricular ejection fraction (LVEF), and the total number of antihypertensives after the procedure were identified as independent predictors. As a result of the ROC analysis, a cutoff value of $\leq 55\%$ for LVEF was determined to have area under the curve (AUC) 0.733, 69.8% sensitivity, and 77.42% specificity ($P < 0.001$). The use of more than 3 antihypertensive drugs after the procedure was found to have AUC 0.624, 34.88% sensitivity, and 82.26% specificity ($P = 0.023$).

Conclusions: LVEF, COPD, and the postprocedural total number of antihypertensives were independent predictors for MAE seen after PTRS in ARAS patients. These predictors can be used to estimate the risk in these patients. To be able to prevent adverse events, it is important that patients with these markers are treated and followed up more closely.

Keywords: Renal artery stenosis, atherosclerosis, hypertension, stent, adverse events

Atherosclerotic renal artery stenosis (ARAS) is the most frequently seen cause of secondary hypertension (HT), and is responsible for approximately 90% of all renal artery stenosis (RAS)

cases [1, 2]. RAS can result in adverse events such as resistant HT, progressive impairments in renal functions and cardiac destabilisation syndromes [3, 4]. ARAS has also been associated with adverse cardio-

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vascular events independently of other traditional cardiovascular risk factors, and increased mortality [5].

Percutaneous transluminal renal arterial angioplasty and stent procedures (PTRA and PTRS) are important methods in ARAS treatment [6]. Various studies have been conducted of the clinical outcomes of patients who have undergone PTRS procedure for ARAS [7, 8]. In studies that have been conducted to investigate predictors of adverse events and mortality in patients with ARAS, different variables have been investigated in different cohorts, and naturally different results have been reported. This has led to a state of uncertainty. In a previous study of patients presenting with myocardial infarction (MI) with ST-elevation, a correlation was determined between the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score and RAS [9]. However, the potential relationship between coronary artery disease (CAD) complexity evaluated with the SYNTAX score, and long-term adverse events after

PTRS procedure is unknown.

The aim of this study was to investigate major adverse events and potential predictors in patients undergoing PTRS for ARAS by evaluating variables before and immediately after the procedure, including the SYNTAX score. It was thus aimed to contribute to the literature by determining high-risk patients in this patient group.

METHODS

Study Design and Population

Approval for the study was granted by the Local Ethics Committee. This was a retrospective study conducted at a single high-volume center. The study population was defined as patients who underwent a PTRS procedure between 1 January 2014 and 1 June 2024. The data required were obtained from the electronic hospital information system, archived records,

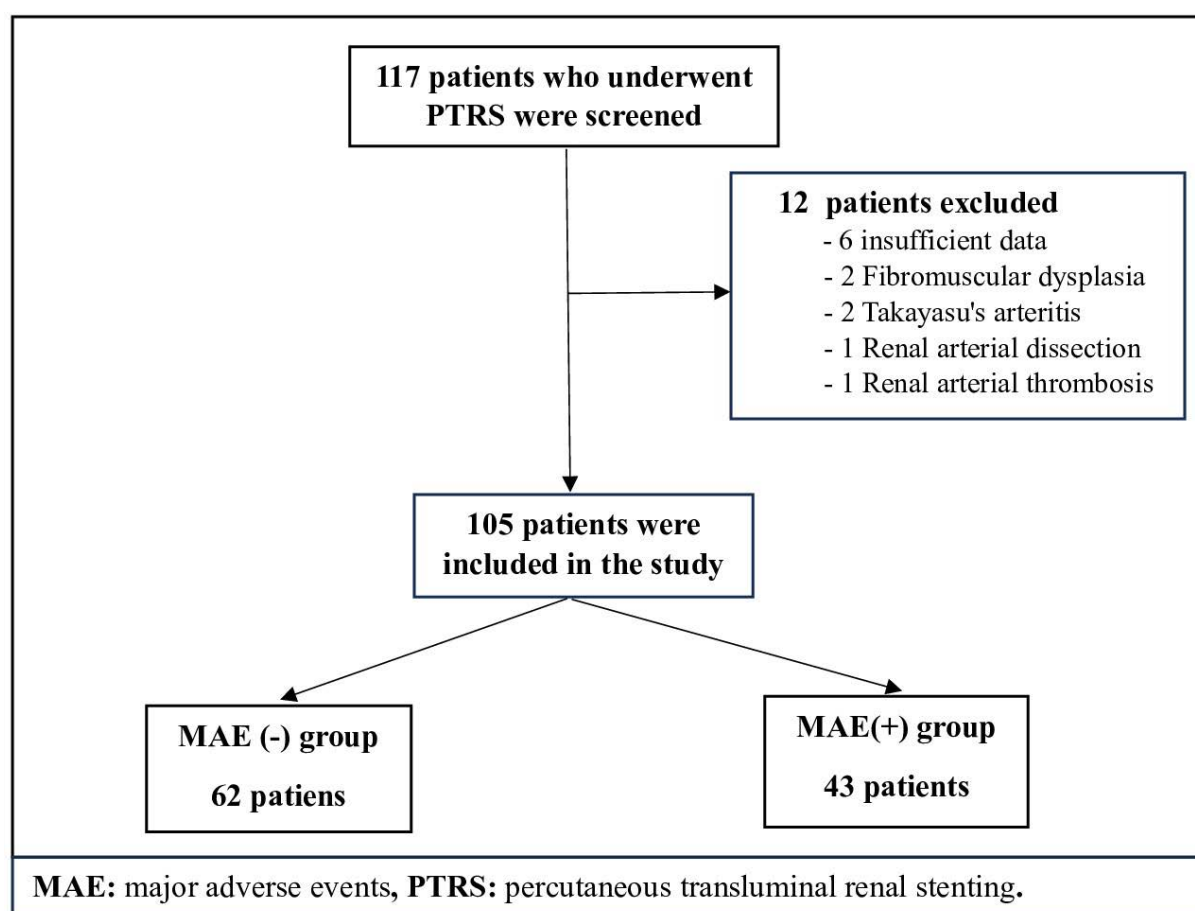


Fig. 1. Study flowchart.

telephone or face-to-face interviews with patients and their relatives, the national health system, and the death notification system records. From the initial inclusion of 117 consecutive patients who underwent PTRS, following the implementation of exclusion criteria, 105 patients were included in the study for analysis (Fig. 1. Study flow chart). The study inclusion criteria were defined as age >18 years, and having undergone PTRS because of resistant HT, reduced renal function, or “flash” pulmonary oedema, associated with ARAS.

The study exclusion criteria were defined as: (i) PTRS performed for a RAS reason other than ARAS, (ii) PTRS performed following renal transplant, (iii) total renal artery occlusion, (iv) incomplete or unreliable data for the pre-procedure and follow-up periods, (v) kidney diameter <7 cm, target renal artery diameter <4 mm, (vi) estimated glomerular filtration rate (eGFR) <10 mL/min/1.73m², (vii) previous target vessel revascularisation (TVR), and (viii) receiving chronic renal replacement therapy.

First Evaluation and Laboratory Analysis

Before the procedure, all the patients underwent detailed evaluations including anamnesis and physical examination, then fasting blood tests were performed for the necessary laboratory analyses. HT was defined as systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg. Patients with high blood pressure measurements recorded despite the use of at least 3 anti-hypertensives, including one diuretic, were accepted as resistant HT patients. On discharge after the procedure, full cure was accepted as blood pressure <140/90 mmHg without medication, and the procedure was accepted as beneficial when there was blood pressure <140/90 mmHg with a decrease or no change in the number of drugs, or a decrease in diastolic pressure of ≥15 mmHg [10].

Patients who were already receiving statin treatment or had non-HDL cholesterol level >130 mg/dL were accepted as hyperlipidemia. The demographic and clinical data, and basal laboratory findings were recorded for all the patients. The eGFR in this study was calculated from the equation of Modification of the Diet in Renal Disease (MDRD) [11]. The diagnosis of contrast nephropathy (CN) was defined as an increase of over 0.5 mg/dL or 25% in the creatinine value within 48-72 hours after contrast exposure [12].

The antihypertensive drugs used by patients before and after the procedure were recorded.

Transthoracic Echocardiography and Electrocardiography

Before the procedure, two-dimensional (2D) transthoracic echocardiography (TTE) was performed on all patients by cardiologists who were experienced in the field of echocardiography and blinded to the patient data. The left ventricle ejection fraction (LVEF) and other parameters examined on the 2D echocardiography device (Epiq 7c Ultrasound System, Philips, Andover, MA, USA) before the procedure were recorded. The findings were evaluated according to the recommendations in the American Society of Echocardiography (ASE) guidelines [13]. All the echocardiographic data used in this study were recorded during the scanning by cardiologists blinded to the patient data.

Before the procedure, 12-derivation electrocardiograms (ECG) at 25mm/sec speed and 10mm/mV were obtained from all the patients. The Socolow-Lyon Index (V1S+V5/V6 longest R wave > 35 mm) was used as the criteria for left ventricle hypertrophy [14].

Interventional Angiography and Renal Stent Procedure

The final decision for PTRS was made without exception by evaluating the invasive coronary angiography and renal angiography as they are often used together for the definitive diagnosis of ARAS patients who have initially been diagnosed using other imaging methods (renal duplex ultrasonography, computed tomography, magnetic resonance imaging angiography). Patients who had previously experienced acute coronary syndrome were accepted as previous MI. The Syntax scores of the patients were obtained by two experienced invasive cardiologists, blinded to the clinical characteristics of the patients, using a web-based online calculator (www.syntaxscore.com, versiyon 2.1).

The PTRS decision was made by at least two experienced interventional cardiologists with the detection of ≥70% unilateral or bilateral ARAS as a result of visual and quantitative angiographic evaluation. Patients were administered 100 mg acetyl salicylic acid (ASA) and 300 mg clopidogrel on the day before the procedure, or 300 mg ASA and 600 mg clopidogrel loading on the day of the procedure. Dual antiplatelet

therapy has been recommended for at least 6 months and ASA indefinitely. The procedure was performed by an experienced interventional cardiologist via the femoral arteries in almost all cases, and in a very small proportion via the left radial artery. Heparin at a dose of 5000-10000 IU bolus was administered to the patients before the procedure. PTRS was performed using standard techniques.

After the placement of a suitable guide catheter to the renal artery, the lesion has passed with 0.014 or 0.018 guidewires. Then, if necessary, first PTRS was performed, then a self-expanding, bare metal renal stent was implanted with a balloon of diameter and length appropriate to the lesion. When PTRS was not required, the renal stent was applied directly. If there was seen to be a geographical mismatch or dissection on the images obtained after the procedure, a second renal stent was implanted. In patients with bilateral ARAS, the procedure was performed on the other renal artery in the same session. The procedure was accepted as technically successful if there was <20% residual narrowing remaining after the intervention. All the patients were followed up under the best personalised medical treatment.

Major Adverse Events

The patients were hospitalised for at least 48 hours after the procedure then followed up in the polyclinic at regular intervals. Major adverse events (MAE) during the follow-up period were defined as all-cause mortality, acute coronary syndrome, stroke, hospitalisation because of heart failure, the requirement for renal replacement therapy or permanent renal replacement therapy, renal transplant treatments because of progressive renal dysfunction, and target vessel revascularisation (TVR). The total follow-up period and the time to the development of MAE were recorded.

Statistical Analysis

All the analyses of the study data were performed using MedCalc 20.0.4 software (MedCalc Software Ltd, Ostend, Belgium). The patients were separated into two groups as those who developed and did not develop MAE, and these groups were compared. Conformity of continuous variables to normal distribution was assessed with the Kolmogorov-Smirnov test. Descriptive statistics were stated as mean±standard deviation (SD) values for data showing normal

distribution and as median (25th-75th percentile) values for those not showing normal distribution. Categorical variables were stated as number (n) and percentage (%). The two groups (MAE positive and negative) were then compared using the Independent Samples t-test for normally distributed continuous variables, and the Mann Whitney U-test when distribution was not normal. In the comparisons of categorical variables, the Chi-square test or Fisher Exact test was used, as appropriate. For the variables found to be significant in the difference tests, univariate Cox regression analysis was performed. Then, variables with significant p values in the univariate analysis were included in the multivariate analysis. Receiver Operating Characteristics (ROC) analyzes were performed on continuous variables for independent predictors identified in multivariate Cox regression analysis. A value of P<0.05 was accepted as statistically significant in all the statistical analyses.

RESULTS

Evaluation was made of 105 patients comprising 52 (49.5%) males and 53 (50.5%) females with a mean age of 63.32±11.62 years (range: 30-83 years). MAE developed in 43 (41%) patients (MAE + group) and did not develop in 62 (59%) (MAE - group). The procedure was performed because of resistant HT in 98 (93.3%) patients, decreasing renal functions in 4 (3.8%), and recurrent “flash” pulmonary oedema in 3 (2.9%).

The demographic characteristics of the patients, blood pressure values before the procedure, and drugs used are shown in Table 1.

The total follow-up period was mean 39 months (range: 22-72 months) and the mean time to the development of MAE was 35 months (range:13-56.5 months). Of the 43 events that occurred in the MAE + group, 29 were all-cause mortality. The other 14 MAE were 6 (13.9%) acute coronary syndrome, 4 (9.3%) stroke, 2 (4.6%) patients started hemodialysis, 1 (2.3%) had renal artery stent thrombosis, and 1 (2.3%) TVR because of renal artery in-stent restenosis. When the causes of death were examined, the causes of the 29 deaths were determined to be multiple organ failure developing due to chronic renal failure in 8 (27.5%) cases, acute coronary syndrome in 5 (17%), COVID-

Table 1. Comparison of baseline demographic and medication data of MAE negative and positive groups.

Variables	MAE (-) group (n=62)	MAE (+) group (n=43)	P value
Age (years)	61.42±11.59	66.07±11.21	0.043
Male, n (%)	30(48.4)	22 (51.2)	0.78
BMI (kg/m ²)	27.63±4.72	29.26±4.63	0.082
Diabetes, n (%)	24 (38.7)	22 (51.2)	0.206
Hyperlipidemia, n (%)	57 (91.9)	38 (88.4)	0.541
Active smoking, n (%)	21 (33.9)	13 (30.2)	0.695
Prior MI, n (%)	9 (14.5)	23 (53.5)	<0.005
Prior CABG, n (%)	9 (14.5)	8 (18.6)	0.576
Prior stroke, n (%)	2 (3.2)	12 (27.9)	<0.005
COPD, n (%)	3 (4.8)	11 (25.6)	0.001
AF, n (%)	4 (6.5)	4 (9.3)	0.588
Syntax score	3(0-10.75), n=56	8.5(3.5-18), n=36	0.003
Systolic BP (mmHg)	165 (150-180)	165 (160-180)	0.372
Diastolic BP (mmHg)	90 (83-105)	95 (85-100)	0.903
ACEI, n (%)	30 (48.4)	19 (44.2)	0.671
ARB, n (%)	17 (27.4)	15 (34.9)	0.414
Beta blocker, n (%)	48 (77.4)	34 (79.1)	0.841
CCB, n (%)	46 (74.2)	32 (74.4)	0.979
Alfa blocker, n (%)	12 (19.4)	7 (16.3)	0.687
Thiazide, n (%)	41 (66.1)	19 (44.2)	0.118
Furosemide, n (%)	6 (9.7)	8 (18.6)	0.186
MRA, n (%)	11 (17.7)	6 (14)	0.604
Statin, n (%)	45 (72.6)	31 (72.1)	0.956
Preprocedural total number of antihypertensives	3 (3-4)	3 (3-4)	0.092

Data are shown as mean±standard deviation or median (25th-75th) or n (%) where appropriate. ACEI=Angiotensin-converting enzyme inhibitor, AF=Atrial fibrillation, ARB=Angiotensin receptor blocker, BP=Blood pressure, BMI=Body mass index, CABG=Coronary artery bypass grafting, CCB=Calcium channel blocker, COPD=Chronic obstructive pulmonary disease, MAE=Major adverse events, MRA=Mineralocorticoid receptor antagonist, SD=Standard deviation.

19 infection in 5 (17%), stroke in 3 (10%), major bleeding developing after the procedure in 1 (3.4%), acute kidney failure developing after the procedure in 1 (3.4%), abdominal aorta rupture in 1 (3.4%), pulmonary emboli in 1 (3.4%), intracranial hemorrhage in 1 (3.4%), chronic obstructive pulmonary disease (COPD) in 1 (3.4%), lung cancer in 1 (3.4%), and septic shock due to bacterial infection in 1 (3.4%). Of these 29 deaths, mortality was due to cardiovascular

reasons in 12 (41.3%).

As 2 of the whole patient group were lost due to complications developing after the procedure, the mortality rate associated with the procedure was accepted as 1.9%. One-month mortality was seen in 3 (2.8%) patients, 6-month mortality in 5 (4.7%), 1-year mortality in 7 (6.6%), and mortality throughout the mean follow-up period (median 39 months) in 29 (27.6%).

Table 2. Comparison of laboratory, echocardiography and electrocardiography data

Variables	MAE (-) group (n=62)	MAE (+) group (n=43)	P value
Laboratory parameters			
Creatinine (mg/dL)	1.06 (0.87-1.50)	1.28 (0.99-1.91)	0.040
CrCl* (mL/min)	61.71 (42.75-87.36)	49.25 (32.73-74.19)	0.014
AST, (IU/L)	19 (14.75-24)	19 (14-22)	0.812
ALT, (IU/L)	15.5 (10.75-20)	15 (11-21)	0.881
Total cholesterol (mg/dL)	192.48±44.75	212.67±61.31	0.054
LDL (mg/dL)	114.78±37.51	133.82±48.88	0.026
HDL (mg/dL)	44.50 (39.70-53.62)	44 (37.90-48.48)	0.479
Non-HDL cholesterol (mg/dL)	114.86±45.12	168.14±58.52	0.023
Triglyceride (mg/dL)	132 (100.25-200)	159.37 (113-234)	0.078
HbA1c (%)	6.2 (5.5-7.12), n=54	6.44 (5.5-7.40), n=40	0.337
Uric acid (mg/dL)	6.32±1.93, n=47	6.59±1.93, n=35	0.534
Albumin (g/L)	41.12±4.65	38.66±8.31	0.082
Hemoglobin (g/dL)	12.78±1.90	12.58±1.78	0.588
White blood cell (× 10 ³ /mL)	8.65±2.56	9.01±2.51	0.482
Neutrophils (× 10 ³ /mL)	5.69±2.03	6.13±2.48	0.321
Lymphocytes (× 10 ³ /mL)	2.18±0.76	2.05±1	0.478
Platelet (×10 ³ /L)	267.79±89.94	255.34±71.47	0.451
RDW (fL)	14 (13.20-15.15)	14.1 (13.5-15.2)	0.483
MPV (fL)	10.38±1.73	9.5±1.48	0.011
PDW (fL)	16.25 (16-16.60)	16.40 (16-16.8)	0.112
TSH (mIU/L)	1.33 (0.78-2.31)	1.39 (0.94-3.17)	0.589
Echocardiography			
LVEDD (mm)	46 (46-50)	47 (45-50)	0.990
LAD (mm)	40 (35-42)	42 (38-45)	0.005
IVS (mm)	13.11±2.33	13.28±2.27	0.700
LVEF (%)	60 (59.5-65)	48 (44-60)	<0.005
PABs (mmHg)	31.69±9.58, n=55	34.86±7.81, n=37	0.098
Electrocardiography			
LVH by Socolow-Lyon index, n (%)	20 (32.3)	13 (30.2)	0.826

Data are shown as mean±standard deviation or median (25th-75th) or n (%) where appropriate. ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, CrCl=Creatinine clearance, EF=Ejection fraction, HDL=High density lipoprotein, IVS=Interventricular septum, LAD=Left atrial diameter LDL=Low density lipoprotein, LVEDD=Left ventricular end-diastolic diameter, LVEF=Left ventricle ejection fraction, LVH=Left ventricular hypertrophy, MAE=Major adverse events, MPV=Mean platelet volume, PABs=Pulmoner artery systolic pressure, PDW=Platelet distribution width, RDW=Red cell distribution width, TSH=Thyroid-stimulating hormone, *Calculated with Modification of Diet in Renal Disease study.

The laboratory, TTE and ECG parameters of the patients are shown in Table 2, and the procedural and the post-procedural variables are shown in Table 3. The PTRS procedure was performed via the left radial artery in 2 (1.9%) patients. With the exception of 2 patients where >20% residual narrowness remained because of calcific renal arteries; the procedure was accepted as technically successful with a technical success rate of 98%. After the procedure, contrast nephropathy developed in 14 (13.3%) patients, which was treated with intravenous hydration, pseudoaneurysm in the femoral artery developed in 3 (2.9%), and femoral hematoma developed in 6 (5.7%), which recovered with medical treatment and rest. PTRS was determined to be beneficial in respect of blood pressure treatment in 81 (77.1%) patients.

Variables accepted as statistically significant as a

result of the comparisons of the two groups were applied first with univariate then multivariate Cox regression analysis. The data of the Cox regression analyses are presented in Table 4.

In the Cox multivariate regression analysis, the LVEF, COPD, and number of antihypertensive drugs used after the procedure were determined to be independent predictors for MAE. ROC analysis was performed on the continuous variables of LVEF, and number of antihypertensive drugs after the procedure (Fig. 2). As a result of the ROC analysis, a cutoff value of $\leq 55\%$ for LVEF was determined to have area under the curve (AUC) 0.733, 69.8% sensitivity, and 77.42% specificity ($P < 0.001$). The use of more than 3 antihypertensive drugs after the procedure was found to have AUC 0.624, 34.88% sensitivity, and 82.26% specificity ($P = 0.023$).

Table 3. Comparison of procedural and postprocedural data of MAE negative and positive groups.

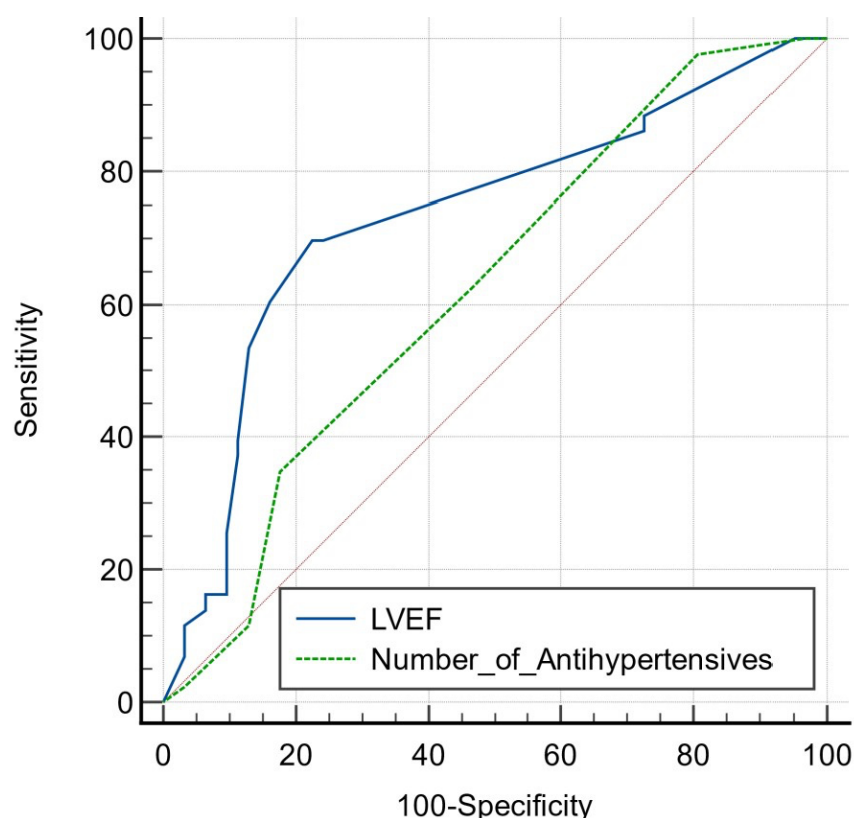
Variables	MAE (-) group (n=62)	MAE (+) group (n=43)	P value
Procedural Data			
Solitary kidney, n (%)	2 (3.2)	2 (4.7)	0.543
Right renal artery, lesion degree (%)	80 (80-95), n=27	80 (80-95), n=24	0.108
Left renal artery, lesion degree (%)	80 (80-95), n=27	80 (80-95), n=13	0.930
Right PTRS, n (%)	27 (43.5)	25 (58.1)	0.141
Left PTRS, n (%)	27 (43.5)	13 (30.2)	0.167
Bilateral PTRS, n (%)	8 (12.9)	5 (11.6)	0.845
PTRA, n (%)	30 (48.4)	13 (30.2)	0.108
Bilateral renal artery stenting, n (%)	8 (12.9)	5 (11.6)	0.845
Total number of stents	1 (1-1)	1 (1-1)	0.397
Mean stent diameter (mm)	6 (5-7)	6 (5-6)	0.992
Mean stent length (mm)	15.5 (14-19)	15 (14-15)	0.063
Postprocedural Data			
Systolic BP (mmHg)	135 (130-148.75)	140 (135-170)	0.016
Diastolic BP (mmHg)	85 (80-85)	85 (80-100)	0.059
Full cure, n (%)	2 (3.2)	0	0.512
Beneficial for HT, n (%)	52 (83.9)	29 (67.4)	0.049
Contrast induced nephropathy, n (%)	6 (9.7)	11 (18.6)	0.186
Postprocedural total number of antihypertensives	2 (2-3)	3 (2-4)	0.026

Data are shown as median (25th-75th) or n (%) where appropriate. BP=Blood pressure, HT=Hypertension, MAE=Major adverse events, PTRA= Percutaneous transluminal renal angioplasty, PTRS=Percutaneous transluminal renal stenting.

Table 4. Univariate and multivariate cox regression analyses for determining independent predictors of MAE.

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95 % CI	P value	HR	95 % CI	P value
Age	1.038	1-1.07	0.017	0.99	0.95-1.04	0.845
Prior MI	3.78	2.01-7.01	<0.005	1.34	0.55-3.30	0.514
Prior stroke	5.47	2.73-10.96	<0.005	1.92	0.66-5.59	0.229
COPD	4.09	2.01-8.32	<0.005	3.69	1.44-9.45	0.006
Postprocedural total number of antihypertensives	1.45	1.14-1.85	0.002	1.48	1-2.2	0.049
Beneficial for HT	0.34	0.17-0.66	0.002	1.17	0.42-3.24	0.755
Syntax score	1.039	1-1.07	0.03	1	0.95-1.06	0.727
CrCl	0.988	0.97-0.98	0.04	0.99	0.98-1.01	0.694
LDL	1.006	1-1.01	0.016	1.004	0.99-1.01	0.530
MPV	1.01	0.82-1.24	0.9			
LAD	1.08-	1.02-1.14	0.006	1.02	0.93-1.11	0.644
LV EF	0.95	0.93-0.98	<0.005	0.95	0.91-0.99	0.042
Postprocedural systolic BP	1	0.99-1.01	0.178			

BP=Blood pressure, COPD=Chronic obstructive pulmonary disease, CrCl=Creatinine Clearance, HT=Hypertension, LAD=Left atrial diameter, LDL=Low density lipoprotein, LVEF=Left ventricle ejection fraction, MAE=Major adverse events.

**Fig. 2.** ROC curve analysis for LV EF, and postprocedural total number of antihypertensives.

DISCUSSION

The aim of this study was to investigate adverse events and the predictors of these observed in patients who underwent a PTRS procedure because of ARAS. Although the SYNTAX score seemed to be significant in the univariate Cox regression analysis, it was not found to be an independent predictor. LVEF, COPD and the number of antihypertensive drugs used after the procedure were determined to be independent predictors for MAE.

In a previous study, the peri-procedural mortality rate was found to be 2.7%, which was close to the rate of the current study (1.9%). The mortality rate was determined to be 27.6% throughout the period of the current study (median 39 months), and when the mean follow-up period is taken into consideration, this rate was seen to be higher than the 24.2% (median 63 months) reported in the study by Wallace *et al.* [15]. However, the results obtained were seen to be similar to the 25.6% mortality rate of the ASTRAL study and the 24% mortality rate of the STAR study in literature [16, 17]. The median follow-up period (42 months) of the CORAL study [1] was very close to that of the current study, and the mortality rate of 13.7% was seen to be much lower than that of this and the above-mentioned studies [16, 17]. It was thought that the higher mortality rate in the current study compared to the CORAL [1] and Wallace *et al.* [15] studies could be attributed to the current study population having much more advanced atherosclerotic disease, especially compared with the CORAL study [1], and that this study was conducted during the COVID-19 pandemic. Another difference of the current study findings from the results of Wallace *et al.* [15] and the CORAL study [1] was that less than half (41.3%) of all the deaths were due to cardiovascular reasons.

In another study that was very similar to the current study in terms of design and results, age, COPD, heart failure, a history of treated subclavian artery stenosis, and advanced chronic renal failure were found to be independent predictors for mortality [18]. In the current study, COPD, LVEF, and the number of antihypertensive drugs after the procedure were determined to be independent predictors for MAE formed from combined end-points, rather than mortality. The current study results support the findings of the previ-

ous study in respect of COPD and heart failure. As COPD and ARAS share similar risk factors such as smoking, this may be related to the increased risk of adverse event. COPD has been proven to be an independent risk factor for mortality after coronary artery bypass grafting and percutaneous coronary intervention for CAD [19, 20]. Ledermen *et al.* [21] demonstrated that the risk of mortality increased with an increase in the severity of CAD in ARAS patients. However, it was interesting that in the current study results no independent association was seen between MAE and the SYNTAX score, which is a current score showing the severity of CAD.

It has been shown in previous studies that a history of MI, low LVEF and/or renal dysfunction are markers of poor prognosis in patients applied with renal arterial stent [7]. With the exception of LVEF, the other factors were not determined to be independent predictors in the current study. A low LVEF is known to be associated with increased mortality in many clinical conditions [22, 23]. However, there are limited data on the subject of the importance and cutoff value of LVEF in studies conducted on ARAS patients. The current study results showed that a cutoff value of ≤ 55 for LVEF was a significant predictor.

From a scan of the relevant literature, no evidence could be found that the total number of antihypertensive drugs used after the procedure could be a predictor of an adverse event. Therefore, the number of antihypertensive drugs after the procedure has been shown as a new predictor for this patient group. The fact of having to take more antihypertensive drugs after the procedure indicates that the patient has higher blood pressure values and has more difficulty in controlling this. A greater number of drugs may be associated with adverse events because of a more unwanted effect and greater drug interactions. This has been previously shown in studies of polypharmacy [24, 25]. This finding also demonstrates that blood pressure control is very important in these patients. Therefore, renal denervation could be considered in patients who cannot obtain blood pressure control despite a renal stenting procedure.

When the efficacy of the renal stent procedure was examined in respect of HT treatment, the procedure was found to be beneficial for 77.1% of the study group within the whole patient group. This rate was

close to the rate of 69.2% reported in a study by Dregoesc *et al.* [26]. The results of a meta-analysis showed that a stented or stentless PTR procedure was not successful in respect of blood pressure control or improving renal functions in approximately 20-40% of patients [27]. The current study results were consistent with those of this meta-analysis.

Limitations

The main limitations of this study were that it was retrospective in design and was conducted with a limited number of patients in a single centre. Due to the retrospective nature of the study, there may not have been standardization in the TTE and PTRS procedures among different cardiologists as can be ensured in prospective studies. A further limitation could be said to be the lack of a control group treated conservatively.

CONCLUSION

The results of this study demonstrated that LVEF, the presence of COPD, and the total number of antihypertensive drugs used after the procedure were independent predictors for MAE seen after a PTRS procedure in ARAS patients. These predictors can be used to estimate the risk in these patients. To be able to prevent adverse events, it is important that patients with these markers are treated and followed up more closely. As these results were obtained from a limited number of patients there is a need for further, large-scale, multi-centre studies to support these findings.

Ethical Statement

This study was approved by the Health Sciences University Bursa Yüksek İhtisas Training and Research Hospital Medical Sciences Ethics Committee (Decision no: 2024-TBEK 2024/07/04 and date: 31.07.2024)

Authors' Contribution

Study Conception: FK, ÖFD; Study Design: FK; Supervision: FK; Funding: FK; Materials: FK; Data Collection and/or Processing: FK, ÖFD; Statistical Analysis and/or Data Interpretation: FK, ÖFD; Literature Review: FK, ÖFD; Manuscript Preparation: FK, ÖFD and Critical Review: FK, ÖFD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Prostate-specific antigen density in prostate cancer screening in diabetes mellitus patients

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ABSTRACT

Objectives: The purpose of this study was to examine the function of prostate-specific antigen (PSA) and prostate-specific antigen density (PSAd) in the screening of prostate cancer in individuals with Diabetes Mellitus (DM).

Methods: This study was retrospective and cross-sectional. 467 patients who underwent transrectal ultrasound-guided 10-12 core prostate biopsy between 01 January and 31 December 2022 were included. Through the hospital information management system, the demographics, radiological, biochemical, and pathological results of the patients were scanned.

Results: PSAd>0.15 ng/mL/cm³ and total PSA (t-PSA)>8.58 ng/mL were substantially associated with an elevated probability of the existence of cancer when all patients were included. PSAd>0.19 ng/mL/cm³ and t-PSA>11.34 ng/mL were shown to be strongly associated with an elevated risk of cancer in patients with DM (P<0.001). PSAd>0.14 ng/mL/cm³ and t-PSA>8.49 ng/mL were substantially associated with an elevated probability of cancer presence in individuals without a diagnosis of DM. PSAd>0.15 ng/mL/cm³ and t-PSA>8.58 ng/mL were substantially associated with an elevated probability of cancer presence in individuals with fasting blood glucose (FBG) <126 mg/dL (P<0.001). It has been established that PSAd cannot be utilized as a marker to predict cancer in people with FBG≥126 mg/dL (P=0.070). Higher cancer risk was substantially correlated with t-PSA values of >5.73 ng/mL (P=0.001).

Conclusions: The change in prostate volume brought on by high blood glucose levels might be the cause of PSAd's lack of selectivity. Patients with DM are a special group in prostate cancer screening, and this should be considered when establishing cancer screening algorithms.

Keywords: Prostate-specific antigen (PSA), PSA density, prostate cancer, diabetes mellitus, risk estimation

It is known that many cancer types are more common in patients with Diabetes Mellitus (DM) [1-3]. However, no consensus has been reached on this issue in prostate cancer [4-7]. Studies suggesting that DM is protective against prostate cancer are at

least as many as those offering the opposite. Furthermore, numerous studies have demonstrated that DM patients had more aggressive prostate cancer [8]. According to a recent study, people with blood glucose levels ≥126 mg/dL cause prostate-specific antigen

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(PSA) to lose its selectivity. As a result, patients may not receive an early cancer diagnosis and present at more advanced stages of the disease [9].

DM is an endocrinological disease characterized by high blood glucose due to decreased insulin secretion or insulin resistance. Its prevalence has been increasing rapidly in recent years [10]. It is a significant cause of mortality and morbidity due to obesity, coronary artery disease, and cancer. Because both diseases are becoming more prevalent as people age, the increased frequency of this condition raises the risk of prostate cancer in DM patients.

PSA is the key test used in prostate cancer screening [11]. For many years, the preferred approach for screening for prostate cancer has been PSA density (PSAd), which is computed by taking the prostate volume into account [12]. Detection of PSAd >0.15 ng/mL/cm³ is essential for many clinicians. When a digital rectal examination reveals a suspicion of cancer and/or the PSA or PSAd is higher than the threshold value, a prostate biopsy is carried out under the supervision of transrectal ultrasonography (USG) [13]. In patients diagnosed with cancer due to biopsy, treatment is planned after determining the risk group according to the D'amico risk classification [14].

According to the guidelines of the Urological Association, using PSA and PSAd values together with a physical examination for prostate cancer screening is recommended. The validity of these screening tests in DM patients is questioned, though. Studying the relationship between PSA, PSAd, and DM could provide a deeper understanding of how diabetes influences prostate health, whether through direct effects on the prostate or indirectly through factors like insulin resistance, inflammation, or other metabolic changes. By exploring this relationship, clinicians could refine diagnostic tools or adjust for the influence of DM when interpreting PSA or PSAd, leading to more accurate prostate cancer screenings and better patient management. In this study, we are interested in understanding how DM might impact PSA and PSAd, which are key metrics for prostate cancer detection, to improve diagnosis and treatment strategies.

METHODS

The study was approved by the, A cross-sectional, ret-

rospective approach was used for the study. Following approval by the Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee (Decision no: 2011-KAEK-25 2022/05-13 and date: 18.05.2022), 467 patients who underwent transrectal USG (trUSG)-guided 10-12 core prostate biopsy between January 1 and December 31, 2022, were included. The patients gave their informed written permission. The patient's demographic characteristics and radiological, biochemical, and pathological results were obtained by scanning through the hospital's information management system. Patients with a diagnosis of DM were enrolled based on the statement in the medical history questioned before the biopsy.

Total PSA (t-PSA), total testosterone, fasting blood glucose, and hemoglobin A1c (HbA1c) values were analyzed among the biochemical test results. The American Diabetes Association (ADA) recommended 126 mg/dL as the cut-off threshold for hyperglycemia [9]. By dividing the t-PSA value by the prostate volume, PSAd was computed.

The D'Amico risk classification, which divides patients based on pretreatment PSA, clinical stage, and biopsy Gleason score (GS), was used to establish prostate cancer risk groups [14]. As a result, three risk categories were created for the patients: low risk (PSA <10 ng/ml and cT1-cT2a or GS), intermediate risk (PSA: 10–20 ng/ml or cT2b or GS7), and high risk (PSA >20 ng/ml or $\geq$ cT2c or GS $\geq$ 8).

Statistical Analysis

A priori power analysis was used to establish the necessary sample size for the study. Satir and Demirci's study [9] was used as a reference for determining the sample size. When the fasting blood glucose level was less than 126, the study's results demonstrated an area under the curve (AUC) of 0.59 for the existence of cancer. Based on this AUC value, $n=467$ was the minimum sample size needed for the study with a type I error of 5% and a power of 90%. To determine if the variables had a normal distribution, the Shapiro-Wilk test was employed. Numbers and percentages were used to represent categorical data, while the median (minimum-maximum) was used to represent continuous variables. The groups were compared using the Mann-Whitney U and Kruskal Wallis tests based on the findings of the normalcy test. After overall significance, the Bonferroni-Dunn test was ap-

plied for subgroup analysis. The chi-square test was applied for group comparisons including categorical data. To determine the total PSA's sensitivity and specificity in identifying the presence of cancer, receiver operator characteristics (ROC) analysis was used. The SPSS Software (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp) was used in analyzing the data. P-values <0.05 were regarded as statistically significant.

RESULTS

The overall features of the patient cohort are presented in Table 1. The mean HbA1c was calculated as 5.69. There were 81 patients with a fasting blood glucose (FBG) value ≥ 126 mg/dL. There were 159 people whose pathology revealed they had cancer.

Table 2 presents biochemical variable comparisons between prostate cancer risk groups and cancer presence. HbA1c readings showed no change between the risk groups ($P=0.579$). The FBG measurements showed no change between the groups ($P=0.614$). There was no difference in the proportion of patients with FBG levels <126 mg/dL and ≥ 126 mg/dL across the groups ($P=0.722$). In contrast, total PSA measurement differed between risk groups ($P<0.001$). The low-risk group's median t-PSA level was 5.92 ng/mL, the intermediate-risk groups was 11.17 ng/mL, and the high-risk groups was 30.67 ng/mL. Subgroup analyses revealed that the high-risk group had a higher t-PSA level than the low-risk and intermediate-risk groups ($P<0.001$ and $P<0.001$, respectively), and the intermediate-risk group had a higher median t-PSA level than the low-risk group ($P<0.001$). Testosterone levels did not differ across the groups ($P=0.110$). The PSA_d indicated a difference ($P<0.001$) between the groups. The low-risk group's median PSA_d level was 0.08 ng/mL/cm³, the intermediate-risk group's median PSA_d level was 0.18 ng/mL/cm³, and in the high-risk groups was 0.45 ng/mL/cm³. PSA_d in the high-risk group was found to be greater than in the low-risk and intermediate-risk groups ($P<0.001$ and $P<0.001$, respectively), while PSA_d in the intermediate-risk group was found to be greater than in the low-risk group ($P<0.001$) within the subgroup analyses.

HbA1C and FBG levels did not differ between the groups of benign and malignant patients when ana-

lyzed based on cancer status ($P=0.766$ and $P=0.477$, respectively). There was no significant difference ($P=0.465$) in the pattern of distribution of patients with FBG levels <126 and ≥ 126 mg/dL based on their cancer status. The t-PSA measurement varied ($P<0.001$) throughout the cancer groups.

For benign patients, the median t-PSA level was 6.56 ng/mL, but for malignant patients, it was 11.17 ng/mL. The groups' testosterone levels did not differ from one another ($P=0.168$). The median PSA_d level was 0.09 ng/mL/cm³ in benign patients and 0.19 ng/mL/cm³ in malignant patients. According to PSA_d, there was a statistically significant ($P<0.001$) difference between the groups.

ROC curve characteristics for total, diabetic, and non-diabetic patients were shown in Table 3. When PSA_d is >0.15 ng/mL/cm³ and t-PCA is >8.58 ng/mL, ROC curve analysis was also used to determine the specificity and sensitivity of PSA_d and t-PCA for predicting the existence of cancer. The PSA_d area under the curve was found to be 0.750 (sensitivity: 60.38%, specificity: 82.14%, $P<0.001$) and 0.756 (sensitivity:

Table 1. General characteristics of the participants

Age (years) (n=467)	66 (47-88)
Total PSA (ng/mL) (n=467)	7.40 (0.66-576)
HbA1c (Hb%) (n=407)	5.69 (4.19-10.98)
Fasting Blood Glucose (mg/dL) (n=454)	99 (65-448)
<126	373/454 (82.20%)
≥ 126	81/454 (17.80%)
Diabetes Mellitus (n=467)	100/467 (21.40%)
Hypertension (n=206)	64/206 (24.50%)
Testosterone (ng/dL) (n=264)	462.81 (10.14-1009.40)
Cancer (n=467)	
Benign	308/467 (66%)
Malign	159/467 (34%)
Prostate volume (mL) (n=467)	70 (22-282)
PSA density (ng/mL/cm³) (n=467)	0.11 (0.01-5.65)

Data are shown as median (interquartile range) and n (%).

Table 2. Comparisons of the biochemical variables between prostate cancer risk groups and cancer presence

Prostate cancer risk groups				Cancer Status						
	n	Low	n	Intermediate	n	High	n	Benign	n	Malign
HbA1c (Hb%)	41	5.69 (4.89-8.58)	40	5.69 (4.59-8.38)	55	5.70 (4.59-10.48)	271	5.69 (4.59-10.48)	136	5.69 (4.59-10.48)
P value				0.579 ^a				0.766 ^b		
FBG (mg/dL)	46	101 (70-255)	44	100 (65-325)	66	97 (66-250)	298	98 (65-448)	156	99 (65-325)
P value				0.614 ^a				0.477 ^b		
FBG (mg/dL)										
<126		37 (80.40%)		38 (86.40%)		56 (84.80%)		242 (81.20%)		131 (84%)
≥126	46		44		66		298		156	
P value		9 (19.60%)		6 (13.60%)		10 (15.20%)		56 (18.80%)		25 (16%)
				0.722 ^c				0.465 ^c		
Total PSA (ng/mL)	47	5.92 (1.34-9.74)	45	11.17 (5.38-19.90)	67	30.67 (5.28-576)	308	6.56 (0.66-69.33)	159	11.17 (1.34-576)
P value				<0.001 ^a				<0.001 ^b		
Testosterone (ng/dL)	25	478.12 (10.30-788.48)	28	506.13 (10.14-956.23)	37	412 (11.20-898.97)	174	462.81 (139.66-1009.40)	90	455.10 (10.14-956.23)
P value				0.110 ^a				0.168 ^b		
PSA density (ng/mL/cm ³)	47	0.08 (0.01-0.30)	45	0.18 (0.06-0.43)	67	0.45 (0.06-5.65)	308	0.09 (0.02-1.65)	159	0.19 (0.01-5.65)
P value				<0.001 ^a				<0.001 ^b		

Data are shown as median (interquartile range) and n (%). HbA1c=glycated haemoglobin, PSA=prostate-specific antigen, FBG=fasting blood glucose
^aKruskal Wallis Test, ^bMann Whitney U Test, ^cChi-Square Test

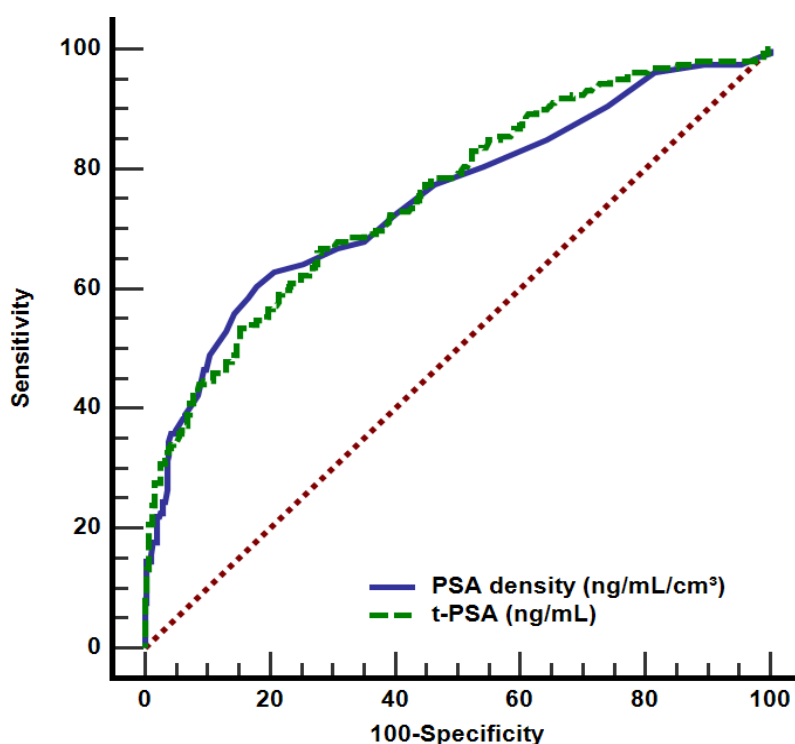


Fig. 1. (for all patients). Receiver-operator characteristic (ROC) curves for determining the presence of cancer when PSAd is >0.15 ng/mL/cm³ and total PSA (t-PSA) is >8.58 ng/mL.

66.04%, specificity: 72.40%, $P<0.001$), respectively (Fig. 1). These values indicate a substantial correlation between an elevated PSAd of >0.15 ng/mL/cm³ and a t-PCA of >8.58 ng/mL with the existence of cancer. Nonetheless, there was no statistically significant distinction in the cancer prediction abilities of PSAd and t-PCA ($P=0.690$).

In diabetic patients, when PSAd is >0.19 ng/mL/cm³ and t-PCA is >11.34 ng/mL, ROC curve analysis was also carried out to determine both the specificity and sensitivity of PSAd and t-PCA for predicting the existence of cancer. The PSAd area under the curve was found to be 0.760 (sensitivity: 60.53%, specificity: 93.55%, $P<0.001$) and 0.806 (sensitivity:

Table 3. ROC curve characteristics for total, diabetic, and non-diabetic patients

	Total (n=467)		Diabetic (n=100)		Non-Diabetic (n=367)	
	PSA density	Total PSA	PSA density	Total PSA	PSA density	Total PSA
Sensitivity	60.38%	66.04%	60.53%	57.89%	62.81%	66.94%
Specificity	82.14%	72.40%	93.55%	93.55%	77.64%	70.73%
Cut-off Value	>0.15	>8.58	>0.19	>11.34	>0.14	>8.49
Jouden J Index	0.43	0.38	0.54	0.51	0.40	0.38
Standard Error of AUC	0.03	0.02	0.05	0.05	0.03	0.03
AUC	0.750	0.756	0.760	0.806	0.745	0.742
Comparison of AUCs	$P=0.690$		$P=0.225$		$P=0.892$	

AUC: Area Under Curve

57.89%, specificity: 93.85%, $P<0.001$), respectively. These values indicate a substantial correlation between an elevated PSAd of $>0.19\text{ ng/mL/cm}^3$ and a t-PCA of $>11.34\text{ ng/mL}$ with the existence of cancer. The ability of t-PSA and PSA density to predict cancer, however, did not vary from one another ($P=0.225$) (Table 3).

ROC curve for fasting plasma glucose is shown in Table 4. For those with an FBG <126 when PSAd is $>0.15\text{ ng/mL/cm}^3$ and t-PCA is $>8.58\text{ ng/mL}$, ROC curve analysis was also carried out to determine both the specificity and sensitivity of PSAd and t-PCA for predicting the existence of cancer. The area under the curve values for PSAd and t-PSA were 0.774 (sensitivity 64.12%, specificity 82.14%, $P<0.001$) and 0.762 (sensitivity 68.70%, specificity 72.31%, $P<0.001$), respectively. Accordingly, PSAd values $>0.15\text{ ng/mL/cm}^3$ and t-PCA values $>8.58\text{ ng/mL}$ indicate a substantial correlation between an elevated risk of cancer existence.

For those with FBG $\geq 126\text{ mg/dL}$ both the specificity and sensitivity of PSAd for cancer, prediction was also estimated using ROC curve analysis. After conducting the study, it was concluded that PSAd was not a reliable indicator of cancer risk in patients with FBG $\geq 126\text{ mg/dL}$. The PSAd area under the curve was 0.634 (sensitivity 52%, specificity 83.93%, $P=0.070$) when PSAd was more than 0.15 ng/mL/cm^3 . However, a significant correlation was found between t-PCA levels of more than 5.73 ng/mL and a greater probability of cancer (AUC=0.713, sensitivity 80%, specificity 51.79%, $P=0.001$).

DISCUSSION

When comparing groups of patients with benign conditions to those with malignant prostate cancer, no significant differences were observed in HbA1c or FBG levels. PSA density and t-PSA show significant differences between prostate cancer presence and risk groups. PSAd $>0.15\text{ ng/mL/cm}^3$ and t-PSA $>8.58\text{ ng/mL}$ were substantially associated with an elevated probability of cancer presence in individuals with FBG $<126\text{ mg/dL}$. We determined that PSAd cannot be utilized as a marker to predict cancer in people with FBG $\geq 126\text{ mg/dL}$. Higher cancer risk was substantially correlated with t-PSA values of $>5.73\text{ ng/mL}$.

Several studies have reported an inverse association between DM and the risk of developing prostate cancer [15, 16]. Men with diabetes tend to have a lower incidence of prostate cancer compared to non-diabetic men. This may be due to lower testosterone levels in diabetic men, as testosterone is a known driver of prostate cancer growth. While diabetes may reduce the overall risk of prostate cancer, elevated blood sugar levels (hyperglycemia) have been associated with more aggressive prostate cancer phenotypes [17]. Hyperglycemia may promote tumor progression through mechanisms such as insulin resistance, chronic inflammation, and oxidative stress. Insulin resistance and elevated levels of insulin-like growth factor 1 (IGF-1) are common in individuals with diabetes or metabolic syndrome. These factors may promote prostate cancer progression by stimulating cell prolifer-

Table 4. ROC curve characteristics for fasting plasma glucose

	Fasting blood glucose <126 (n=373)		Fasting blood glucose ≥126 (n=81)	
	PSA density	Total PSA	PSA density	Total PSA
Sensitivity	64.12%	68.70%	%52	80%
Specificity	82.64%	72.31%	83.93%	51.79%
Cut-off value	>0.15	>8.58	>0.15	>5.73
Jouden J index	0.47	0.41	0.36	0.32
Standard error of AUC	0.03	0.03	0.07	0.06
AUC	0.774	0.762	0.634	0.713
Comparison of AUCs	0.450		-	

PSA=Prostate-Specific Antigen, AUC=Area Under Curve

eration and inhibiting apoptosis [18]. Screening and monitoring of blood sugar levels in men with prostate cancer may be important, especially in those with aggressive disease. Lifestyle interventions, such as weight loss and glycemic control, could potentially reduce the risk of prostate cancer progression.

Multiparametric MRI (mpMRI) has become a cornerstone in the diagnosis and management of prostate cancer. It combines T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast-enhanced imaging to improve the detection of clinically significant prostate cancer [19]. The advantages of mpMRI are Improved detection of clinically significant prostate cancer, reduced detection of low-grade, indolent tumors, and better localization of tumors for targeted biopsies.

PSAd can find its place in prostate cancer screening models as an easy-to-apply method. Although PSAd has lost popularity in the last 20 years, it is considered an important parameter in study risk prediction. According to Yusim *et al.* [20], individuals with PSAd values between 0.09 and 0.19 and prostate volumes less than 33 milliliters had a higher predictive value for clinically relevant prostate cancer. Omri *et al.* [21] discovered similarly that the International Society of Urological Pathology (ISUP) PCa class group and PSAd level were directly correlated. As a result, they concluded that PSAd is a practical, affordable, and easy-to-use tool for individuals who have small and medium-sized prostates while making treatment decisions. Both studies emphasized that PSAd is more valuable when the prostate volume is low. According to our research, individuals with blood glucose levels of 126 and higher had a loss of PSAd's selectivity for prostate cancer. This study's result is consistent with previous research, given that people who had elevated blood sugar levels had increased prostate volume. PSAd may play a critical role in improving the specificity of prostate cancer detection, especially in patients with high blood sugar or diabetes. Adjusting PSA levels for prostate size, it helps to reduce the confounding effects of benign conditions and gives a clearer indication of whether prostate cancer may be present, making it a more reliable diagnostic tool in such cases.

The American Urological Association and the European Association of Urology both recognize biopsy as a screening technique in situations where the t-PSA

test result is more than 3-4 ng/mL [22]. For screening, life expectancy should be at least 10-15 years, general health status should be good, and the person should be informed about prostate cancer screening [23]. Men who belong to an ethnic minority and have a family history of prostate cancer are considered high-risk individuals and should be screened [24]. However, the PSA test does not have a threshold value that all authors accept [25]. PSA levels are influenced by several variables, including age, acute prostatitis, ejaculation, catheterization, and certain comorbidities and drugs [23]. The link between diabetes, prostate cancer, and PSA has been examined in recent research. The PSA threshold that is most frequently employed in current practice to assess whether a biopsy is necessary (3-4 ng/mL) appears to be different from other thresholds in patients with diabetes [23]. However, if the normal PSA threshold (3-4 ng/mL) is used in diabetic patients, the possibility of missing smaller tumors in these patients is considered high [26-28]. The present study observed higher t-PSA threshold values in diabetic patients. A previous study showed that t-PSA had no value in predicting cancer in individuals with 126 mg/dL and above blood glucose levels. In the present study, while t-PSA helped predict cancer in individuals with a blood glucose level of 126 mg/dL and above, it was observed that the threshold values increased. Diabetes mellitus (independent of blood glucose regulation) is also associated with increased t-PSA cut-off values.

CONCLUSION

This study highlights the complex interplay between glycemic markers, PSA parameters, and prostate cancer risk. While HbA1c and FBG levels did not differ significantly between benign and malignant prostate conditions, PSAd and t-PSA emerged as valuable indicators for predicting prostate cancer risk, particularly in individuals with FBG levels below 126 mg/dL. However, PSAd loses its predictive utility in individuals with elevated blood glucose levels (≥ 126 mg/dL), likely due to increased prostate volume associated with hyperglycemia. Additionally, t-PSA thresholds for cancer prediction were higher in diabetic patients, underscoring the need for adjusted diagnostic criteria in this population. These findings align with existing

literature, which suggests that diabetes may reduce overall prostate cancer risk but is associated with more aggressive disease phenotypes and altered PSA dynamics. The integration of metabolic profiling, PSA parameters, and advanced imaging techniques like mpMRI could enhance prostate cancer screening and risk stratification. Moving forward, personalized approaches that account for glycemic status, prostate volume, and PSA thresholds may improve diagnostic accuracy and guide clinical decision-making, particularly in high-risk populations. Further research is needed to refine these strategies and optimize prostate cancer management in the context of metabolic disorders.

Ethical Statement

The study was approved by the Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee (Decision no: 2011-KAEK-25 2022/05-13 and date: 18.05.2022).

Authors' Contribution

Study Conception: AS, HD; Study Design: AS, HD; Supervision: HD; Funding: N/A; Materials: N/A; Data Collection and/or Processing: AS, HD, AE, GAÖ; Statistical Analysis and/or Data Interpretation: GO; Literature Review: AS; Manuscript Preparation: AS, GO, AE, GAÖ and Critical Review: HD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Advances in acute pancreatitis management: From guidelines to clinical practice

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ABSTRACT

Objectives: This study aimed to evaluate current management strategies and early outcomes in patients with acute pancreatitis (AP) to provide insights into effective practices and contribute to the discourse on optimizing AP care.

Methods: A retrospective observational study was conducted on 350 AP patients admitted to Kanuni Sultan Süleyman Training and Research Hospital between January 2015 and December 2022. Data were extracted from electronic medical records, including demographics, clinical presentation, laboratory findings, imaging results, treatment strategies, and outcomes. Patients were assessed for severity using the Revised Atlanta Classification and Bedside Index for Severity in Acute Pancreatitis (BISAP) scores, and management protocols included controlled fluid resuscitation, pain management, nutritional support, selective antibiotic use, and endoscopic interventions.

Results: Of 350 patients (male: 54%, mean age: 50 years), 79.7% had mild AP, 14.9% moderately severe AP, and 5.4% severe AP. Goal-directed fluid resuscitation and early nutritional support were implemented, with early oral feeding initiated in 81.4% of cases. Antibiotics were used in 20% of patients with confirmed or suspected infections, and Endoscopic retrograde cholangiopancreatography (ERCP) was performed in 24.6% of patients with biliary pancreatitis. The mean hospital stay was 7, 14, and 21 days for mild, moderately severe, and severe AP, respectively. Intensive care unit (ICU) admission was required for 8.6%, and in-hospital mortality was 2%. Recurrence within six months occurred in 9.1% of cases.

Conclusions: Individualized management strategies adhering to current guidelines led to favorable early outcomes, including reduced complications and a high six-month survival rate (98%). Future multicenter studies are recommended to confirm these findings and assess long-term outcomes.

Keywords: Acute pancreatitis, fluid resuscitation, nutritional support, severity assessment, endoscopic intervention, BISAP score, early outcomes

Acute pancreatitis (AP) is an abrupt inflammatory condition of the pancreas. The disease manifests when pancreatic enzymes become prematurely activated within the pancreas, leading to autodigestion and subsequent inflammation [1]. Glob-

ally, AP is a leading cause of gastrointestinal hospital admissions, with its incidence showing an upward trend in recent years [2].

The clinical presentation of AP varies widely. While approximately 80% of cases are mild and self-

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limiting, about 20% progress to moderately severe or severe forms [3]. Severe AP is characterized by persistent organ failure and local or systemic complications, which can result in a mortality rate as high as 20% [4]. Early recognition and management are crucial, as they significantly influence the disease trajectory and patient outcomes [5].

Initial management within the first 72 hours is critical and encompasses several key strategies: accurate assessment of disease severity, goal-directed fluid resuscitation, effective pain control, early initiation of nutritional support, selective use of antibiotics, and timely endoscopic interventions when indicated [6]. Recent shifts in clinical practice emphasize individualized care based on patient-specific factors and evidence-based protocols [7].

Advancements in understanding the pathophysiology of AP have led to changes in management approaches. For instance, moderate fluid resuscitation with isotonic crystalloids is now preferred over aggressive hydration to prevent complications associated with fluid overload [8]. Early enteral nutrition is encouraged to maintain gut integrity and reduce infection risks, moving away from the traditional "pancreatic rest" approach [9]. The use of prophylactic antibiotics is now limited to cases with confirmed or highly suspected infections to avoid antibiotic resistance and other adverse effects [10].

Despite these advancements, several areas remain contentious, such as the optimal timing and volume of fluid resuscitation, the role of various analgesics in pain management, and the indications for endoscopic interventions like endoscopic retrograde cholangiopancreatography (ERCP) [11]. Addressing these controversies is essential for improving patient care and outcomes.

This study aims to evaluate the current management strategies and early outcomes of patients with acute pancreatitis. By analyzing clinical characteristics, treatment modalities, and patient responses, we seek to provide insights into effective practices and contribute to the ongoing discourse on optimizing AP management.

METHODS

This retrospective observational study was conducted

at Kanuni Sultan Süleyman Training and Research Hospital, focusing on patients who were diagnosed with acute pancreatitis (AP) between January 2015 and December 2022.

Approval for the study was obtained from the Institutional Ethics Committee affiliated with the Istanbul Provincial Health Directorate (Approval Number: KAEK/2024.10.225). Given the retrospective nature of the research, the ethics committee waived the requirement for informed consent. To ensure patient confidentiality, all data were anonymized before analysis.

Patients were included in the study based on the following criteria:

a. *Age*: Patients aged 18 years or older.

b. *Diagnosis of Acute Pancreatitis*: Confirmed by at least two of the following three criteria: (1) Abdominal pain characteristic of AP; (2) Serum amylase and/or lipase levels elevated to at least three times the upper limit of normal; (3) Imaging findings consistent with AP observed on abdominal ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI).

c. *Demographics*: Age, sex.

d. *Clinical Presentation*: Symptoms at admission, vital signs.

e. *Laboratory Results*: Serum amylase, lipase, hematocrit, blood urea nitrogen (BUN), C-reactive protein (CRP), procalcitonin levels when available.

f. *Imaging Findings*: Results from abdominal ultrasound, CT, or MRI.

Patients were excluded if they had incomplete medical records or if they were transferred from another healthcare facility more than 48 hours after their initial presentation.

Data were extracted from electronic medical records and included variables such as patient demographics, clinical presentation, laboratory results, imaging findings, treatment modalities, and early outcomes.

Severity Assessment

Classified according to the Revised Atlanta Classification into mild, moderately severe, and severe AP [3]. Severity scores were calculated using the Systemic Inflammatory Response Syndrome (SIRS) criteria and the Bedside Index for Severity in Acute Pancreatitis (BISAP) score upon admission and daily for the first 72 hours [14].

Management Strategies

a. *Fluid Resuscitation*: Type of fluids administered (isotonic crystalloids, primarily lactated Ringer's solution), initial bolus volumes, and maintenance rates adjusted based on hemodynamic parameters [15].

b. *Pain Control*: Use of acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids when necessary [16].

c. *Nutritional Support*: Timing of initiation, route of feeding (oral, enteral via feeding tubes, or parenteral nutrition), criteria for nutritional support decisions [17].

d. *Antibiotic Use*: Indications for antibiotic therapy, types of antibiotics used, duration of treatment, use of procalcitonin-guided algorithms [18].

e. *Endoscopic Interventions*: Indications for endoscopic retrograde cholangiopancreatography (ERCP), timing (urgent within 24 hours, elective within 72 hours), and criteria for patient selection [19].

Outcome Measures

1. Length of hospital stay.
2. Development of local complications (e.g., pseudocysts, walled-off necrosis).
3. Development of systemic complications (e.g., organ failure).
4. Need for intensive care unit (ICU) admission.
5. In-hospital mortality.
6. Recurrence rates within six months of discharge.

Management Protocols

a) *Severity Assessment*: All patients underwent severity assessment upon admission using SIRS criteria and BISAP scores. Assessments were repeated daily for the first 72 hours to monitor disease progression [14].

b) *Fluid Resuscitation*: Patients received isotonic crystalloids. An initial bolus of 15-20 mL/kg was administered over the first hour for patients with hypovolemia. Maintenance fluids were given at 1.5 mL/kg/h, adjusted based on heart rate, mean arterial pressure, urine output, hematocrit levels, and BUN [15].

c) *Pain Management*: Analgesia was initiated with acetaminophen and NSAIDs. Opioids were administered to patients whose pain was not adequately controlled with non-opioid analgesics [16].

d) *Nutritional Support*: Early oral feeding was en-

couraged and initiated within 48 hours when tolerated. Patients unable to tolerate oral intake received enteral nutrition via nasogastric or nasojejunal tubes. Parenteral nutrition was reserved for patients with contraindications to enteral feeding [17].

e) *Antibiotic Therapy*: Antibiotics were reserved for patients with suspected or confirmed infections. Procalcitonin levels were used to guide antibiotic therapy when available. No prophylactic antibiotics were administered to patients without signs of infection [18].

f) *Endoscopic Interventions*: ERCP was performed in patients with gallstone pancreatitis accompanied by cholangitis or persistent biliary obstruction. Urgent ERCP was conducted within 24 hours for cholangitis cases, and elective ERCP within 72 hours for biliary obstruction [19].

Statistical Analysis

Data were analyzed using SPSS software version 29.0. Patient demographics, clinical features, management strategies, and outcomes were summarized using descriptive statistics. Depending on the distribution, continuous data were presented as means with standard deviations or as medians accompanied by interquartile ranges. Categorical variables were expressed as frequencies and percentages. Survival analysis with Kaplan-Meier curves was compared using the log-rank test. A p-value less than 0.05 was considered to indicate statistical significance. All patient data were de-identified before analysis to ensure confidentiality. Data were stored securely in password-protected systems accessible only to authorized personnel involved in the study.

RESULTS

A total of 350 patients diagnosed with acute pancreatitis (AP) were included in the study. There were 189 male patients (54%) and 161 female patients (46%), with a mean age of 50 years (range 18-85 years). The etiologies of AP among these patients were as follows: gallstones in 162 patients (46.3%), alcohol use in 105 patients (30%), hypertriglyceridemia in 33 patients (9.4%), post-endoscopic retrograde cholangiopancreatography (ERCP) in 18 patients (5.1%), and idiopathic or other causes in 32 patients (9.1%) (Table 1).

Table 1. Patient demographics and clinical characteristics

Characteristic	Data
Total number of patients	350
Gender (Male/Female)	189 161
Mean age (range) (years)	50 (18-85)
Etiology, n (%)	
Gallstones	162 (46.3%)
Alcohol	105 (30%)
Hypertriglyceridemia	33 (9.4%)
Post-ERCP	18 (5.1%)
Idiopathic/Other	32 (9.1%)

Severity Assessment

According to the Revised Atlanta Classification, 279 patients (79.7%) had mild AP, 52 patients (14.9%) had moderately severe AP, and 19 patients (5.4%) had severe AP. Systemic Inflammatory Response Syndrome (SIRS) criteria were positive in 117 patients (33.4%), and a Bedside Index for Severity in Acute Pancreatitis (BISAP) score of ≥ 3 was noted in 28 patients (8%) (Table 2).

Fluid Resuscitation

All patients received isotonic crystalloid solutions for fluid resuscitation. Patients presenting with hypovolemia were administered an initial bolus of 15-20 mL/kg over the first hour.

Maintenance fluids were given at a rate of 1.5 mL/kg/h and adjusted based on hemodynamic parameters such as heart rate, mean arterial pressure, urine output, hematocrit levels, and blood urea nitrogen (BUN).

Pain Control

Adequate pain management was achieved with acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) in 245 patients (70%). Opioids were required in 105 patients (30%) due to severe pain unresponsive to non-opioid analgesics. No significant adverse events related to analgesic use were reported.

Nutritional Support

Early oral feeding was initiated within 48 hours of admission in 285 patients (81.4%). Enteral nutrition

via feeding tubes was necessary for 43 patients (12.3%) who could not tolerate oral intake. Parenteral nutrition was administered to 22 patients (6.3%) who had contraindications to enteral feeding, such as intestinal obstruction or severe ileus.

Antibiotic Use

Antibiotics were administered to 70 patients (20%) who had suspected or confirmed infections. Procalcitonin-guided algorithms were utilized when available to guide antibiotic therapy. No prophylactic antibiotics were given to patients without signs of infection, adhering to the principle of minimizing unnecessary antibiotic use.

Endoscopic Interventions

Endoscopic retrograde cholangiopancreatography (ERCP) was performed in 86 patients (24.6%) diagnosed with gallstone pancreatitis. Among these, urgent ERCP within 24 hours was conducted in 24 patients

Table 2. AP severity assessment and clinical outcomes

Characteristic	Data
Severity of AP, n (%)	
Mild	279 (79.7%)
Moderately severe	52 (14.9%)
Severe	19 (5.4%)
Positive SIRS criteria, n (%)	117 (33.4%)
BISAP score ≥ 3 , n (%)	28 (8%)
Mean hospital stay (days)	
Mild AP	7
Moderately severe AP	14
Severe AP	21
Complications	
Local complications (pseudocysts, walled-off necrosis)	42 (12%)
Systemic complications (organ failure)	12 (3.4%)
ICU admissions, n (%)	30 (8.6%)
Mortality, n (%)	7 (2%)
Recurrence within six months, n (%)	3 (9.1%)

AP=acute pancreatitis, SIRS=Systemic inflammatory response syndrome, BISAP=Bedside Index for Severity in Acute Pancreatitis, ICU=Intensive care unit

(27.9%) who presented with cholangitis. Elective ERCP within 72 hours was performed in 62 patients (72.1%) with persistent biliary obstruction but without cholangitis.

Early Clinical Outcomes

The mean length of hospital stay varied according to the severity of AP: 7 days for patients with mild AP, 14 days for those with moderately severe AP, and 21 days for patients with severe AP (as shown in Table 2). Local complications, such as pseudocysts and walled-off necrosis, developed in 42 patients (12%). Systemic complications, primarily organ failure, occurred in 12 patients (3.4%).

Among the 19 patients with severe AP, the majority developed systemic complications, including respiratory failure (7 patients, 36.8%), renal failure (5 patients, 26.3%), and cardiovascular failure (3 patients, 15.8%). Eight patients required mechanical ventilation, and five underwent renal replacement therapy. The overall ICU mortality rate for severe AP patients was 21.1% (4 patients).

Intensive Care Unit (ICU) admission was required for 30 patients (8.6%), predominantly those with severe AP. The overall in-hospital mortality rate was 2% (7 patients), all of whom had severe AP complicated by multiple organ failure.

Within six months of discharge, 32 patients (9.1%) experienced a recurrence of AP. The recurrences were

mainly attributed to gallstones and alcohol use, emphasizing the need for addressing etiological factors during the convalescent period.

The overall survival rate at six months was 98% (Fig. 1). The Kaplan-Meier curve indicates that all deaths occurred during hospitalization, with no mortality observed after discharge. Recurrence-free survival at six months was 90%, with most recurrences occurring within the first 60 days (Fig. 2).

DISCUSSION

In this study, we evaluated the management strategies and early outcomes of 350 patients diagnosed with acute pancreatitis (AP) between 2015 and 2022. Examining the demographic characteristics, we found a relatively balanced distribution between males and females (189 males, 161 females), with an average age of 50 years (range 18-85). The most common etiological factors were gallstones (46.3%) and alcohol use (30%), while hypertriglyceridemia, post-ERCP, and idiopathic causes were less frequently observed. This distribution aligns with the literature, where gallstones and alcohol are reported as the most prevalent causes of AP [13].

In terms of severity assessment, according to the Revised Atlanta Classification, the majority of patients experienced mild AP (79.7%), with moderately severe

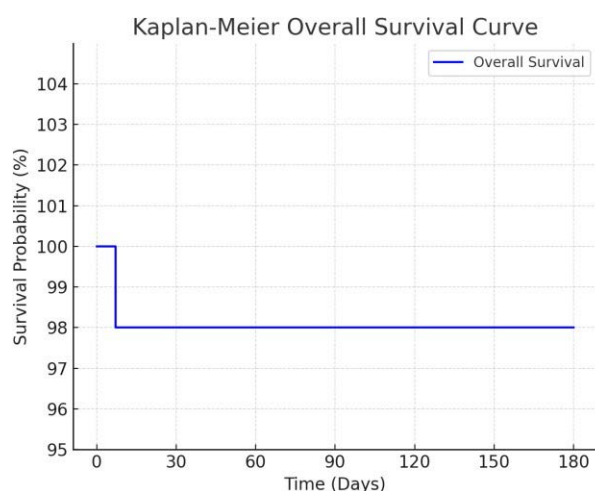


Fig. 1. Kaplan-Meier curve illustrating the overall survival rate of patients with acute pancreatitis over a six-month follow-up period.

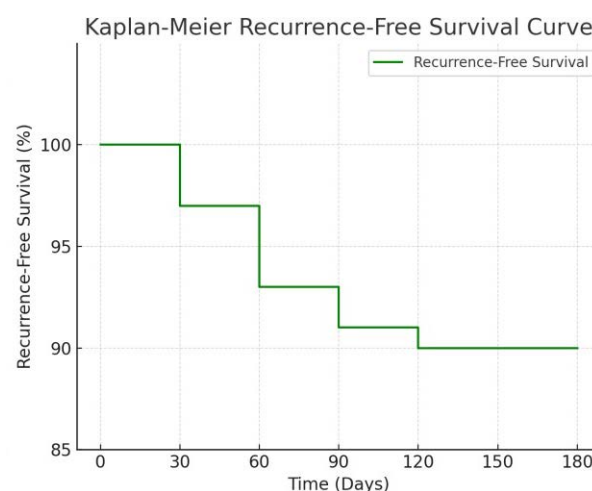


Fig. 2. Kaplan-Meier curve showing recurrence-free survival among patients with acute pancreatitis over a six-month follow-up period.

AP in 14.9% and severe AP in 5.4% of cases. The presence of SIRS criteria in 33.4% of patients and a BISAP score of ≥ 3 in 8% indicates that these scoring systems can be beneficial in the early detection of severe AP cases [14]. These findings emphasize the significant impact of early severity assessment on patient management and prognosis.

Patients with severe AP in our cohort demonstrated notably worse outcomes compared to those with mild or moderately severe AP. The ICU admission rate in this group was 100%, with a substantial proportion requiring advanced organ support, including mechanical ventilation and renal replacement therapy. The mortality rate of 21.1% in severe AP patients underscores the critical nature of this condition and highlights the importance of early aggressive management. These findings align with existing literature, which reports a higher morbidity and mortality rate among patients with severe AP due to systemic inflammatory response and organ failure [15].

Fluid resuscitation was administered with isotonic crystalloids in all patients and adjusted based on hemodynamic parameters. Patients with hypovolemia received an initial bolus of 15-20 mL/kg in the first hour, followed by maintenance infusion at a rate of 1.5 mL/kg/h. This approach is consistent with goal-directed therapy recommended in the literature and contributes to preventing complications such as fluid overload or insufficient fluid administration [15]. No serious complications related to fluid resuscitation were reported, highlighting the importance of controlled and individualized fluid therapy.

For pain management, acetaminophen and NSAIDs were sufficient in 70% of patients, while opioid use was required in 30%. No significant side effects related to opioid use were observed. These results are consistent with studies indicating that opioids can be safely used in AP and provide an effective approach to pain management [16].

Regarding nutritional support, early oral feeding was initiated within the first 48 hours in 81.4% of patients. Enteral feeding via tubes was necessary in 12.3%, and parenteral nutrition was applied in 6.3% who had contraindications to enteral feeding. Early nutritional support is known to be effective in preserving intestinal integrity, reducing bacterial translocation, and decreasing the risk of infection [17]. In our study, early feeding likely contributed to shortening

hospital stays and reducing complications.

In the severe AP group, nutritional management was more challenging, with 10 patients (52.6%) requiring enteral feeding through nasogastric or nasojejunal tubes and 6 patients (31.6%) necessitating parenteral nutrition. This highlights the need for tailored nutritional strategies in severe cases to minimize metabolic stress and support recovery.

Antibiotic use was applied only in patients with suspected or confirmed infections (20%). When possible, antibiotic therapy was guided by procalcitonin levels. Prophylactic antibiotic use has been reported in the literature not to reduce mortality or infection rates in AP, and in our study, antibiotics were not given to patients without signs of infection [11]. This approach helps prevent the development of antibiotic resistance by reducing unnecessary antibiotic use.

Endoscopic interventions were performed in 86 patients (24.6%) with gallstone pancreatitis. Urgent ERCP was conducted within the first 24 hours in 24 patients with cholangitis, while elective ERCP was performed within 72 hours in 62 patients with persistent biliary obstruction. This timing aligns with current guidelines on the indications and optimal timing of ERCP in acute biliary pancreatitis [18]. Literature indicates that urgent ERCP does not provide benefits in patients without cholangitis, and in our study, ERCP indications were carefully evaluated.

Assessing early outcomes, it was observed that the length of hospital stay increased significantly with the severity of AP (mild AP: 7 days, moderately severe AP: 14 days, severe AP: 21 days). Complications included local complications (12%) and systemic complications (3.4%). Local complications consisted of pseudocysts and walled-off necrosis, while systemic complications manifested as organ failure. Intensive care unit admission was required in 30 patients (8.6%), predominantly in severe AP cases. The mortality rate was 2%, with all deaths occurring in patients with severe AP and multiple organ failure. These findings support the relationship between the severity of AP and increased mortality and morbidity [19].

Recurrence was observed in 32 patients (9.1%) within six months, mainly associated with gallstones and alcohol use. This underscores the importance of managing etiological factors during the convalescent period. Timely cholecystectomy in patients with gallstone pancreatitis and providing alcohol intervention

and counseling in alcoholic AP cases are critical for preventing recurrences [20].

In assessing early outcomes, the Kaplan-Meier survival analysis demonstrated a high overall survival rate of 98% at six months. Since all deaths occurred during the initial hospitalization period, the survival curve plateaued after day 7, indicating no additional mortality during follow-up. The recurrence-free survival rate at six months was 90%, with most recurrences occurring within the first 60 days post-discharge. Although patients with gallstone-induced and alcohol-induced AP showed higher recurrence rates, the difference was not statistically significant, possibly due to the sample size.

The results of our study demonstrate that individualized treatment strategies applied following current guidelines in AP management lead to favorable early outcomes. Specifically, early severity assessment, controlled fluid resuscitation, effective pain management, early nutritional support, selective antibiotic use, and appropriate endoscopic interventions positively affected patient outcomes.

Limitations

There are some limitations to this study. Its retrospective design may increase the risk of bias in data collection and analysis. Additionally, being a single-center study limits the generalizability of the results. The lack of long-term follow-up data hinders the evaluation of the long-term effects and complications of AP. Future research should support these findings with larger patient populations and multicenter studies, and evaluate long-term outcomes.

CONCLUSION

The management of acute pancreatitis has evolved to prioritize individualized treatment strategies based on current evidence. Our study demonstrates that adhering to guidelines emphasizing early assessment, moderate fluid resuscitation, effective pain control, early nutritional support, selective antibiotic use, and timely endoscopic interventions results in favorable early outcomes. Future research should aim to refine these strategies further and explore new therapeutic options to enhance patient care.

Ethical statement

Ethics committee approval (number: KAEK/2024.10.225) was obtained from the Clinical Research Ethics Committee of Kanuni Sultan Süleyman Training and Research Hospital.

Authors' Contribution

Study Conception: AH; Study Design: AH; Supervision: AH; Funding: N/A; Materials: N/A; Data Collection and/or Processing: AH, AÇ; Statistical Analysis and/or Data Interpretation: AH, AÇ; Literature Review: AH, AÇ; Manuscript Preparation: AH and Critical Review: AH.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The effect of obesity on FibroScan parameters, cytokeratin-18, and fibroblast growth factor-21 levels

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ABSTRACT

Objectives: This study aimed to evaluate the differences in anthropometric, clinical, laboratory, and radiological parameters between obese and non-obese adolescents, focusing on the role of FibroScan parameters, Cytokeratin-18 (CK-18), and Fibroblast growth factor (FGF-21) in assessing metabolic and liver health.

Methods: Anthropometric data were collected, and blood pressure was measured. Laboratory parameters, including fasting glucose, insulin, HOMA-IR, liver enzymes, lipids, CK-18, and FGF-21 levels, were assessed. Liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) were measured using Fibroscan. Pearson's correlation analyses were performed to identify associations between CK-18/FGF-21 levels and metabolic parameters.

Results: A cross-sectional study involved 193 adolescents aged 10-18, including 87 obese and 106 non-obese participants. Obese adolescents had significantly higher fasting insulin, HOMA-IR, AST, ALT, GGT, uric acid, triglycerides, and LDL-cholesterol, with lower HDL-cholesterol levels (all $P < 0.001$). CK-18 ($P = 0.05$) and FGF-21 levels ($P = 0.002$) were elevated in the obese group. CAP and LSM values were also significantly higher in obese participants ($P < 0.001$). CK-18 and FGF-21 were positively correlated with fasting insulin, HOMA-IR, GGT, and triglycerides, indicating their potential as biomarkers for metabolic dysfunction. LSM correlated significantly with CK-18 ($P = 0.005$) and FGF-21 ($P = 0.007$).

Conclusions: Obese adolescents exhibited significant metabolic and liver dysfunction. Elevated CK-18 and FGF-21 levels, along with abnormal FibroScan parameters, highlight the importance of these biomarkers in identifying early liver injury and metabolic abnormalities. These findings suggest that CK-18 and FGF-21 may be valuable non-invasive tools for assessing and managing obesity-related liver disease.

Keywords: Adolescent obesity, non-alcoholic fatty liver disease (NAFLD), FibroScan, cytokeratin-18 (CK-18), fibroblast growth factor-21 (FGF-21)

Adolescent obesity has emerged as a significant public health concern globally, with its prevalence rising at an alarming rate. This condition is not merely a cosmetic issue but a serious health problem associated with an increased risk of various

comorbidities, including type 2 diabetes, cardiovascular diseases, and non-alcoholic fatty liver disease (NAFLD) [1]. Among the complications of obesity, NAFLD stands out due to its potential to progress to more severe liver conditions such as non-alcoholic

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steatohepatitis (NASH), fibrosis, and cirrhosis [2, 3]. Early detection and assessment of liver health in obese adolescents are therefore crucial to prevent the escalation of liver damage.

FibroScan®, a non-invasive imaging technique, has gained attention for its utility in assessing liver stiffness and quantifying liver fat content, providing valuable insights into hepatic steatosis and fibrosis [4, 5]. This technology offers a safer and more patient-friendly alternative to liver biopsy, making it particularly suitable for use in the pediatric population. However, while FibroScan® provides a clear picture of liver structure, biochemical markers such as CK-18 and FGF-21 offer a window into the underlying metabolic and cellular processes associated with liver health and obesity.

Cytokeratin-18 (CK-18) fragments, released during hepatocyte apoptosis, serve as a promising biomarker for detecting and monitoring liver cell injury and necrosis, particularly in the context of NASH [6]. Fibroblast Growth Factor-21 (FGF-21), a hormone involved in metabolic regulation, has been implicated in the pathophysiology of obesity and related liver diseases [7]. Elevated levels of FGF-21 have been associated with hepatic steatosis and insulin resistance, highlighting its potential role in identifying adolescents at risk of metabolic and liver complications [8, 9].

Despite the growing recognition of these tools, there remains a paucity of data on their combined application in assessing the health of obese adolescents. This study aims to bridge this gap by evaluating anthropometric, clinical, laboratory, and radiological differences between obese and non-obese adolescents, focusing on the roles of FibroScan parameters, CK-18, and FGF-21. By investigating these parameters and their interrelationships, we seek to enhance our understanding of the metabolic and hepatic alterations associated with adolescent obesity and identify potential biomarkers for early detection and management. This comprehensive analysis provides valuable insights into the complex interplay between obesity, liver health, and metabolic dysfunction in adolescents.

METHODS

Study Design and Participants

This cross-sectional study was conducted to evaluate

the differences in anthropometric, clinical, laboratory, and radiological parameters between obese and non-obese adolescents and to explore the roles of FibroScan parameters, CK-18, and FGF-21 in this context.

Inclusion and Exclusion Criteria

Inclusion criteria for the study were adolescents aged 10-18 years classified as either obese or of normal weight based on BMI percentiles. Exclusion criteria included any chronic disease, acute infection, or use of medications that could affect metabolic parameters.

Anthropometric and Clinical Measurements

Anthropometric measurements, including height, weight, and waist circumference, were taken using standardized procedures. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Blood pressure was measured using a calibrated sphygmomanometer, and systolic and diastolic pressures were recorded.

Laboratory Assessments

Blood samples were collected after an overnight fast. The following laboratory parameters were measured: fasting glucose, fasting insulin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), uric acid, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, ferritin, CK-18, and FGF-21. The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using the formula: $[\text{fasting insulin } (\mu\text{IU}/\text{mL}) \times \text{fasting glucose } (\text{mg}/\text{dL})] / 405$.

Assessment of the Liver Fibrosis

FibroScan (Echosens, Paris, France) assessed liver stiffness and hepatic steatosis. The controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) were recorded. CAP values are expressed in decibels per meter (dB/m) and LSM values in kilopascals (kPa).

Ethical Considerations

The Institutional Review Board (IRB) of the Ethics Committee of Konya Karatay University Faculty of Medicine (2021/19) approved the study protocol. Written informed consent was obtained from all participants and their guardians before enrollment.

Statistical Analysis

All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Data normality was confirmed using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median (25th–75th percentile) as appropriate. Independent samples t-test was used for normally distributed data, while the Mann-Whitney U test was employed for non-normally distributed data. Categorical variables were compared using the Chi-square test.

Correlation analyses between various parameters and CK-18/FGF-21 levels were conducted using Pearson's correlation coefficient (r). Significant correlations were considered those with $P < 0.05$. Receiver operating characteristic (ROC) curves were generated to determine the cut-off values for CK-18 and FGF-21 in distinguishing obese from non-obese adolescents. The area under the curve (AUC), sensitivity, and specificity were calculated.

RESULTS

The study included 193 participants aged 10-18 re-

cruited from a pediatric outpatient clinic. Of these, 87 were classified as obese based on their body mass index (BMI) percentiles for age and sex, and 106 were classified as controls with normal BMI percentiles.

The comparison of anthropometric and clinical parameters between the obese and control groups is detailed in Table 1. There was no significant difference in age between the groups (14.34 ± 2.64 vs. 14.32 ± 2.49 years, $P = 0.85$). The proportion of females was also similar between the groups (60% in control vs. 55% in obese, $P = 0.46$). Significant differences in waist circumference and blood pressure were observed. The obese group had a greater waist circumference (100.80 ± 16.41 cm vs. 69.23 ± 7.25 cm, $P < 0.001$). The systolic and diastolic blood pressures were also significantly elevated in the obese group (118.22 ± 11.56 mmHg vs. 108.87 ± 9.13 mmHg, $P < 0.001$ for systolic; 75.47 ± 9.35 mmHg vs. 68.77 ± 7.52 mmHg, $P < 0.001$ for diastolic).

The laboratory parameters are summarized in Table 2. Obese adolescents had significantly higher fasting insulin ($P < 0.001$), HOMA-IR ($P < 0.001$), liver enzymes (AST, ALT, GGT; all $P < 0.001$), uric acid ($P < 0.001$), and unfavorable lipid profiles, including higher triglycerides ($P < 0.001$) and LDL-cholesterol

Table 1. Comparison of anthropometric and clinical parameters of obese and control groups

	Control group (n=106)	Obese group (n=87)	P value
Age (year)	14.34 ± 2.64	14.32 ± 2.49	0.85 [±]
Female, n (%)	64 (60)	48 (55)	0.46 [¶]
Body weight (kg)	49.0 ± 10.87	80.68 ± 20.11	<0.001 [‡]
Body weight sd	-0.38 ± 0.82	2.58 ± 1.22	<0.001 [‡]
Height (cm)	157.47 ± 11.89	161.07 ± 10.99	0.02 [±]
Height sd	-0.07 ± 0.93	0.35 ± 1.16	0.005 [‡]
BMI (kg/m ²)	19.45 ± 2.32	30.69 ± 5.48	<0.001 [±]
BMI sd	-0.40 ± 0.79	2.43 ± 0.81	<0.001 [±]
Waist circumference (cm)	69.23 ± 7.25	100.80 ± 16.41	<0.001 [‡]
Systolic blood pressure (mm/Hg)	108.87 ± 9.13	118.22 ± 11.56	<0.001 [±]
Systolic blood pressure sd	0.1 ± 0.90	0.83 ± 0.88	<0.001 [±]
Diastolic blood pressure (mm/Hg)	68.77 ± 7.52	75.47 ± 9.35	<0.001 [±]
Diastolic blood pressure sd	0.45 ± 0.76	1.03 ± 0.77	<0.001 [±]

Data are shown as mean $\pm$ standard deviation or n (%). BMI=body mass index, sd=standard deviation

Chi-square test [±]Mann-Whitney U [‡]Independent samples t-test

Table 2. Laboratory parameters of groups

	Control group (n=106)	Obese group (n=87)	P value
Fasting glucose (mg/dL)	85.82±7.86	87.10±7.37	0.24 [‡]
Fasting insulin (μIU/mL)	11.81±5.73	31.31±19.35	<0.001 [±]
HOMA-IR	2.52±1.33	6.85±4.58	<0.001 [±]
AST (U/L)	17.42±4.25	24.83±13.78	<0.001 [±]
ALT (U/L)	12.862±6.85	38.66±36.77	<0.001 [±]
GGT (U/L)	10.90±3.70	22.30±14.78	<0.001 [±]
Uric acid (mg/dl)	4.03±0.96	5.48±1.55	<0.001 [±]
Total cholesterol (mg/dL)	143.97±30.27	162.57±29.87	<0.001 [±]
Triglycerides (mg/dL)	80.10±33.53	142.93±60.07	<0.001 [±]
HDL-cholesterol (mg/dL)	54.72±13.61	45.37±10.75	<0.001 [±]
LDL-cholesterol (mg/dL)	76.11±24.61	87.73±25.90	<0.001 [±]
Ferritin (ng/mL)	30.77±20.08	48.92±31.98	<0.001 [±]
CK-18 (ng/mL)	0.63±0.72 0.46 (0.22-0.70)	1.06±2.01 0.56 (0.29-1.07)	0.05 [±]
FGF-21 (pg/mL)	7.29±14.81 3.05 (0.7-9.67)	16.42±29.5 6.2 (2.2-16.4)	0.002 [±]

Data are shown as mean±standard deviation or median (25%-75%). CK-18=cytokeratin-18, FGF-21=fibroblast growth factor-21, AST=aspartate aminotransaminase, ALT=alanine aminotransaminase, GGT=gamma-glutamyl transferase, HDL=high-density lipoprotein, LDL=low-density lipoprotein, HOMA-IR=Homeostasis model assessment insulin resistance index

[±]Mann-Whitney U, [‡]Independent samples t-test

(P<0.001), and lower HDL-cholesterol (P<0.001). CK-18 levels were elevated in the obese group (0.56 vs. 0.46 ng/ml, P=0.05), as were FGF-21 levels (6.2 vs. 3.05 pg/mL, P=0.002).

Table 3 presents the Fibroscan parameters. The controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) were significantly higher in the obese group. The CAP values were 274.40±55.41

dB/m compared to 198.08±30.60 dB/m in the control group (P<0.001). Similarly, the LSM values were elevated in the obese group (5.40±1.50 kPa vs. 4.13±0.71 kPa, P<0.001).

The correlation analyses between anthropometric parameters and FGF-21/CK 18 levels are depicted in Table 4. There was a significant positive correlation between body weight standard deviation and FGF-21

Table 3. Radiological parameters of groups

	Control group (n=106)	Obese group (n=87)	P value
CAP (dB/m)	198.08±30.60 195.5 (180.5-223)	274.40±55.41 270 (237-312)	<0.001 [‡]
LSM (kPa)	4.13±0.71 4.1 (3.6-4.6)	5.40±1.50 5 (4.4-6.1)	<0.001 [±]

Data are shown as mean±standard deviation or median (25%-75%), CAP=controlled attenuation parameter. LSM=liver stiffness measurement

[‡]Independent samples t-test, [±]Mann-Whitney U

Table 4. Correlation analyses between anthropometric parameters and FGF-21/CK 18 levels in study groups

Parameters	CK 18		FGF-21	
	r	P value*	r	P value*
Age	-0.04	0.55	-0.07	0.35
Body weight	0.10	0.18	0.12	0.09
Body weight sd	0.11	0.14	0.15	0.03
Height	0.07	0.32	0.06	0.36
Height sd	0.11	0.13	0.12	0.11
BMI	0.08	0.25	0.13	0.08
BMI sd	0.09	0.21	0.15	0.04
Waist circumference	0.10	0.17	0.16	0.02

CK-18=cytokeratin-18, FGF-21=fibroblast growth factor-21, BMI=body mass index

*Pearson correlation

Table 5. Correlation analyses between laboratory parameters and FGF-21/CK 18 levels in study groups

Parameters	CK 18		FGF--1	
	r	P value*	r	P value*
Fasting glucose	0.14	0.05	0.19	0.01
Fasting insulin	0.24	0.001	0.22	0.003
HOMA-IR	0.26	<0.001	0.24	0.001
AST	0.68	0.37	0.41	0.58
ALT	0.11	0.12	0.09	0.22
GGT	0.15	0.03	0.15	0.04
Uric acid	0.15	0.04	0.19	0.009
Total cholesterol	-0.03	0.67	0.04	0.60
Triglycerides	0.16	0.03	0.233	0.002
HDL-cholesterol	-0.05	0.48	0.003	0.97
LDL-cholesterol	-0.80	0.29	-0.14	0.06
Ferritin	0.12	0.09	0.14	0.05

CK-18=cytokeratin-18, FGF-21=fibroblast growth factor-21, AST=aspartate aminotransaminase, ALT=alanine aminotransaminase, GTT=gamma-glutamyl transferase, HDL=high-density lipoprotein, LDL=low-density lipoprotein

*Pearson correlation, in multivariate regression analysis of correlated parameters, no independent risk factor effect could be demonstrated.

Table 6. Correlation analyses between CAP/LSM and FGF-21/CK 18 levels in study groups

Parameters	CK 18		FGF-21	
	r	P-value*	r	P-value*
CAP	0.12	0.10	0.11	0.13
LSM	0.21	0.005	0.20	0.007

CK-18=cytokeratin-18, FGF-21=fibroblast growth factor-21, CAP=controlled attenuation parameter, LSM=liver stiffness measurement

*Pearson correlation

Table 7. CK18 and FGF-21 cut-off values of obese and control group

Variables	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	P value
CK-18 (ng/mL)	0.53	52.7 (40.7-64.7)	60.0 (49.7-69.7)	0.588 (0.510-0.662)	0.04
FGF-21 (pg/mL)	2	75.9 (65.3-84.6)	46.6 (36.1-57.5)	0.638 (0.562-0.710)	0.001

CK-18=cytokeratin-18, FGF-21=fibroblast growth factor-21

levels ($r=0.15$, $p=0.03$) and between BMI standard deviation and FGF-21 levels ($r=0.15$, $P=0.04$). Additionally, waist circumference was positively correlated with FGF-21 levels ($r=0.16$, $P=0.02$).

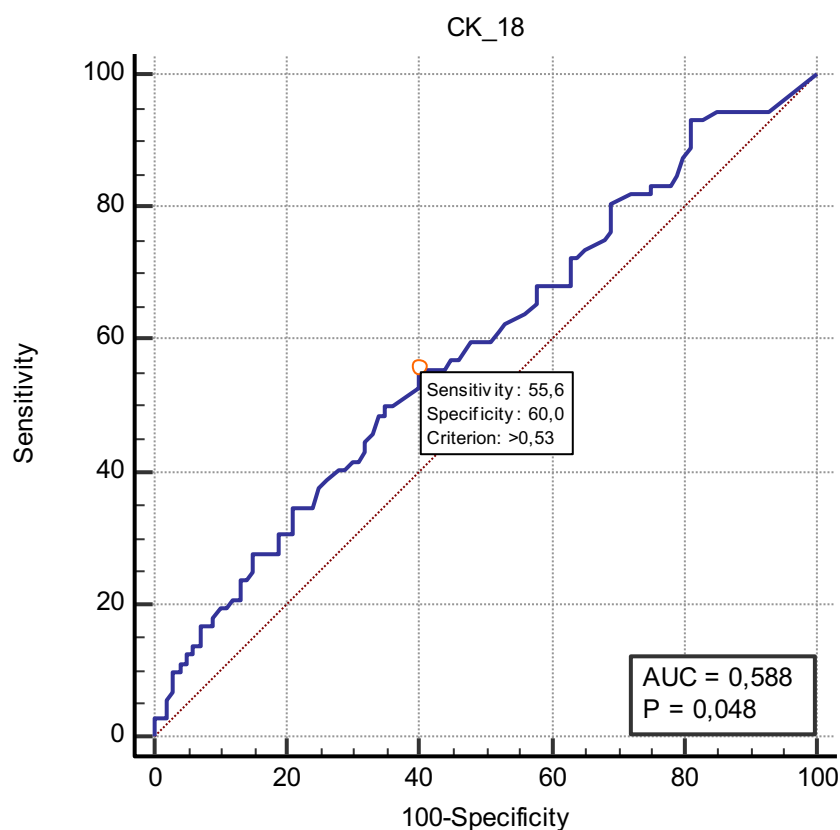
CK-18 showed significant positive correlations with fasting insulin ($r=0.24$, $p=0.001$), HOMA-IR ($r=0.26$, $P<0.001$), GGT ($r=0.15$, $P=0.03$), uric acid ($r=0.15$, $P=0.04$), and triglycerides ($r=0.16$, $P=0.03$), indicating its association with insulin resistance and liver enzyme activity (Table 5).

Similarly, FGF-21 was positively correlated with fasting glucose ($r=0.19$, $P=0.01$), fasting insulin

($r=0.22$, $P=0.003$), HOMA-IR ($r=0.24$, $P=0.001$), GGT ($r=0.15$, $P=0.04$), uric acid ($r=0.19$, $P=0.009$), and triglycerides ($r=0.23$, $P=0.002$), highlighting its involvement in metabolic dysfunction and lipid abnormalities (Table 5).

Liver stiffness measurement (LSM) was positively correlated with both CK-18 ($r=0.21$, $P=0.005$) and FGF-21 ($r=0.20$, $P=0.007$). However, the controlled attenuation parameter (CAP) did not significantly correlate with CK-18 or FGF-21 levels (Table 6).

The cut-off values for CK-18 and FGF-21 for distinguishing between obese and control groups are pre-

**Fig. 1. ROC curve. CK 18 cut-off value according to the study and control group.**

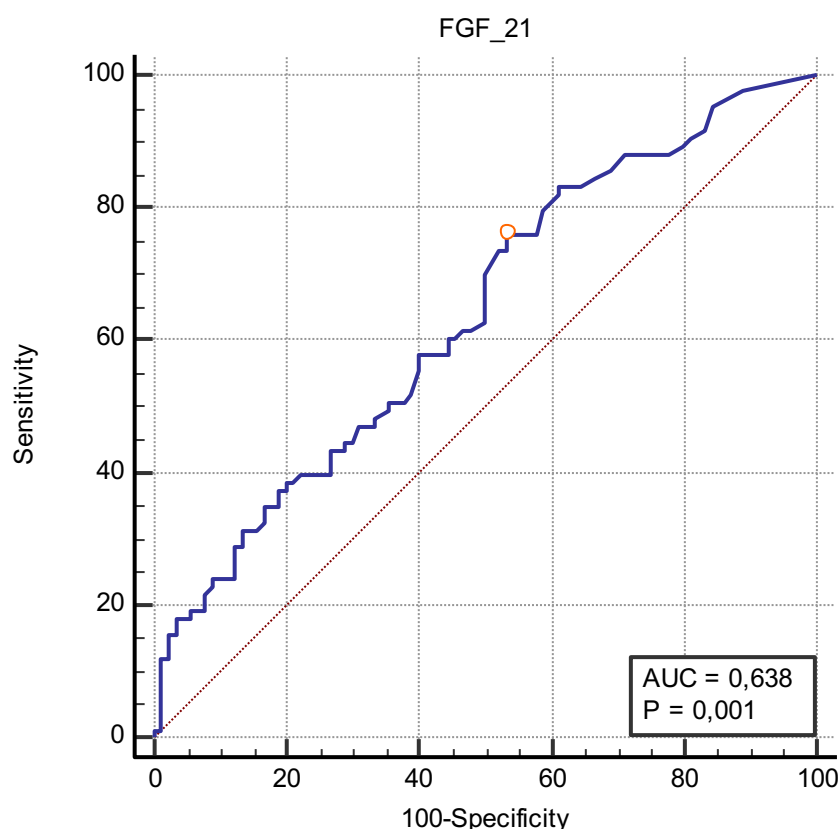


Fig. 2. ROC curve. FGF-21 cut-off value according to the study and control group.

sented in Table 7. The optimal cut-off value for CK-18 was 0.53 ng/mL, with a sensitivity of 52.7% and specificity of 60.0% (AUC=0.588, P=0.04) (Fig. 1). For FGF-21, the cut-off value was 2 pg/mL, with a sensitivity of 75.9% and specificity of 46.6% (AUC=0.638, P=0.001)(Fig. 2).

DISCUSSION

This study revealed several significant differences between obese and non-obese adolescents across various parameters. Obese adolescents exhibited significantly higher waist circumference compared to their non-obese counterparts. Clinically, they also had elevated systolic and diastolic blood pressures. Laboratory results indicated that obese adolescents had higher fasting insulin levels, HOMA-IR, AST, ALT, GGT, uric acid, total cholesterol, triglycerides, and LDL-cholesterol levels, while HDL-cholesterol levels were lower. Radiologically, FibroScan assessments showed significantly higher CAP and LSM values in the obese

group, indicating more significant hepatic steatosis and stiffness. Additionally, CK-18 and FGF-21 levels were significantly elevated in obese adolescents, with positive correlations between these biomarkers and various metabolic and anthropometric parameters.

Numerous studies have demonstrated the correlation between FGF-21 levels, which are involved in metabolic control, and obesity. Several investigations indicate that serum FGF-21 levels are markedly elevated in obese children relative to their lean counterparts [9, 10]. A study by Baek *et al.* [11] revealed that serum FGF-21 levels were elevated in obese children with metabolic syndrome compared to their counterparts without metabolic syndrome. In a comparable study, Li *et al.* [12] demonstrated that circulating FGF-21 levels were elevated in obese children. A recent study by El-Masry *et al.* [13] indicated that serum FGF-21 levels were significantly elevated in obese children; however, it could not serve as a reliable predictor for metabolic disorders, including waist circumference, fasting blood glucose, insulin, HOMA-IR, and lipid profile in prepubertal obese children. The

study revealed that FGF-21 levels were markedly elevated in obese adolescents relative to the control group. This result aligned with the prior investigations [9-11]. Moreover, substantial positive correlations were identified between FGF-21 levels and anthropometric metrics such as body weight standard deviation, BMI standard deviation, and waist circumference, as well as laboratory results including fasting blood glucose, GGT, insulin, HOMA-IR, uric acid, and triglyceride levels. In contrast to our study, El-Masry *et al.* [13] identified a negative association between serum FGF-21 and BMI in obese children, with no significant correlations observed with fasting blood glucose, insulin, HOMA-IR, or lipid profile. Furthermore, whereas a positive association was identified between blood FGF-21 and HDL levels in the aforementioned study, our analysis discovered no significant correlation between these two parameters. We examined the connection between serum FGF-21 levels and liver CAP and LSM values obtained by the Fibroscan equipment. Previous investigations have identified a correlation between elevated FGF-21 levels and obesity and fatty liver disease [14, 15]. Rusli *et al.* [16] demonstrated a strong correlation between serum FGF-21 levels and hepatic fat content in mice with NAFLD. Another study, including adults, revealed that the sensitivity and specificity of FGF-21 for diagnosing NAFLD were 72.6% and 85.1%, respectively, whereas for diagnosing NASH, the sensitivity, and specificity were 53.7% and 71.9%, respectively [17]. Giannini *et al.* [18] revealed a link between serum FGF-21 levels and liver fat accumulation as well as liver damage in obese young individuals. Consequently, FGF-21 has been proposed as a possible biomarker for NAFLD in adults and children [19-22]. Our investigation revealed a substantial positive association between LSM measurements obtained via Fibroscan and serum FGF-21 levels; however, no positive correlation was observed with CAP measurements. The serum FGF-21 cut-off value demonstrated moderate sensitivity but low specificity in differentiating between the non-obese control group and obese adolescents, according to our study.

CK-18 is the major intermediate filament protein in hepatocytes. There is a strong correlation between hepatocyte apoptosis and the release of caspase-coated and uncoated M30 and M65 fragments of cytokeratin-

18 and their levels in serum [23]. It was demonstrated in various studies that serum CK-18 levels are elevated in patients compared with simple fatty liver disease. These findings have shown a positive correlation between high CK-18 levels and inflammation, steatosis severity, and liver fibrosis [6, 24, 25]. CK-18 fragments have recently been confirmed as a marker of NASH and even defined as the most promising non-invasive test for the diagnosis and management of NASH in recent NAFLD guidelines [26]. In a study conducted by Lebensztejn *et al.* [27] in children with NAFLD, CK-18 levels were significantly higher in children with fibrosis compared to those without fibrosis. In the same study, the sensitivity and specificity in detecting fibrosis using serum CK-18 levels were found to be 79% and 60%, respectively, and it was concluded that it may be appropriate to determine serum CK-18 levels to detect fibrosis in children with NAFLD. Mandelia *et al.* [28] reported that CK-18 level was a promising new biomarker for fibrosis in children with NAFLD. In our study, CK-18 levels were found to be higher in the obese group compared to the control group. Simultaneously, a significant positive correlation was found between LSM levels, indicators of fibrosis, and CK-18 levels. However, the performance of the CK-18 level was insufficient for diagnosing NAFLD due to the low area under the receiver operating characteristics curve, according to our study. Similarly, a study by Koot *et al.* [29] found that novel biomarkers such as FGF-21 and CK-18 and non-invasive predictive scores did not have sufficient diagnostic accuracy to diagnose and exclude NAFLD in severely obese children and adolescents.

Limitations

One of the limitations of our study is that we did not use the Steatotic Liver Disease (SLD), Metabolic Associated Steatotic Liver Disease (MASLD), and Metabolic Associated Steatohepatitis (MASH) terminology because we did not assess the full range of metabolic parameters required for these classifications. Our focus was limited to identifying fatty liver using non-invasive FibroScan parameters rather than conducting a comprehensive metabolic evaluation. Future studies incorporating detailed metabolic assessments would allow for the application of these standardized terms.

CONCLUSION

In conclusion, obesity and NAFLD in teens rise gradually, like in all age groups. Early identification and prevention of NAFLD are crucial since certain people can develop NASH and hepatic fibrosis. Liver biopsy, an invasive diagnostic procedure, is not always possible or repeatable in children and adolescents. Thus, reliable and reproducible non-invasive imaging technologies like Fibroscan and serum indicators are essential for disease diagnosis and monitoring. This study found a correlation between serum FGF-21 and CK-18 in obese NAFLD patients and Fibroscan results. However, both serum indicators limited diagnostic sensitivity and specificity. Since hepatic apoptosis and fibrosis had not yet formed, serum CK-18 levels were ineffective in diagnosing adult NAFLD patients. Noninvasive imaging and serum biomarkers would be better for early NAFLD diagnosis and disease progression monitoring in children and adolescents.

Ethical Statement

The study received approval from the the Institutional Review Board (IRB) of the Ethics Committee of Konya Karatay University Faculty of Medicine (2021/19). Written informed consent was obtained from all participants and their guardians before enrollment.

Authors' Contribution

Study Conception: MK; Study Design: NK; Supervision: MK; Funding: MK; Materials: MK; Data Collection and/or Processing: MK; Statistical Analysis and/or Data Interpretation: NK; Literature Review: NK; Manuscript Preparation: NK; and Critical Review: MK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Retention of knowledge after basic life support course for professional football coaches: A prospective study

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ABSTRACT

Objectives: Teaching more people high-quality CPR through more efficient training methods can improve the rates and quality of Cardiopulmonary resuscitation (CPR) in cases of out-of-hospital cardiac arrest and help save more lives. In this study, we aimed to provide online Basic Life Support (BLS) training to football coaches who are in close contact with the risk group, and to examine the effectiveness of the training, to what extent they retained basic life support knowledge after completing the training program, and to determine the time of booster training.

Methods: Online BLS training was provided to football coaches. Pre- and post-tests were administered to measure the effectiveness of online BLS training. A retention test was administered to one group after 3 months and to one group after 6 months to evaluate the permanence of the training.

Results: Knowledge gain was significant immediately after the BLS course. There was no difference between the two groups in the post-training test results. Overall level of knowledge decreased significantly after three and six months. While there was a 5-point decrease in the retention test performed after three months, a 12-point reduction after six months.

Conclusions: There is no clear answer yet regarding the time and frequency of booster training. Rather than single training, the most effective approach will be to integrate booster content with short training videos at intervals of 3-6 months. Online BLS training videos can serve as an alternative.

Keywords: Basic cardiac life support, cardiopulmonary resuscitation, online education

Exercise-induced sudden cardiac arrest (SCA) is defined as a cardiac arrest occurring outside of a hospital setting during physical exertion, sports, or exercise, or within one hour following the cessation of such activities. SCA represents the leading cause of sudden death among competitive athletes during physical activity, with survival rates remaining low—only one in three patients survive the event [1]. Evidence indicates that bystander interventions, such

as cardiopulmonary resuscitation (CPR) and the use of automated external defibrillators (AED), are strongly associated with improved survival outcomes after SCA. A systematic review of survivors following exercise-related SCA demonstrated that up to 80% of individuals had an initial shockable rhythm. Additionally, 56-93% of survivors had received bystander-administered CPR and AED applications. These findings underscore the critical role of immediate bystander in-

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tervention in maximizing survival following exercise-related SCA [2]. Given that coaches are likely to be present during such emergencies, the American Heart Association and the American College of Cardiology recommend that this group receive formal training in recognizing cardiac events, utilizing AEDs, and performing effective CPR (Class I recommendation; Level of Evidence B) [3].

The International Liaison Committee on Resuscitation, in its formula for survival in cardiac arrest, emphasized that efficient training is one of the three multipliers that will affect survival [4, 5]. Expanding access to high-quality CPR training through more efficient instructional methods can enhance both the frequency and quality of CPR performed during out-of-hospital cardiac arrest, ultimately increasing survival rates and saving more lives [6]. Therefore, it has been advocated for so long that lay-rescuer CPR training be targeted to those most likely to be at the scene of out-of-hospital cardiac arrest [7]. For this reason, ensuring that the team in charge of sports fields, and especially football fields, which are widely accepted and participated in all over the world, receive periodic training to be adequate and effective in cardiopulmonary resuscitation will be of great benefit to both the athletes and the spectators, and will reduce sudden deaths.

Studies show that survival rates of out-of-hospital cardiac arrest cases can increase two to three times if effective basic life support is provided [8]. Even if adequate training is provided, basic life support skills acquired decrease over time. Sustaining effective education is only possible with booster training. This is also recommended in the AHA 2020 guide as providing booster training [9]. Although AHA guidelines show evidence that frequent training improves CPR skills, there is no definitive information on when and how often to perform booster training after initial training. In some studies, booster training was provided for various periods between 3 to 15 months, and all of them were shown to give positive results compared to situations where no booster training was given. In another study, booster training was given to healthcare personnel every month, and it was found to be more effective than the training given at 3, 6 and 12 months. It is obvious that these trainings, which require regular participation every month, are not applicable for public rescuers. As a result of all these

studies, it has been shown that it is necessary to provide at least one booster training after the initial training, whether for healthcare personnel or lay rescuers [10, 11]. FIFA has also emphasized in its emergency action plan for sudden cardiac arrest the training of potential first responders and their rehearsal at least once a year.

Online education has become an integral part of the field of healthcare and medical education, especially as technology continues to advance. The retention of information learned in training can directly impact the performance of life-saving techniques and skills in real-life emergencies. Therefore, assessing knowledge retention after online basic life support training is crucial to ensure the effectiveness and quality of training in this critical area [12]. In this study, we aimed to provide online BLS training to football coaches who are in close contact with the risk group, and to examine the effectiveness of the training, to what extent they retained basic life support knowledge after completing the training program, and to determine the effect of booster training.

METHODS

The study received approval from the Balıkesir Atatürk City Hospital Scientific Research Ethics Committee (Decision no: 2023/1/10 and date: 06.04.2023) was carried out in compliance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participating football coaches before their enrollment in the study. Additionally, each coach provided informed consent following regulations under the Personal Data Protection Authority before responding to the questionnaire. The study was conducted between May and October 2023.

Our study was conducted in six parts:

Part 1, a pre-test was administered to assess the baseline knowledge of all coaches regarding BLS. Part 2, the BLS course was given online to all coaches. Part 3, the same assessment (post-test) was administered immediately following the completion of the course to evaluate the improvement in knowledge. Part 4, the coaches were randomly assigned into two groups (Group 1 and Group 2) using simple randomization.

Part 5, the retention test was performed in group 1 after three months to evaluate the permanence of the information. (16 people did not attend the exam).

Part 6, the retention test was performed in group 2 after six months to evaluate the long-term retention of the information.

Description of Courses and Exams

The course was designed as an online training program tailored for professional football coaches and was conducted by a team of three emergency medicine specialists certified to provide BLS training. This training is a mandatory requirement for obtaining the Union of European Football Associations coaching certificate. Football coaches completed the course by accessing pre-recorded instructional videos over 7 days. The online format allowed participants to complete the training at their convenience, whether at home, work, or any location with internet access. The course was accessible from any internet-enabled device. To ensure active participation, a pop-up notification appeared on the screen every 5 minutes during the video sessions. Participants were required to click on the alert within 10 seconds; failure to do so resulted in the video being restarted from the beginning. Similarly, if the video was fast-forwarded, the session was marked as incomplete and had to be replayed in its entirety. Additionally, no option to increase the playback speed of the videos was provided.

This course, modeled after the American Heart Association's (AHA) BLS course, aimed to equip participants with the necessary skills to promptly recognize various life-threatening emergencies and provide effective interventions. The key topics covered in the course included: (1) High-quality CPR for adults, children, and infants; (2) AHA Chain of Survival with a focus on BLS components; (3) Early use of an automated external defibrillator (AED); (4) Effective ventilation using a barrier device; (5) The role of teamwork in multi-rescuer resuscitation and the importance of effective team performance during CPR; (6) Management of foreign body airway obstruction (choking) in adults and infants; and (7) Approach to life-threatening trauma, particularly head and spinal injuries.

This comprehensive training aimed to enhance participants' competencies in delivering timely and effective life support during emergencies.

The exams were administered by the same team of emergency medicine specialists. The exam content was aligned with the AHA's BLS guidelines and consisted of 40 multiple-choice questions, each with four options. Participants could score a maximum of 100 points, with no penalties for incorrect answers. To ensure fairness, the order of questions and answer options was randomized for each participant. However, the evaluation was conducted on a question-by-question basis. The exam was only accessible via a computer and required the use of a camera for monitoring to prevent cheating. Participants were granted a single login session, and the system did not permit simultaneous logins from different locations using the same credentials. If a login attempt was made from another location, the system automatically terminated the session. Upon accessing the exam system, participants' computers were monitored to detect whether other websites or applications were opened. Eye-tracking technology was employed through the camera to monitor where participants looked on the screen, for how long, and how frequently. This provided insights into their gaze patterns, focus areas, and potential distractions. Additionally, the entire examination process was recorded via video to maintain the integrity of the evaluation.

Sample

The sample size was determined using G*Power[®] software (v.3.1.9.4). Based on an estimated effect size (d) of 0.5, an alpha level (α) of 0.05, and a power of 0.95, the minimum required sample size for the t-test was calculated to be 220 participants. The final study sample included 242 volunteer football coaches who completed the online BLS training within the designated time frame. A total of 226 volunteers participated in the entire study. Of those included in the study, 211 were male and 15 were female. The median age was 36 years. 195 football coaches had not received any previous BLS training. 13 of them had a high school degree, 204 had a bachelor's degree and 9 had a master's degree. Of these, 211 had previously performed basic life support. The coaches had not attended any other formal BLS or AED courses during the 2 tests.

Including Criteria

1. To be a professional football coach

2. Giving consent for the study
3. Having received BLS training within the specified time and fully participating in all tests.

The study design is presented in Fig. 1.

Measuring Instrument

The first section of the study collected demographic information, including age, gender, educational background, prior participation in any BLS course, and previous experience in a situation requiring BLS.

The second section consisted of a validated BLS knowledge assessment containing 40 multiple-choice questions administered before the training, immediately after the training, and 3-6 months post-training. Each question had five answer options, with only one correct answer. Each correct response was worth 2.5 points, allowing participants to achieve a maximum score of 100 points. The test was administered before and immediately after training. In Part 5, the test was administered again with the same questions three months later for group 1, and in Part 6, six months

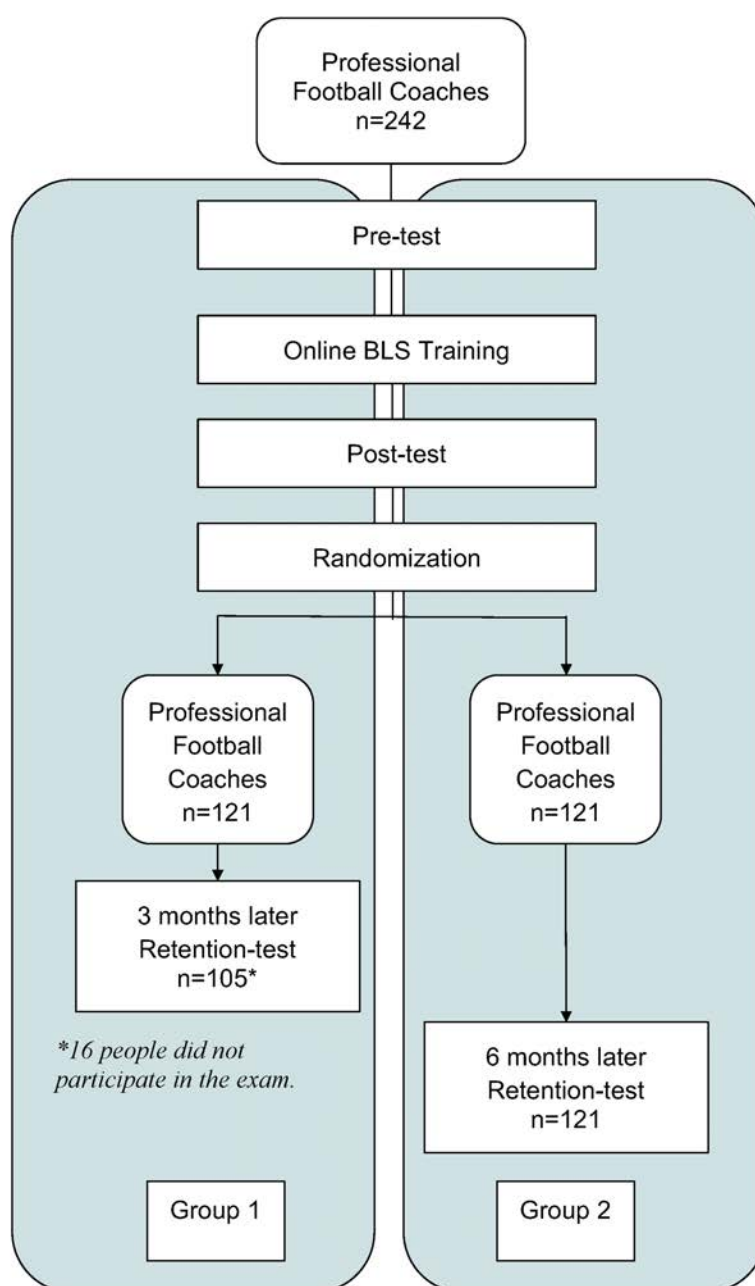


Fig. 1. Flow chart.

later for group 2. Informed consent (within the scope of PDPL) was obtained from each coach before answering the questions in each study.

Practical Skill Test

No practical skill assessment was performed for the coaches.

Statistical Analysis

Statistical analyses were conducted using SPSS version 23 (SPSS Inc, Chicago, IL, USA). The normality of the data distribution was assessed through both visual methods (histograms) and analytical tests (Kolmogorov-Smirnov). Descriptive statistics were presented as mean and standard deviation for normally distributed variables and as median, interquartile range (IQR), minimum, and maximum values for non-normally distributed variables. Data for Group 1 and Group 2 do not conform to normal distribution. Pairwise comparisons for Group 1 and Group 2 were calculated using the chi-square test and Mann Whitney-u test. Repeated measurements were examined using the Friedman test. Wilcoxon test was applied to find the difference between the groups. Type-1 error level was determined as 5% for statistical significance.

RESULTS

Baseline Characteristics

For baseline characteristics, refer to Table 1. The median age of participants in Group 1 was 36 years (IQR: 26-51), while the median age in Group 2 was 36 years (IQR: 28-52). Group 1 consisted of 96 males and 9 females, whereas Group 2 included 115 males and 6 females. In terms of educational background, 5 coaches in Group 1 and 4 coaches in Group 2 had completed a master's degree.

Theoretical Test Results

It was determined that the test results of the 1st group were higher before the training (Pre-test: Group 1=63.6±5.2; Group 2=55.2±4.9; P<0.001). As expected, knowledge gain was significant immediately after the BLS course (Pre-test > Post-test increase P<0.001 for both groups). However, there was no difference between the two groups in the post-training test results (Post-test: Group 1=80.8±5.8; Group 2=81.6±4.7; P=0.091). While there was a 5-point decrease in the retention test performed after three months (78, IQR: 73-78; P<0.001), there was a 12-point decrease in the test performed after six months

Table 1. Baseline characteristics

		Group 1 (3-Months)	Group 2 (6-Months)	P value*
Age (years), Median (IQR)		36 (26-51)	36 (28-52)	0.799
Gender, n (%)	Female	9 (8.6)	6 (5)	0.277
	Male	96 (91.4)	115 (95)	
Educational level, n (%)	High school	8 (7.6)	5 (4.1)	0.441
	College	92 (87.6)	112 (92.6)	
	Master Degree	5 (4.8)	4 (3.3)	
Those who have previously been in an emergency situation where BLS was required, n (%)	Yes	93 (88.6)	118 (97.5)	
	No	12 (11.4)	3 (2.5)	
	1 time	77 (73.3)	110 (90.9)	
	2 times	5 (4.8)	3 (2.5)	
	3 times	7 (6.7)	1 (0.8)	
	4 times	4 (3.8)	4 (3.3)	

IQR=Interquartile range

*Mann Whitney U

Table 2. Theoretical test results

	Group 1 (3-months)	Group 2 (6-months)	p value*
Pre-test			
Mean±SD	63.6±5.2 ^a	55.2±4.9 ^d	<0.001
Median (IQR)	63 (63-68)	55 (55-60)	a>d
Min-Max	28-70	15-60	
Post-test			
Mean±SD	80.8±5.8 ^b	81.6±4.7 ^e	0.091
Median (IQR)	83 (78-83)	80 (80-85)	
Min-Max	35-88	50-90	
Retention-test			
Mean±SD	76.8±5.4 ^c	68.3±6.3 ^f	<0.001
Median (IQR)	78 (73-78)	68 (65-70)	c>f
Min-Max	33-83	40-85	
P value**	<0.001	<0.001	
	b>a	e>d	
	b>c	e>f	
	c>a	f>d	

SD=Standard deviation, IQR=Interquartile range, Min=Minimum, Max=Maximum
*Mann Whitney U, **Friedman Test

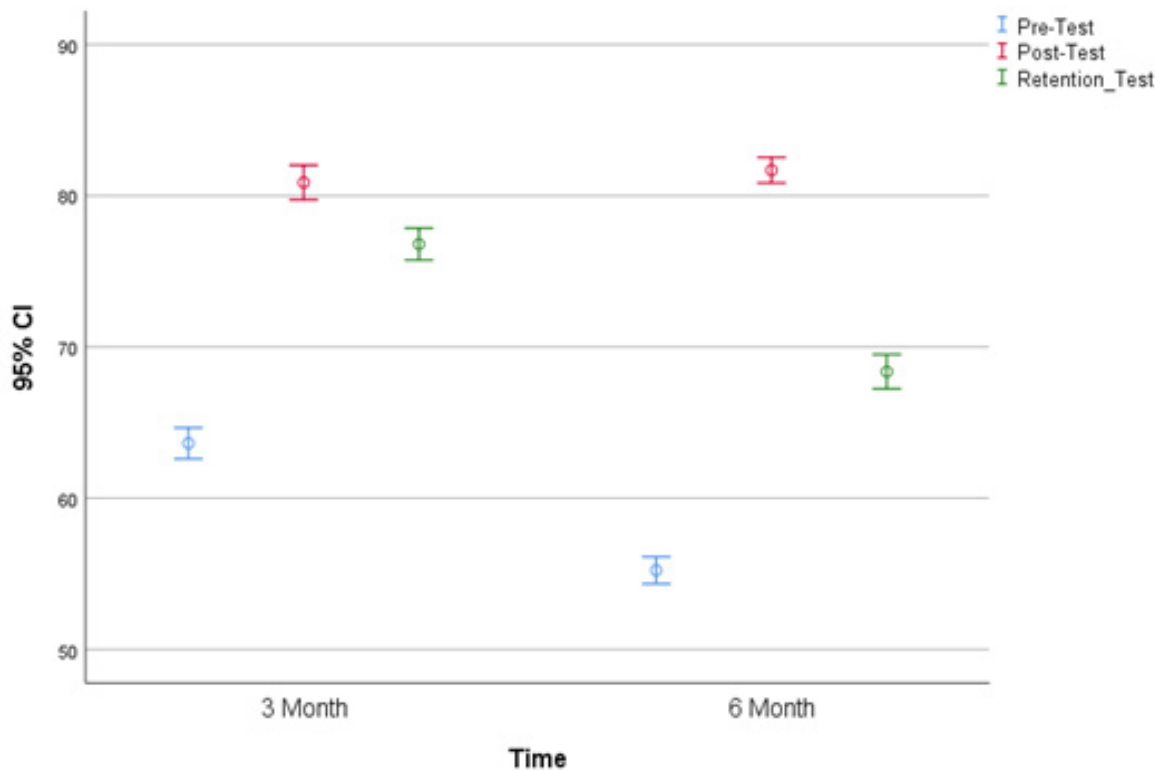


Fig. 2. Theoretical test results.

(68, IQR: 65-70; $P < 0.001$). The between-group comparison of retention test scores demonstrated that the six-month group had significantly lower scores than the three-month group ($P < 0.001$). Additionally, retention test scores at both three and six months remained significantly higher than the pre-test baseline levels (Group 1: $P < 0.001$; Group 2: $P < 0.001$). The comparative results for Theoretical Test are shown in Fig. 2. and Table 2.

DISCUSSION

Online basic life support training is increasingly accepted in medical education and emergency response fields today. Resuscitation guides also say that online courses can be used as resources in basic life support training. This method offers a powerful option, especially for individuals who find it difficult to study in a traditional classroom setting due to time constraints and physical limitations. In our study, pre-course and post-course tests were conducted to evaluate the effectiveness of the online basic life support training program. The data obtained shows that the post-course test results are significantly higher than the pre-course test results ($P < 0.001$). This finding, as expected, in line with the literature, shows that online basic life support training can be effectively implemented and used as an alternative to traditional training methods [13, 14].

It is vitally important that BLS qualifications are maintained over the long term. Even if a satisfactory level of theoretical learning is achieved after a course or training, the permanence of life support skills tends to decrease over time. Maintaining BLS information, like most training, requires regular reminder training. Online education can make this easier. Unfortunately, sufficient evidence is not currently available in the literature to recommend optimal intervals or methods for BLS booster training, although numerous studies are showing that skills decline within the 3 -12-month time frame after initial BLS training [15-17]. Although it is important to measure the effectiveness of online basic life support training, examining the permanence of knowledge through evaluations made immediately afterward is at least as important as post-training evaluation. Our study is also compatible with the results of previous studies in the literature where similar per-

manence tests were applied. Our main finding that stands out is that BLS information decreases over time starting from the third month and when it approaches the sixth month, nearly half of the newly acquired information is lost.

In our study, the theoretical knowledge level decreased from a success level of 83% in the post-training evaluation to a success level of 78% after 3 months, while this loss rate was much higher at 6 months. In a study conducted with medical students on compression-related issues, it was determined that the knowledge level dropped by almost half after 3 months, and there was also a serious decrease in general competence in self-assessment [18]. It is known that frequent BLS training increases the rescuer's self-confidence, the desire to perform CPR when needed, and general resuscitation performance. Therefore, it is seen that reinforcement training is seriously important in terms of increasing not only the knowledge level but also the person's self-confidence.

It has been reported that the chance of survival decreases by approximately 10% for every minute CPR is not initiated [19]. It should not be forgotten that time is one of the most critical factors for effective CPR. In our study, it was determined that 93% of the coaches had been in an environment requiring BLS intervention at least once before. This shows how important and appropriate the target audience chosen for education is. Although FIFA has emphasized the training of potential first responders in its emergency action plan for sudden cardiac arrest and their rehearsal at least once a year, our study has shown that even in as little as three months, the level of knowledge decreases [20]. Considering that professional medical teams are not always present on the fields, it is clear that football coaches, who are most likely to be near the athletes, will play the main role in BLS. For this reason, after the first BLS course for football coaches, we recommend booster training with the help of educational short videos in 3-6-month periods.

Although rare, sudden cardiac death in young athletes who represent a healthy human model is a traumatic event that has a great impact on society. When a prominent athlete suddenly collapses and either dies during a game or requires immediate BLS intervention, it resonates as a global tragedy. Such incidents underscore the significant impact of sudden athlete deaths, extending beyond the sports community to af-

fect the general public. Despite clear recommendations from athletic organizations and medical societies worldwide, there are still unfortunate instances where CPR is not initiated at the scene, and tragically, these situations have a 100% mortality rate. [21]. However, it is now known to everyone that BLS training increases bystander CPR rates, which is of extraordinary importance in terms of survival [22]. High-quality CPR with rapid defibrillation is the focus of resuscitation in adult and pediatric cardiac arrest cases. Although it is known that cardiac arrest in most athletes is caused by a shockable rhythm, an AED was used in only 31% of these cases [2]. Although shockable rhythms are in the majority, the fact that AED use is at such a low level of 31% shows that booster training, especially regarding AED use, is mandatory. The results of our study support that these training can be given online with short training videos at 3-6 month intervals without losing their effectiveness, and when combined with the information in the literature, we think that these training can play a critical role in increasing the survival chances of athletes.

Systematic dissemination of training will be a very important step towards protecting athlete and public health by increasing the quality of responses to emergencies on football fields, especially as football coaches who cannot receive training in a traditional classroom environment due to difficult working conditions and time constraints receive basic life support training online. As far as we found in the literature review, our study is the first study in which the permanence of football coaches' basic life support theoretical knowledge was evaluated after online training and 3-6 months later and tested.

Limitations

In our study, no practical training or practical exam was conducted. Football coaches' confidence levels and satisfaction with the training they received before and after the course were not measured.

CONCLUSION

Although we found in our study that BLS knowledge decreased three months after training, there is no clear answer yet regarding the time and frequency of booster training. Rather than being content with a sin-

gle training, it is clear that the most effective approach will be the integration of booster content with the help of short training videos at intervals of 3-6 months after the first course. For groups who cannot attend continuous traditional training, online BLS and especially AED training videos can serve as an alternative. We also support the slogan of the FIFA health committee, 'No AED, No Match, No Training', and we would like to point out that booster education is equally important to keep the survival rate at 80%.

Ethical Statement

The study received approval from the Balıkesir Atatürk City Hospital Scientific Research Ethics Committee (Decision no: 2023/1/10 and date: 06.04.2023) was carried out in compliance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participating football coaches before their enrollment in the study.

Authors' Contribution

Study Conception: MY, AOK; Study Design: TŞ, AOK, BK; Supervision: TŞ, AOK; Funding: N/A; Materials: MY, AOK; Data Collection and/or Processing: BK, TŞ; Statistical Analysis and/or Data Interpretation: AOK, MY; Literature Review: MY, TŞ, BK; Manuscript Preparation: MY, AOK; and Critical Review: BK, MY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Assessment of food allergies in patients under two years of age with skin manifestations referred to pediatric immunology and allergy outpatient clinic

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ABSTRACT

Objectives: In the first two years of life, patients with cutaneous manifestations with suspicion of food allergy are frequently referred to clinicians in daily practice. The aim of this study was to investigate the frequency of food allergy (FA) in infants presenting with cutaneous manifestations.

Methods: Patients aged <2 years with suspected food allergy and cutaneous manifestations who were admitted to the pediatric immunology and allergy outpatient clinic at Sincan Training and Research Hospital were included. Demographic, clinical and laboratory features of patients were recorded. The severity of atopic dermatitis (AD) was classified using the SCORing AD index.

Results: The study included 217 children with a median age of 9.7 months (IQR 5.8-13.6) (55.8% males). AD (77.9%) was the most common skin manifestation in all patients. Other cutaneous manifestations were urticaria/angioedema (12.4%) and flushing (9.7%). 23 (13.6%) patients were classified as moderate-severe AD and 146 (86.4%) patients as mild AD. The age at diagnosis is lower in the moderate-severe AD group [9 months (IQR 4-15)] compared to the mild AD group [14 months (IQR 9-18)] ($P=0.011$). In all AD patients, food allergy was detected in 54 (32%) patients. The percentage of food allergy was higher in the moderate-severe AD group (82.6%) than in the mild AD group (24%) ($P<0.001$). Multiple FA was shown in 13 (7.7%) patients and the percentage of Multiple FA was higher in the moderate-severe AD group (21.7%) than in the mild AD group (5.5%) ($P=0.018$). When the most common food allergies were compared, hen's egg and cow's milk allergy were found to be higher in the moderate-severe AD group [(56.5%) vs. (47.8%)] than in the mild AD group [(18.5%) vs. (9%)] ($P<0.001$ and $P<0.001$, respectively). Forty oral food challenges (OFC) tests were performed on patients who were found to have food sensitivity and all passed. In 58 (26.7%) patients, food allergy was identified and food elimination was started. In 54 (24.8%) patients with AD culprit food was eliminated from the diet. No food allergy was found in any patient presenting with flushing. Cow's milk allergy was found in two patients and hen's egg allergy in two patients who presented with urticaria.

Conclusions: We identified food allergy in only one out of every four patients presenting with suspected food allergy and cutaneous manifestations. Correct evaluation of hypersensitivity reactions to foods is important to avoid unnecessary food elimination from infants' diet.

Keywords: Skin manifestations, atopic dermatitis, childhood, food allergy

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The skin is one of the most common targeted organs in food hypersensitivity reactions. Clinical manifestations are classified into IgE-mediated reactions (flushing, urticaria, angioedema), cell-mediated reactions (dermatitis herpetiformis and contact dermatitis) and mixed IgE-mediated and cell-mediated reactions (atopic dermatitis [AD]) [1, 2]. AD is the most common inflammatory cutaneous disease characterized by pruritic, repetitive lesions [3]. Immunological, genetic, and environmental factors play an important role in the pathophysiology of AD, which is thought to cause skin barrier disorder and chronic inflammation in the skin [4]. The effect of food allergy on the pathogenesis and severity of this condition is controversial. In AD, the allergic sensitization process called atopic march is thought to occur in the form of food allergy in early childhood [5, 6]. Food allergens can cause urticarial lesions, pruritus, and eczematous exacerbations, especially in susceptible infants [7]. Particularly, patients with severe atopic dermatitis in the early ages should be evaluated for food allergy. It is necessary to perform a skin test and/or determine the serum level of specific IgE antibodies to confirm food allergen sensitization [8]. The compatibility of the history and laboratory findings with the allergy clinic in the patient should be questioned. The diagnosis should be confirmed by oral food challenges (OFC) tests [2, 9]. In the first 2 years of life, parents perceive a higher rate of food hypersensitivity than objectively assessed food hypersensitivity [10]. Therefore, in case of suspicion of food allergy, the patient should be examined in detail and allergy tests should be performed to avoid unnecessary food elimination. In this study, we aimed to investigate the frequency of food allergy in infants presenting with skin manifestations and suspected food allergy.

METHODS

Study Population

The study included children aged <2 years with suspected food allergies who were admitted to the pediatric immunology and allergy outpatient clinic at Sincan Training and Research Hospital between December 2023 and September 2024. In this retrospec-

tive study, there were 317 patients with suspected food allergies, and patients with gastrointestinal symptoms and other food allergy symptoms were excluded. A total of 217 patients with cutaneous manifestations were analyzed. Cutaneous manifestations were categorized as urticaria/angioedema, flushing, and atopic dermatitis [11]. From the patients' medical records, we collected information regarding gender, age, presenting symptoms, absolute eosinophils count, skin prick test (SPT), sIgE, total serum IgE, and OFC results.

Multiple food allergy (≥ 2 allergens) was specified as more than one type of food group. The diagnosis of AD was defined according to international guidelines and the diagnostic criteria of Hanifin and Rajka. SCORing AD (SCORAD) index was used to assess the severity of AD. Patients with a SCORAD index <25 were categorized as mild AD; patients with a SCORAD index between 25-50 were categorized as moderate AD; and patients with a SCORAD index >50 were categorized as severe AD [3, 12]. In this study, patients were categorized into two groups as "mild" and "moderate-severe" according to the severity of AD.

Study Procedures and Measurements

In the routine practice of the pediatric immunology and allergy outpatient clinic, SPT was performed with common food allergens (cow's milk, egg white, egg yolk, wheat, walnut, hazelnut, peanut, sesame, lentil) in case of suspected food allergy. SPT with food allergen extracts [Lofarma®, (Italy)] was applied on the volar surface of the forearm or back along with negative and positive controls and measured after 15 minutes. Positive results were defined as a mean wheal diameter 3 mm greater than the negative control. The Immuno-CAP method (Thermo Fisher Scientific, Uppsala, Sweden) was used to measure allergen-specific IgE levels in serum, and specific IgE (≥ 0.35 kU/L) was considered positive.

OFCs were made based on the physician's clinical judgment in conjunction with detailed clinical history and results of allergy tests. OFCs were performed according to national guidelines that were consistent by administering step by step of food protein at intervals of 15 to 30 minutes based on the quantity of protein contained in the food [13]. In the case of positive SPT and/or sIgE, the diagnosis of food allergy was based

on either a positive OFC or a clear and clear-cut history of IgE-mediated symptoms after exposure with food or in the presence of a positive SPT and/or sIgE suggesting clinical reactivity with >95% positive predictive value (PPV) for each food allergen [Cow's milk: SPT ≥ 8 mm than the negative control and/or sIgE ≥ 15 kU/L and for Egg white: SPT ≥ 7 mm than the negative control and/or sIgE ≥ 7 kU/L] [14, 15].

This study was made in accordance with the declaration of Helsinki principles. Ethics committee approval was obtained from Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee for this retrospective study (Decision number: 2024/189)

Statistical Analysis

IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Descriptive analysis was used to characterize the patients. Pearson's Chi-square (χ^2) test or Fisher's exact test was used for between-group comparisons. Levels are shown as the median and interquartile range for data not normally distributed. The Mann-Whitney U test or Kruskal-Wallis test was used to compare values. All statistical tests were two-sided, and the value of statistical significance was set at $P < 0.05$.

RESULTS

Study Population

The study included 217 patients presenting with cutaneous manifestations among 317 children with a pre-diagnosis of food allergy (Fig. 1). All patients were <2 years of age with a median age of 9.7 months (IQR 5.8-13.6) (55.8% males) (Table 1). AD (77.9%) was the most common skin manifestation in all patients. Other cutaneous manifestations were urticaria/angioedema (12.4%) and flushing (9.7%).

Evaluation of Allergy Tests

SPT with food allergens was performed in 209 (96.3%) patients and 76 (35%) patients had positive SPT. The most prevalent allergen sensitivities included egg white (15.2%), egg yolk (9.7%), cow's milk (12.4%), sesame (4.1%), peanut (3.7%), and wheat (4.1%). Allergen sIgE was performed in 76 (35%) patients and 87 (40%) positive allergen sIgE were detected. Of these, 39 (18%) were egg white sIgE positive and 29 (13.4%) were cow's milk sIgE positive. The median value egg white sIgE level was [1.87 kU/L (Min-Max 0.41-95)] and cow's milk sIgE [1.95 kU/L (Min-Max (0.54-24)] (Table 1).

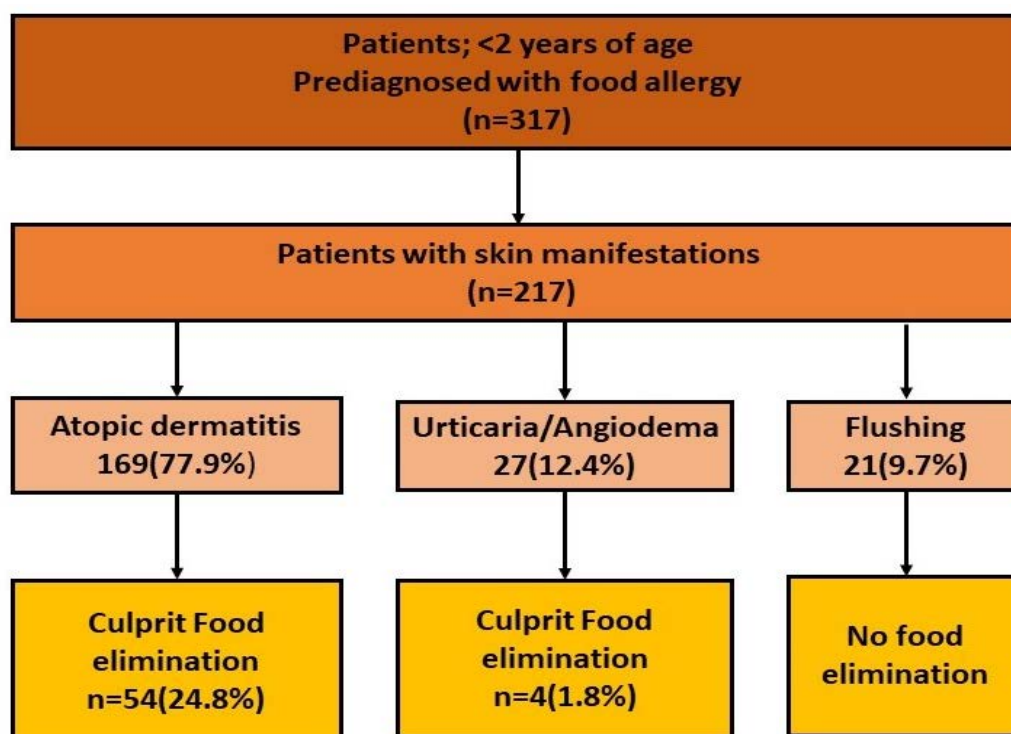


Fig. 1. Flow chart of analyzed patients according to skin manifestations.

Table 1. The characteristics of the study group (n=217)

	Data
Age (month)	9.7 (5.8-13.6)
Gender-male, n (%)	121 (55.8)
Presenting symptoms, n (%)	
Eczema	169 (77.9)
Urticaria / Angioedema	27 (12.4)
Flushing	21 (9.7)
Food sensitivity with SPT, n (%)	
Egg white	33 (15.2)
Egg yolk	21 (9.7)
Cow's milk	27 (12.4)
Wheat	9 (4.1)
Sesame	9 (4.1)
Peanut	8 (3.7)
Walnut	8 (3.7)
Hazelnut	5 (2.3)
Lentil	3 (1.4)
Laboratory values	
Eosinophil (cells/ μ L)	330 (200-540)
Total IgE (kU/L)	19 (5.7-80)
Egg white sIgE (kU/L)	1.87 (0.41-95)
Egg yolk sIgE (kU/L)	2.1 (1.02-41)
Cows' milk sIgE (kU/L)	1.95 (0.54-24)

Data are shown as median (IQR=interquartile range) (Minimum-Maximum) or n (%). SPT=Skin Prick Test

Patients with Atopic Dermatitis

One hundred sixty-nine (77.9%) patients had current atopic dermatitis with a median age of 9.4 months (IQR 5.3-14). Twenty-three (13.6%) patients were classified as moderate-severe AD and 146 (86.4%) patients as mild AD. The age at diagnosis is lower in the moderate-severe AD group [9 months (IQR 4-15)] compared to the mild AD group [14 months (IQR 9-18)] ($P=0.011$). In all AD patients, food allergy was detected in 54 (32%) patients. The percentage of food allergy was higher in the moderate-severe AD group (82.6%) than in the mild AD group (24%) ($P<0.001$). Multiple FA was shown in 13 (7.7%) patients and the percentage of multiple FA was higher in the moderate-severe AD group (21.7%) than in the mild AD

group (5.5%) ($P=0.018$). When the most common food allergies were compared, hen's egg and cow's milk allergy were detected to be higher in the moderate-severe AD group [(56.5%) vs. (47.8%)] than in the mild AD group [(18.5%) vs. (9%)] ($P<0.001$ and $P<0.001$, respectively). There was no difference between moderate-severe AD and mild AD subgroups in terms of gender and total IgE levels (Table 2).

Patients with Food Allergy

Forty oral food challenges were performed on patients with food sensitivity and all of them passed. OFC was performed with hen's egg (47.5%), tree nuts (22.5%), and cow's milk (15%), respectively. OFC was not made in 58 (26.7%) patients with both SPT results and/or allergen-specific IgE values much above the cut-off values and have a consistent and clear-cut history of IgE-mediated symptoms within 2 hours after the exposure to food. As a result, in 58 (26.7%) patients, food allergy was identified and the culprit food was eliminated. Among these patients, 54/58 (93%) were diagnosed with AD. No food allergy was found in any patient presenting with flushing. Cow's milk allergy was found in two patients and hen's egg allergy was found in two patients who presented with urticaria. Hen's egg allergy was diagnosed in 31 (53.4%) patients and cow's milk allergy was diagnosed in 15 (25.8%) patients. Both hen's egg and cow's milk allergy were detected in 11 (19%) patients. Walnut allergy was found in three patients, peanut allergy in three patients, wheat allergy in two patients, and sesame allergy in three patients (Fig. 2). These foods were eliminated from the diet of these patients.

DISCUSSION

Food allergy is an increasing health problem, especially in infants and young children. In this study, infants with cutaneous manifestations and suspected food allergies were evaluated. Food allergy was identified in a quarter of the patients and culprit foods were eliminated from the diet. The most common cutaneous manifestation was AD and hen's egg was the most culprit food.

The clinical spectrum of food allergy is broad, skin manifestations are the most common clinical symptom among them. Urticaria, angioedema, and flushing are

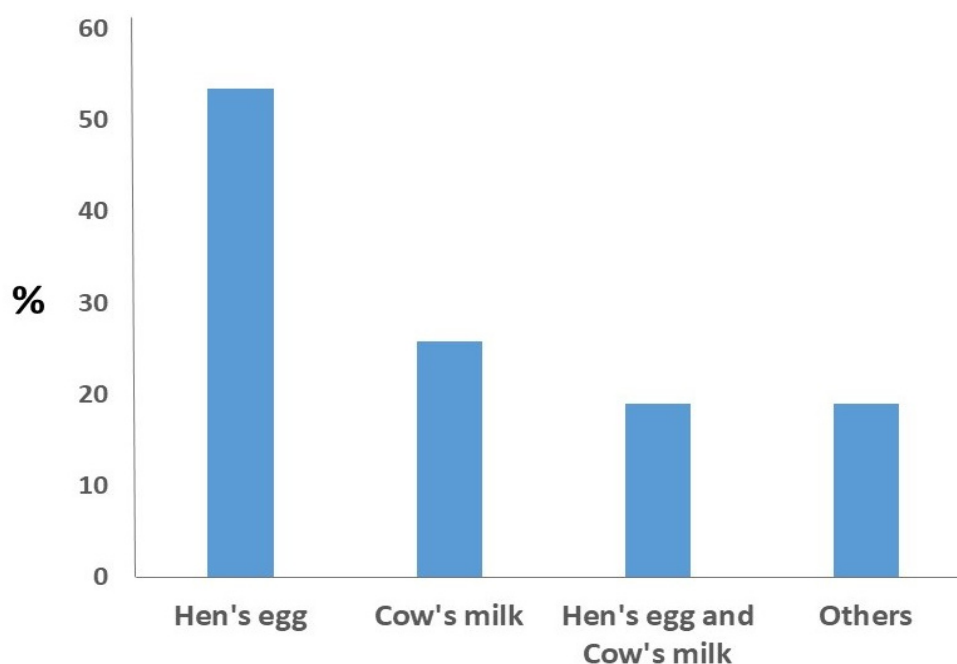


Fig. 2. Food allergies in the study group

categorized as immediate symptoms. Exacerbation or worsening of eczema (AD) and exanthema are delayed symptoms [11]. In a study conducted in our country, eczema was the most common diagnosis (36.8%) when the reasons for the first consultation to the physician in food allergy were analyzed. In the same study, 23.7% were found as urticaria and angioedema [16]. In our study, AD (77.9%) was the most common cutaneous manifestation in all patients and urticaria/angioedema

was in the second place.

The correct diagnosis of IgE-mediated food allergies is very important. It is based on a combination of a detailed medical history, allergen-specific IgE investigation with SPT and specific IgE in serum, elimination diet followed by OFCs. In this study, we found positive SPT in 35% of patients and positive allergen sIgE in 40% of patients. Many studies have attempted to determine the true diagnostic value of SPT and it

Table 2. The characteristics of the atopic dermatitis patients and its subgroups according to severity of atopic dermatitis

	AD (n=169)	Moderate-Severe AD (n=23)	Mild AD (n=146)	P value
Age (month)	9.4 (5.3-14)	9 (4-15)	14 (9-18)	0.011
Gender-male, n (%)	98 (58)	15 (65.2)	83 (56.8)	0.450
FA, n (%)	54 (32)	19 (82.6)	35 (24)	<0.001
Multiple FA, n (%)	13 (7.7)	5 (21.7)	8 (5.5)	0.018
Hen's egg, n (%)	40 (23.7)	13 (56.5)	27 (18.5)	<0.001
Cow's milk, n (%)	24 (14.2)	11 (47.8)	13 (9)	<0.001
Other food allergy, n (%)	13 (7.7)	5 (21.7)	8 (5.5)	0.007
Eosinophil (cells/ μ L)	330 (200-547)	460 (312-680)	310 (182-517)	0.053
Total IgE (kU/L)*	19 (5.7-90)	26 (4.8-164)	17.5 (5.8-84)	0.475

Data are shown as median (IQR=interquartile range) or n (%). FA=food allergy, AD=atopic dermatitis

has become clear that a negative test excludes food allergy 90% of the time, whereas a positive test result does not confirm the diagnosis of food allergy, but is instead a case of sensitization [14, 17, 18]. The probability of being allergic increases with increasing skin prick test wheal diameter, and therefore some studies have established diagnostic decision levels for some allergens with a cut-off of 95%-100% positive predictive value (PPV). In vitro, s-IgE testing is another way to investigate IgE-mediated food allergies. As with SPT, there is a similar relationship between the concentration of specific s-IgE and the likelihood of a clinical reaction to the specific food. Several reports have aimed to determine precise diagnostic predictive values. Undetectable s-IgE values are associated with a low risk (10-25%) of reaction to food, with the risk increasing with increasing s-IgE levels. The levels also vary depending on the kind of allergen [14].

Atopic dermatitis is one of the most prevalent skin disorders in children. Patients with AD have a higher risk for food allergies than those without AD [19]. Previous studies that investigated the association between AD and food allergy have shown that severe and earlier onset AD is associated with the development of food sensitization and food allergy at an early age [20-22]. In our study, similar to the literature, age at diagnosis was found to be lower in the moderate-severe AD group compared to the mild AD group. It was shown that food sensitization was significantly higher in children with the moderate-severe AD group and SCORAD index was higher in patients with food allergy, in a report performed in our country [23]. Studies have shown that the prevalence of food allergy is high between 33% and 39%, especially in patients with severe AD [20, 24]. Similarly, in our study, food allergy was detected in 32% of AD patients. The percentage of food allergy was significantly higher in the moderate AD group (82.6%) than in the mild AD group (24%).

The OFC is recommended to avoid unnecessary food elimination and is the gold standard for diagnosing correct food allergy, particularly in food-sensitive AD patients [8]. Previous studies have showed that the rate of food sensitization in AD patients is high, but the rate of food allergy confirmed by OFC test is lower and food allergy is mostly found in severe AD patients [25, 26]. In a study of AD patients aged 6 months to 6 years, it has been shown that sensitization to food al-

lergens is detected in approximately 53% of patients, and food allergy is confirmed in only 15% of these patients [27]. In our study, an oral food challenge test was made on forty patients with food sensitivity and all of them passed. Fleischer *et al* investigated 125 children aged 1-19 years and the outcome of oral food challenges in patients, they reported OFCs were helpful in food allergy diagnosis because most (89%) were negative [28]. Although most food-induced hypersensitivity reactions are thought to be food allergies, non-immunological food reactions are much more common. In a survey of children and adults in the UK, the prevalence of food allergy complaints was 20%, whereas a double-blind placebo-controlled provocation test showed that the actual prevalence was 2% [4]. In a study on infants with AD, serum eosinophil and serum total IgE levels were detected to be higher in the group with food sensitization and it was shown that elevations in serum eosinophil and serum total IgE levels were effective in predicting food sensitization in patients with severe AD [29]. In another report, no difference was reported between food sensitization, serum eosinophil total and serum IgE levels [30]. In our report, there was no difference between moderate-severe AD and mild AD subgroups in terms of eosinophil count and total IgE levels.

Foods that cause hypersensitivity reactions differ according to age and geography. Mavroudi *et al.* found that clinically active food allergies were recognized in 26.13% of children with AD and they reported that a total percentage of one in every four children, of children with AD were truly allergic to egg proteins and/or cow's milk [31]. In this study, we identified food allergy in only 26.7% of the patients referred with a pre-diagnosis of food allergy. No food allergy was found in any patient presenting with flushing. Cow's milk allergy was found in two patients and hen's egg allergy in two patients who presented with urticaria. The other patients consumed the food comfortably and had no complaints during follow-up. In our study, sensitivity to egg white/yolk, cow's milk, was found most frequently similar to other studies in the literature [20, 32].

Limitations

The main limitation of this retrospective study is that the study was conducted in a single center creating a limitation in terms of the generalizability of the re-

sults. However, in accordance with the aim of the study, the relationship between food sensitivity and skin manifestations commonly seen in daily life in infants was examined.

CONCLUSION

In conclusion, this study evaluated infants with cutaneous manifestations and suspected food allergies. We identified food allergy in approximately one out of every four patients presenting with suspected food allergy. Among these patients, 93% were diagnosed with AD. In particular, the elimination of essential nutrients from the diet negatively affects the quality of life of both infants and their parents. Correct evaluation of hypersensitivity reactions to foods is important to avoid unnecessary food elimination from infants' diets.

Ethics Statement

The study was initiated with the approval of the Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee (Date: 2024, Decision No: 189). This study was made in accordance with the declaration of Helsinki principles. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Authors' Contribution

Study Conception: HÜ; Study Design: HÜ; Supervision: HÜ; Funding: N/A; Materials: N/A; Data Collection and/or Processing: BA; Statistical Analysis and/or Data Interpretation: HÜ; Literature Review: BA, HÜ; Manuscript Preparation: HÜ and Critical Review: HÜ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Japanese disaster nursing readiness evaluation index: Turkish adaptation validity and reliability study

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ABSTRACT

Objectives: Disaster is a global problem all over the world, and it is essential to measure the readiness of nurses, who play a major role in disaster response, with a valid and reliable tool. This study was conducted to adapt the Japanese Disaster Nursing Readiness Evaluation Index into Turkish and to analyze its validity and reliability.

Methods: A total of 202 nurses were reached in this methodological study. The reliability parameters of the scale were examined with Cronbach Alpha and split-half. In addition, Confirmatory Factor Analysis was performed for the construct validity of the scale and 27% sub-item analysis was performed for item discrimination.

Result: According to Confirmatory Factor Analysis, the structural equation model, indicating its associated with 31 items and the six-factor structure of the scale. The factor loading values of all items were between 0.450 and 0.920. The alpha values obtained from the subscales of the scale ranged between 0.771 and 0.883, and the overall alpha value was calculated as 0.905.

Conclusions: Based on the findings of the study, it was concluded that the Japanese Disaster Nursing Preparedness Assessment Index is valid and reliable for the Turkish society.

Keywords: Disaster management, disaster nursing, Japanese disaster nursing readiness evaluation index, self-assessment scale, Turkey

Natural disasters are natural phenomena that disrupt the normal life order in a society [1]. As a country, we witness many devastating effects of earthquakes, a natural disaster we frequently experience. Most recently, on February 6, 2023, two devastating earthquakes occurred on the Eastern Anatolian Fault in Turkey, nine hours apart. The first earthquake had a magnitude of 7.7 at 04:17, and the second,

at 13:24 local time, had a magnitude of 7.6. The earthquakes severely affected a total of 11 provinces in the country, including Hatay, Kahramanmaraş, Adıyaman, Malatya, Gaziantep, Elazığ, Osmaniye, Şanlıurfa, Diyarbakır, Kilis, and Adana, leading to damage and destruction in these provinces. According to official records, 50 thousand 96 people died in these earthquakes as of 02.04.2023. Unfortunately, earthquakes

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affect many areas and adversely impact human life and health [2]. Besides causing high mortality rates due to the traumas they induce, earthquakes also lead to situations requiring emergency intervention [3]. In the face of such situations, it is crucial for the first healthcare professionals arriving at the scene to be effective and competent in disaster situation assessment, communication, management, and intervention [3, 4]. As healthcare professionals, nurses play a critical role in providing access to health services for the affected population, treating traumas and wounds, and managing cases, including protocols, medications, and materials [1, 4].

During the response phase of a disaster, nurses have clinical nursing roles that include general and advanced practices, including triage, perioperative care, emergency and critical care, infection control, public health, supportive and palliative care [4, 5]. Their experience in disaster response significantly influences their perception of disaster preparedness [6]. Nurses must be ready for disaster when assigned to a disaster area [7, 8, 9].

Due to the earthquakes we experience in our country, nurses' preparedness for disasters plays a crucial role in disaster management. The Japanese Disaster Nursing Readiness Evaluation Index (JDNREI), developed by Maeda *et al.* in Japan in 2018, is an important measurement tool to determine whether nurses are ready for disaster situations [10]. The aim of this study was to adapt the JDNREI to the Turkish population and to assess its Turkish validity and reliability through the nurses who participated in our study.

METHODS

Purpose

This research was conducted to adapt JDNREI, developed by Maeda and colleagues in Japan in 2018, to Turkish to determine nurses' readiness for disaster situations and perform validity and reliability analyses.

Study Population and Sample

The study population consisted of nurses working at an education and research hospital in Istanbul during the dates when the research was conducted. This methodological research was carried out between Oc-

tober and December 2023. The literature suggests that a sample size of five to ten times the number of items on a scale should be sufficient [11]. We planned to use a sample of between 185 and 370 health professionals, 5 to 10 times the number of items in the 37-item scale. The study included 202 nurses who met the specified criteria.

Data Collection Tools and Data Collection

The research data were collected through face-to-face interviews using data collection forms. Data was collected between October and December 2023. The Nurse Introduction Form and JDNREI, prepared by the research team in accordance with the literature, were used for data collection.

Nurse Introduction Form

This form includes six questions related to participants' gender, age, working unit, years of experience in the profession, experience in disasters, and assignment to disaster-stricken areas.

Japanese Disaster Nursing Readiness Evaluation Index

This scale consists of 37 items with six sub-themes that assess nurses' self-evaluations regarding their readiness and preparedness to provide medical care in disaster areas. The sub-themes include (I) emergency nursing skills, (II) practical skills in disaster response, (III) communication skills in teamwork, (IV) effective coping with daily stress, (V) collaboration skills, and (VI) adaptation to stressful situations in disaster areas. The scale is designed for self-assessment and preparedness measurement by nurses assigned to disaster areas. Additionally, nurse managers can use this scale to select nurses for disaster response, and it can contribute to preparedness practices before sending nurses to disaster areas. Individual disaster preparedness should be evaluated using the overall score of the JDNREI, not each subscale. As the total score on the scale increases, nurses' disaster preparedness increases.

Linguistic Equivalence

During the scale adaptation, linguistic equivalence studies were conducted initially, followed by item analyses for structural validity and reliability. To en-

sure linguistic equivalence of the scale, JDNREI was first translated from Japanese to Turkish. The created form was translated back into Japanese. Finally, the items in the Japanese-translated form and the original scale items were reviewed by seven experts for grammar, semantics, and vocabulary. A consensus was reached on the similarity of both forms, and the final version of the scale was established. After the translation process was completed, the application phase was initiated to determine the linguistic equivalence statistically. During the pilot application phase, 29 nurses working in a public hospital were interviewed. In the analysis, the Cronbach's Alpha value for the overall scale was calculated as 0.893, while the alpha value for its subscales was calculated between 0.738-0.896. A Cronbach's Alpha value greater than 0.60 indicates that the scale is reliable [12]. Upon examination of the results, it was seen that the internal consistency of the measurement tool and its subscales used in the study was as desired. Following the pilot application, the

main data collection process was initiated without the need to eliminate any item from JDNREI. The pilot application group was not included in the sample.

Ethical Aspect of Research

Written approvals were obtained from Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Research Ethics Committee in İstanbul (Ethics No/Date: 43/08.03.2023) and Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Chief Physician in İstanbul to conduct the study. After stating that participation in the study is voluntary, written consent was obtained from the participants. The research was carried out in accordance with the Principles of the Declaration of Helsinki. Necessary permission was obtained from the scale owner.

Statistical Analysis

The data obtained in the study were analyzed

Table 1. Demographic characteristics of participants

		n	%
Gender	Female	112	55.4
	Male	90	44.6
Age (years) (mean±SD)(min-max) 34.31±6.02 (22.0-50.0)	30 years and under	63	31.2
	31-40 years	103	51.0
	41 years and above	36	17.8
Worked unit	Intensive care units	49	24.6
	Inpatient treatment settings	96	47.1
	Outpatient treatment settings	57	28.3
Years of work experience	5 years and below	35	17.3
	6-10 years	54	26.7
	11-15 years	58	28.8
	16 years and above	55	27.2
Previous disaster experience	Yes	144	71.3
	No	58	28.7
Number of disaster assignments	None	88	43.6
	1 assignment	55	27.1
	2 assignments	29	14.4
	3 or more assignments	30	14.9

SD=standard deviation

using SPSS (Statistical Package for Social Sciences) for Windows 25 and AMOS 21 software. Descriptive statistical methods (number, percentage, mean, standard deviation) were used when evaluating the data. Reliability parameters of the scale were examined by Cronbach Alpha, split-half. Additionally, Confirmatory Factor Analysis was performed for the scale's construct validity, and 27% sub-item analysis was performed for item discrimination.

RESULTS

Findings Regarding Participants' Individual Characteristics

The participants' ages ranged from 22 to 50 years, and the average age was calculated as 34.31 ± 6.02 years. Among the participants, 55.4% were female, 28.7% had 11-15 years of work experience, 71.3% had experienced a disaster before, and 43.6% had not previously served in a disaster (Table 1).

Findings on the Japanese Disaster Nursing Readiness Evaluation Index

When the lowest and highest scores obtained from the scale items, as well as the mean scores and standard deviations of the items, were examined, it was seen that the lowest score was one and the highest score was five, with no reverse items in the scale sections. JDNREI has 37 items in total. The internal consistency of the adapted scale was examined using the

Cronbach Alpha method. When JNDREI item score distributions are analyzed, it is seen that item 24 received the lowest score (2.59 ± 1.58), while item 16 received the highest score (4.81 ± 0.59). Upon evaluating the relevant results, it was observed that all items could be included in the factor analysis of the adapted scale. Since removing an item from the measurement tool does not cause a significant increase in alpha value, it was decided not to exclude any items, and the analysis proceeded to the confirmatory factor analysis stage.

Construct Validity

According to the first-level multifactor confirmatory factor analysis results, the scale's goodness of fit indices showed an acceptable fit (RMSEA = 0.061) (Table 2). According to confirmatory factor analysis, the structural equation model result of the scale is showing that it is related to the scale structure with 31 items and 6 factors (Figs. 1 and 2).

Item Discrimination

The item-total test correlation values were analyzed, and there were no items below 0.30. Although the item-total test correlation values of all the items varied between 0.439 and 0.828, all the items were related to each other. To determine the discriminability of the items in each scale, the rankings of the items in the scale were ordered from highest to lowest, and the mean scores of the groups in the bottom 27% and the top 27% were compared using an independent group t-test. The comparison showed a statistically significant

Table 2. Findings regarding confirmatory factor analysis of the JDNREI

Index	Excellent fit criteria	Acceptable fit criteria	Before modification	After modification
χ^2/SD	$0 \leq \chi^2/df \leq 3$	$3 \leq \chi^2/df \leq 5$	1.960	1.739
RMSEA	$0.00 \leq RMSEA \leq 0.05$	$0.05 \leq RMSEA \leq 0.08$	0.069	0.061
CFI	$0.95 \leq CFI$	$0.85 \leq CFI$	0.881	0.910
GFI	$0.90 \leq GFI$	$0.85 \leq GFI$	0.789	0.814
AGFI	$0.90 \leq AGFI$	$0.85 \leq AGFI$	0.755	0.781
IFI	$0.90 \leq IFI \leq 1.00$	$0.80 \leq IFI$	0.882	0.911
TLI	$0.90 \leq TLI$	$0.80 \leq TLI$	0.870	0.900
NFI	$0.90 \leq NFI$	$0.80 \leq NFI$	0.786	0.812

SD=Standard Deviation, RMSEA=Root Mean Square Error of Approximation, CFI=Comparative Fit Index, GFI=Goodness-of-Fit Index, AGFI=Adjusted Goodness-of-Fit Index, IFI=Incremental Fit Index, TLI=Tucker-Lewis Index, NFI=Normed Fit Index

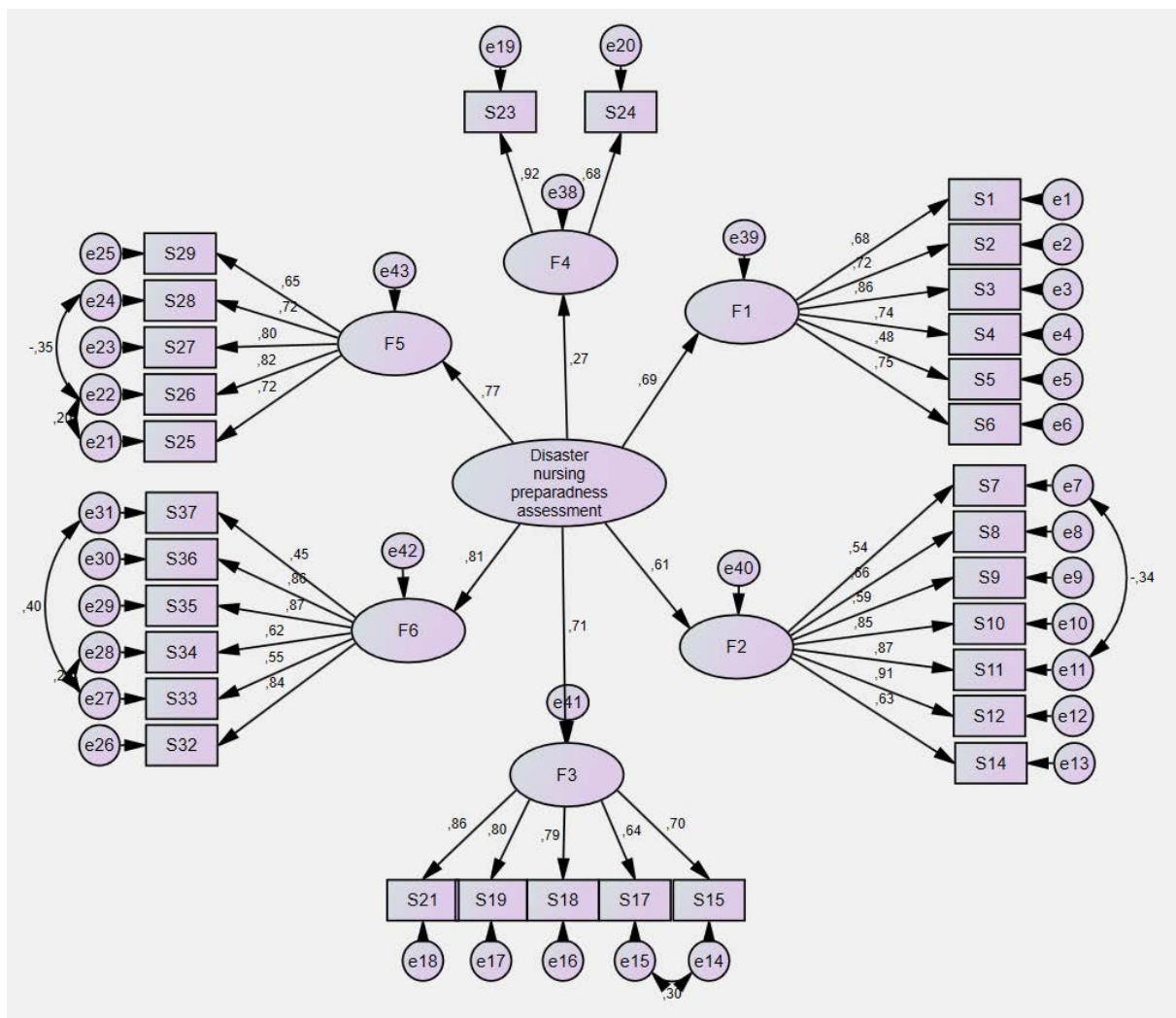


Fig. 1. Level one multifactor model confirmatory factor analysis of the Japanese Disaster Nursing Readiness Evaluation Index (standardised).

cant difference between the mean item scores of the lower and upper groups.

Reliability

Upon examination of the results, the overall alpha value of JDNREI was calculated as 0.905. The alpha values obtained from the subscales of the scale range between 0.771 and 0.883 (Table 3). According to the results, the correlation coefficient between the two halves was calculated as 0.899; the Spearman-Brown coefficient was 0.947, and the Guttman coefficient was 0.946. Based on these findings, the tool was deemed reliable (Table 4).

Scale bias was analyzed using the Hotelling T2 analysis method. Individuals answered the items ac-

cording to their own opinions when answering the items of the scale, and there was no response bias in the scales ($P < 0.001$).

DISCUSSION

As a result of this study, the findings showing whether the JDNREI is valid and reliable in the Turkish population are discussed in this section in the light of the literature.

JDNREI was first translated from Japanese to Turkish to ensure the linguistic equivalence of the scale. The created form was translated back into Japanese. Finally, the items in the form translated into

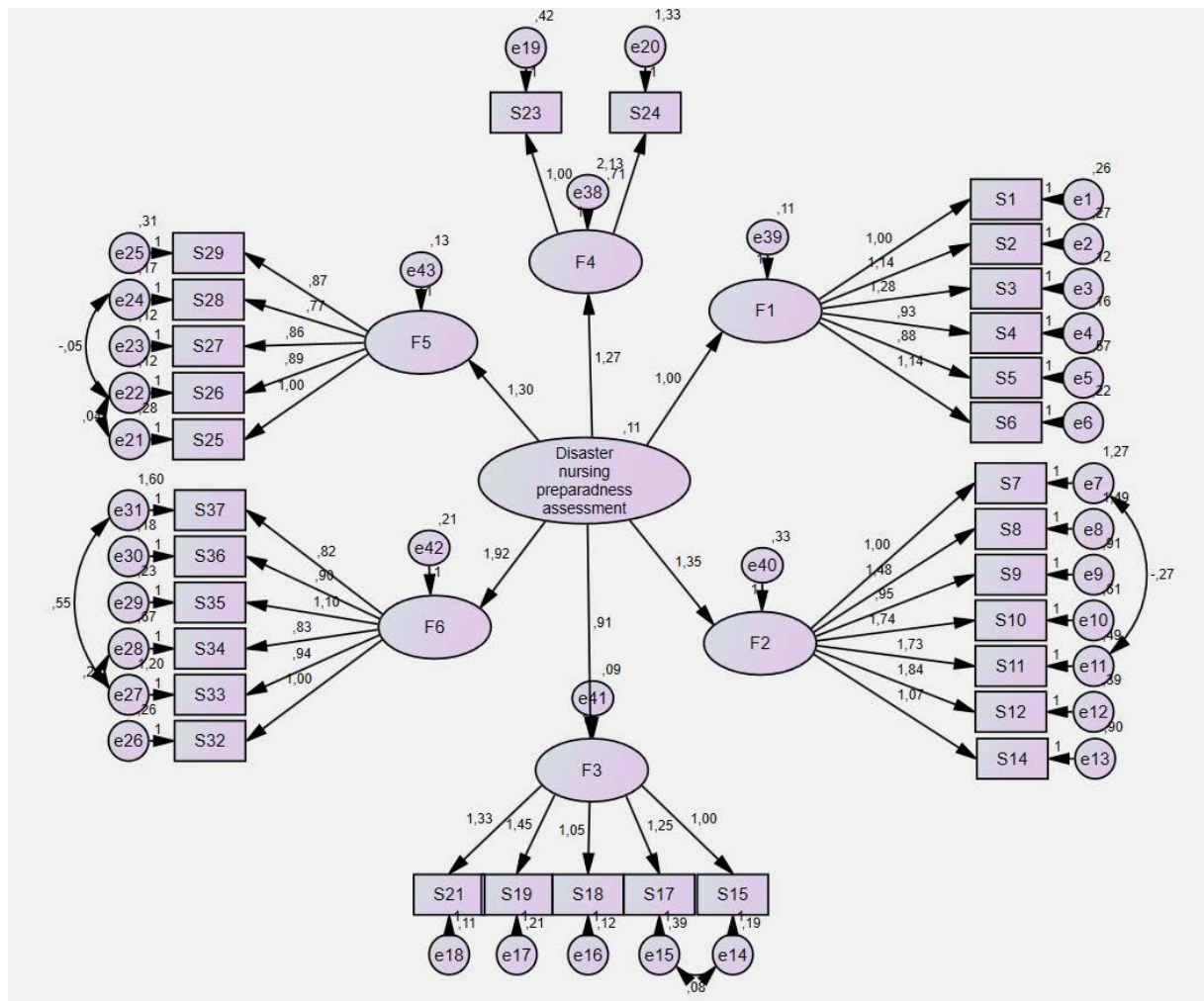


Fig. 2. Level one multifactor model confirmatory factor analysis of the Japanese Disaster Nursing Readiness Evaluation Index (non-standardised).

Japanese and the original scale items were presented to expert opinion (seven people) to evaluate scope, content, and language suitability. A consensus was obtained from experts that both forms were similar to each other, and the final version of the scale was achieved. In the literature, conducting a pilot application to a small group representing the sample is recommended after the expert opinion assessment of the scale [13, 14]. Thus, a pilot study was carried out with 29 nurses to ensure the understandability of the draft scale items. After the pilot application, it was determined that there were no expressions that were not understood. The internal consistencies of the measurement tool and its subscales used in the study were found to be good. According to the literature, the high Cronbach alpha coefficient emphasizes that the

scale's reliability is high. If this value is between 0.60 and 0.80, the scale is reliable, and if it is between 0.80 and 1.00, it indicates that the scale has high reliability [12]. The alpha value for the responses of the 29 individuals obtained in the pilot application was calculated as 0.893 for the overall scale, while the alpha value for its subscales was calculated between 0.738 and 0.896. It was concluded that the scale was highly reliable, and the main study was started. In Gheshlagh's study adapting the scale into Farsi, a pilot study was conducted with five nurses, and the nurses read the questionnaire aloud and identified ambiguous and unclear statements. They ended the pilot study by making suggestions to improve each item and proceeded to the main study [15]. The pilot study sample of this study is larger than the pilot study sample in the study

Table 3. Reliability analysis for JDNREI

Scale and subscales	Cronbach Alfa
Factor 1	0.845
Factor 2	0.883
Factor 3	0.872
Factor 4	0.771
Factor 5	0.852
Factor 6	0.850
Disaster Nursing Readiness Evaluation Index	0.905

JDNREI= Japanese Disaster Nursing Readiness Evaluation Index

in which the scale was translated into Farsi. A larger sample provides more robust and reliable results in both validity and reliability analyses. The results of the pilot study in this study made the validity and reliability of the scale stronger than the Farsi study before proceeding to the main study. In calculating the required sample size for scale development studies, 5-10 times the number of people in the scale's total number of items should be reached [14, 16]. The minimum number of people to be reached in the study was calculated as 185, and the study was completed with 202 nurses. Whether the scale had internal consistency was examined using the Cronbach Alpha method. All items of the adapted scale were included in the factor analysis. In a Farsi study [15] of the scale with 200 nurses, five items were removed due to demographic differences between Iranian and Japanese nurses and differences in the perception of problems, while no items were removed in this study. Sample size is one of the factors affecting this situation, but the sample sizes of the two studies are very close to each other. This difference, which is not due to sample size, can be attributed to cultural and linguistic differences as well as

professional working experience and conditions.

According to the literature, construct validity determines which concepts and features the scale measures and how accurately it measures [16, 13]. Following confirmatory factor analysis, whether the theoretical structure of the relevant model is sufficient to explain is tested. According to Confirmatory Factor analysis, the Structural Equation Modelling Results of the scale were $p=0.000$ level and were related to the 31 items and six-factor scale structure that make up the scale. Covariance was created between errors of the same factor in the model. RMSEA, a fit criterion, is a measure that means the square root of the approximate averages with values between zero and one. For RMSEA, below 0.05 indicates a good fit, below 0.08 is a reasonable fit, and between 0.08-0.10 is considered a moderate fit indicator [17]. In the confirmatory factor analysis, items that disrupted model fit were excluded (items 13, 16, 20, 22, 30, 31). According to the first level multifactor confirmatory factor analysis results, when the goodness of fit indices of the relevant scale is examined, RMSEA showed acceptable fit with 0.061, and χ^2 (Cmin/df) showed excellent fit with 1.739, indicating that the structural validity of the scale was established. In Maeda's study, root mean square error (RMSEA)=0.058 [10]. In Gheshlagh's study, items 16, 17, 27, and 29 were excluded, and RMSEA=0.051 [15]. Similar studies have shown reasonable agreement in parallel with the results of this study. In both studies translated into Turkish and Persian, it was observed that the items that disrupted the agreement belonged to the sub-theme of "Collaboration skills". Rapid decision-making, efficient use of resources and coordination skills of emergency medical teams are vital for large numbers of seriously injured and critically ill patients during a disaster [18]. Since it is more important to catch up with the urgency of the work rather than the work done in cooperation during a disaster, it is thought that the skills for cooperation showed poor agreement in both studies.

The minimum value required for the item-total test correlation to be sufficient is stated as 0.30 [19]. Among the scale items whose item correlations we examined, items below 0.30 should not be included in the analysis. By examining the item-total test correlation values of the participants' answers to the scale questions, it was determined that there were no items below 0.30. Since each subscale was evaluated sepa-

Table 4. Split-half method

Cronbach's Alpha	Section 1	0.803
	Section 2	0.832
Correlation between the two halves		0.899
Spearman-Brown coefficient		0.947
Guttman Split-Half coefficient		0.946

ately, when the subscale-based item total correlation values were examined, the correlation coefficients of the items were found to be between 0.439 and 0.828 and were significant. In Maeda's study, correlation coefficients were found between 0.376 and 0.699 and no item was below 0.30, which is parallel to the results of this study [10]. This shows that the scale items adapted into Turkish are compatible and consistent with the scale and have high internal reliability. However, unlike the original study of the scale and this study, in Gheshlagh's study, items 17 and 27 were removed due to low intra-item correlation [15]. It is seen that the removed items are related to humor and error acceptance. In fact, it is known that these situations, which vary depending on personal differences even in a normal process, are difficult to apply and accept during a disaster. It is thought that the place of work and years spent in the profession, especially cross-cultural work and experiences, affect these parameters.

Reliability analysis is carried out to test whether the statements in the scales are consistent among themselves. Cronbach's Alpha (α) coefficients between 0-1 indicate that the scale is not reliable. A value between 0.40 and 0.60 indicates low reliability, between 0.60 and 0.80 moderate reliability, and between 0.80 and 1.00 high reliability [12]. The analysis results showed an alpha value of 0.905 for the overall scale and between 0.771-0.883 for the subscales. In Maeda's study, the alpha value for the whole scale was calculated as 0.93, and the alpha value for the subscales was calculated between 0.83-0.93 [10]. In the Farsi study [15] of the scale, the alpha value was calculated as 0.93 for the whole scale, while the alpha value of the subscales was calculated between 0.83 and 0.93. All three studies demonstrate high reliability in the scale total score. This study concluded that Factor 4 was moderately reliable, in contrast to the original study and the Farsi translation of the scale. In Factor 4, stress was associated with family and financial situations. This result can be attributed to the different family structure and challenging processes of economics in Turkish society.

The split-half method is a reliability assessment technique used when a test can be divided into two halves to obtain a score. The method relies on the assumption that if the measurement tool is reliable, the scores obtained from both halves of the sample should be similar. The method can be performed as odd-even

or in random order [20]. The correlation between the two halves indicates whether the measurement tool is reliable. A correlation coefficient above 0.70, that is, close to one, indicates that the tool is reliable [21]. In the present research, the items were divided into two with odd and even order numbers. According to the results, the correlation coefficient between the two halves was 0.899, the Spearman-Brown coefficient was 0.947, and the Guttman coefficient was 0.946, concluding that the instrument is reliable. In the studies on the JNDREI, the split-half method was not found, but in Maeda's study, it was reported that significant, moderately strong correlations were obtained in the scale by looking at Spearman correlation coefficients [10]. The results of the main study and this study are parallel to each other, and it can be concluded that both scales are sufficiently reliable.

The response bias of the scale was analysed using the Hotelling T^2 analysis method. The homogeneity of responses for each item is considered in assessing response bias. In other words, it is determined whether the question averages are equal to each other. The Hotelling's T-test helps assess whether participants perceive the questions in the scale in the same way and also measures the difficulty level of each question [17]. In the present study, the participants answered the items according to their own opinions, and there was no response bias in the scales (Hotelling $T^2 = 572.363$; $P < 0.001$). In the literature, bias analysis with Hotelling T^2 was not found in the studies of JNDREI. However, in the Farsi study, it is reported that the questionnaire was distributed to nurses online to reduce social desirability bias, and the questionnaire was shared with the nurse managers in the hospital [15]. The analyses conducted determined that JDNREI is a sufficiently valid and reliable instrument for the Turkish population.

Limitations

The research is limited to the information of 202 nurses working in a training and research hospital in Istanbul in 2023 and the data obtained from the scale items. Limiting the study to only one hospital may limit the overall findings. Studies conducted with nurses working in different regions of Turkey will yield different results. The adaptation of the Japanese Disaster Nursing Preparedness Assessment Index to Turkey requires consideration of cultural and local dif-

ferences. Nurses' attitudes towards disasters, their training, and their awareness of disaster response may vary according to the cultural context. Disaster experiences of nurses, Turkey's general policies on disaster response, and past disaster experiences may affect the applicability of the scale. The workload and working conditions of the nurses during the study (such as stress, intensity, and professional experience) may affect the measurement results.

CONCLUSION

Disasters can be devastating for every society if no precautions are taken. We hope that with the Turkish validity and reliability of this index for nursing, the necessary practices during disasters can be implemented more safely in Turkish society.

Ethical Statement

Written approvals were obtained from Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Research Ethics Committee in İstanbul (Ethics No/Date: 43/08.03.2023) and Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Chief Physician in İstanbul to conduct the study. After stating that participation in the study is voluntary, written consent was obtained from the participants. The research was carried out in accordance with the Principles of the Declaration of Helsinki.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restriction.

Authors' Contribution

Study Conception: HA, EK, DHE, BİK, FEA; Study Design: HA, EK, DHE, BİK, FEA; Supervision: HA, EK, DHE, BİK, FEA; Funding: HA, EK, DHE, BİK; Materials: AY, KO; Data Collection and/or Processing: HA, DHE, BİK; Statistical Analysis and/or Data Interpretation: HA, EK, DHE, BİK; Literature Review: HA, EK, DHE, BİK; Manuscript Preparation: HA, DHE; and Critical Review: FEA, EK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Cryptogenic cirrhosis and Common variable immunodeficiency: an unrecognized relationship

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ABSTRACT

Objectives: This study investigates the prevalence of Common Variable Immunodeficiency (CVID) in patients with cryptogenic cirrhosis. It aims to highlight CVID's role in liver involvement and raise awareness of its potential as an underlying cause of cryptogenic cirrhosis.

Methods: This retrospective cohort study, approved by the ethics committee, included patients diagnosed with cryptogenic cirrhosis at a university hospital. Comprehensive evaluations were performed to exclude other causes of cirrhosis, and patients were screened for CVID based on the European Society for Immunodeficiencies (ESID) criteria.

Results: This study included 30 patients with cryptogenic cirrhosis, among whom 6.7% (n=2) were diagnosed with CVID. Both CVID patients had low immunoglobulin levels and abnormal immune cell profiles, leading to recurrent infections in one case and suspicion due to low total protein levels in the other. IVIG treatment was initiated for both, and liver biopsy findings in one patient suggested CVID-related liver involvement.

Conclusions: Determining the underlying causes of chronic liver diseases is crucial for guiding treatment and follow-up, potentially preventing cirrhosis progression and influencing liver transplantation eligibility. CVID screening in patients with cryptogenic cirrhosis should be considered, with appropriate treatments initiated as needed.

Keywords: Common variable immunodeficiency, cryptogenic cirrhosis, nodular regenerative hyperplasia

Common Variable Immunodeficiency (CVID) is the world's most common symptomatic primary immunodeficiency. Inadequate immunoglobulin (IgG, IgA/IgM) synthesis and poor response to antigens are the leading causes of CVID formation. It

is a heterogeneous group of diseases. In this disease, quite different clinical findings are seen due to lymphocytic end-organ damage and recurrent infections. The basic pathophysiology of CVID is the impairment of humoral immunity resulting from impaired B cell

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maturation and loss of plasma and memory B cells [1, 2]. In CVID, in addition to B cell impairments, T cell defects (decrease in naive CD4⁺ T cells and increase in CD8⁺ cytotoxic T lymphocytes) lead to lymphoinfiltrative involvement in organs such as the liver [3]. Although precise data on the prevalence of CVID are lacking, it is estimated to range between 1 in 100,000 and 1 in 10,000. However, the prevalence of CVID varies significantly across different regions [4]. CVID is typically diagnosed between the ages of 20 and 40, with no sex preference. Common presentations include recurrent infections and respiratory or gastrointestinal diseases. In some cases, autoimmune and lymphoproliferative disorders may occur, complicating the diagnosis [2, 5]. The clinical manifestations of CVID can affect multiple organ systems, and diagnosis is often delayed due to low disease awareness. Patients presenting without significant infections but with inflammatory or autoimmune complications can further complicate the diagnostic process. As a result, a delay of 4-6 years in diagnosis is typical [4].

Histologically confirmed liver involvement in CVID has been reported in approximately 10% of cases in various studies [6, 7]. Cryptogenic cirrhosis is a type of liver cirrhosis with an undetermined etiology despite comprehensive evaluation, and it is considered a diagnosis of exclusion. With the increasing accumulation of knowledge and technological advancements, the incidence of this condition is steadily decreasing [8].

This study aims to investigate the prevalence of CVID in patients with cryptogenic cirrhosis and to raise awareness of CVID liver involvement, thereby increasing awareness of CVID in cryptogenic cirrhosis.

METHODS

Study Design and Patient Selection Process

This retrospective cohort study was conducted at the Nacmettin Erbakan University Hospital. The local ethics committee approved the study protocol, with approval number 2023/4251. The study was conducted on patients diagnosed with cryptogenic cirrhosis who were followed at the Gastroenterology Clinic of our hospital. These patients were referred to the Adult Allergy-Immunology Clinic for screening for underlying

CVID. The patient's medical records were retrospectively reviewed, and Child-Turcotte-Pugh and MELD (Model for End-Stage Liver Disease) scores and immunological parameters were obtained from the patient files. Height and weight were measured using standard measuring devices, and body mass index (BMI) was calculated. CVID was diagnosed based on the latest criteria established by the European Society for Immunodeficiencies (ESID) [9].

Inclusion Criteria:

- Patients diagnosed with cryptogenic cirrhosis following a detailed evaluation by the Gastroenterology department.
- Evaluations performed to exclude other causes of cryptogenic cirrhosis, including:
 - Hepatitis B and C serology and PCR were evaluated.
 - Laboratory tests to investigate metabolic causes included serum ceruloplasmin, 24-hour urinary copper excretion, iron and ferritin levels, and tests to exclude Wilson's disease, hemochromatosis, and storage diseases.
 - Serological tests for autoimmune hepatitis included antinuclear antibody, smooth muscle antibody, liver-kidney microsomal antibody, and soluble liver antigen antibody to rule out autoimmune hepatitis and related conditions.
 - Assessment of Metabolic Associated Fatty Liver Disease (MAFLD)
 - Celiac Disease was excluded by evaluating anti-tissue transglutaminase antibodies (tTG), anti-endomysium antibodies (EMA)
 - History of hepatotoxic injury, especially alcohol use, drug exposure, and methotrexate usage.
 - Cirrhosis diagnosis confirmed by histological examination. For patients who did not undergo liver biopsy, the clinical diagnosis was based on the presence of portal hypertension signs and a cirrhotic appearance of the liver.
- Patients aged >18 years.

Exclusion Criteria:

- Patients with BMI ≥ 30 kg/m² (due to the high prevalence of MAFLD in cryptogenic cirrhosis).
- Patients with Type 2 diabetes mellitus.
- Patients with missing data.

Serum Immunoglobulin Measurements

Serum immunoglobulin levels were measured using nephelometric methods with the Siemens BNII System (Erlangen, Germany).

Flow Cytometry

Peripheral blood lymphocyte subsets were analyzed by flow cytometry using a panel that included CD3⁺ (T cells), CD3⁺CD4⁺ (helper/inducer T cells), CD3⁺CD8⁺ (cytotoxic T cells), CD19⁺ (B cells), CD3-CD16⁺CD56⁺ (NK cells), and IgM-CD27⁺ switched memory B cells.

Statistical Analysis

The analysis performed in this study was mainly descriptive. Data were processed using SPSS software, version 22.0. Descriptive statistics included the frequency of occurrences (n) and percentages (%). The normality of numerical data was examined using the Shapiro-Wilk test, which is more appropriate for small sample sizes (<50). Data not conforming to normal distribution were presented using median, minimum, and maximum values.

RESULTS

The study included 30 patients, with a predominance of females (76%). The median age of the participants was 57.5 years (range: 26-70 years). The median follow-up duration was 13.5 months (3-240 months). Among the study population, 6.7% (n=2) were diagnosed with Common Variable Immunodeficiency (CVID).

The clinical, laboratory, and demographic characteristics of cryptogenic cirrhosis patients with and without CVID are summarized in Table 1. Based on the Child-Pugh classification at the time of cirrhosis diagnosis, 26 patients were classified as Class A, three as Class B, and one as Class C.

The medical histories of the two CVID patients are briefly summarized below.

Case 1

A 56-year-old male patient presented approximately four years ago with complaints of fatigue, weakness, and abdominal distension. Initial evalua-

tions at the referring center revealed pancytopenia, diffuse ascites, and splenomegaly on abdominal ultrasonography and esophageal varices on endoscopy. The patient refused a liver biopsy. Investigations for known causes of cirrhosis yielded negative results, leading to a diagnosis of cryptogenic cirrhosis.

During follow-up, the patient experienced recurrent infections and required hospitalization for pneumonia four times in the past year. Given this history, he was referred to the Adult Allergy and Immunology Department for further evaluation. A detailed immunodeficiency workup revealed the following results: IgG < 1.5 g/L, IgM < 0.05 g/L, IgA < 0.05 g/L, CD3 = 79%, CD4 = 23%, CD8 = 59%, CD4/CD8 ratio = 0.39, CD16 = 9%, and CD27⁺ switched memory B cells = 2%, albumin = 3.2 g/dL, total protein = 5.3 g/dL. Based on the clinical findings and laboratory investigations, including absent isohemagglutinins and/or poor response to vaccines, the patient was diagnosed with CVID. The patient was started on intravenous immunoglobulin (IVIG) treatment every three weeks.

Case 2

A 25-year-old woman presented to the emergency department with abdominal bloating. Abdominal ascites and elevated liver function tests were detected, and she was admitted to the Gastroenterology clinic. Evaluations revealed pancytopenia, a cirrhotic appearance of the liver on abdominal ultrasonography, splenomegaly, and esophageal varices. A liver biopsy showed chronic hepatitis (stage 4).

Investigations into all known possible causes of liver cirrhosis were conducted, but no etiology was identified. The attending physician noted that the patient's total protein level was 4.7 g/dL and albumin level was 3.7 g/dL and suspected that the low total protein might be due to immunoglobulin deficiency. Immunoglobulin levels were measured, and significant decreases were found (IgG: 2.5 g/L, IgM: 0.36 g/L, IgA: <0.24 g/dL). The patient was referred to the Adult Allergy and Immunology clinic for further evaluation.

The detailed immunodeficiency panel revealed the following results: CD3 = 82%, CD4 = 29%, CD8 = 51%, CD16 = 8%, and CD27⁺ switched memory B cells = 0.9% with a CD4/CD8 ratio of 0.5. The patient's HIV serology test was negative. Despite the ab-

Table 1. Clinical, laboratory, and demographic characteristics between cryptogenic cirrhosis patients with and without CVID

	Non-CVID Patients (n=28)	CVID Patients (n=2)	Non-CVID Patients (n=28)	CVID Patients (n=2)	
Sex (female), n (%)	22 (78)	1 (50)	GGT (U/L)	42 (10-278)	89 (58-120)
Current age (years)	55 (30-70)	41 (26-56)	CD3 ⁺ T cells, n (%)	71 (54-79)	80 (79-82)
Follow-up (months)	13.5 (3-240)	30 (12-48)	CD4 ⁺ T cells, n (%)	40.5 (32-54)	26 (23-29)
BMI (kg/m ²)	24.7 (16.5-29)	23.2 (23.1-23.4)	CD8 ⁺ T cells, n (%)	23 (15-32)	55 (51-59)
MELD Score	8.5 (6-20)	14 (12-16)	CD4 ⁺ / CD8 ⁺ ratio	1.8 (1.1-3.6)	0.4 (0.3-0.5)
Child-Pugh Score, n (%)	5 (5-8)	9 (7-11)	CD19 ⁺ B cells, n (%)	14 (8-31)	2
IgG (g/L)	15.3 ± 3.7	1.9 (1.5-2.4)	CD16 ⁺ -56 ⁺ NK cells, %	9 (5-28)	8.5 (8-9)
IgM (g/L)	1.1 (0.2-2.7)	0.1 (0.05-0.3)	Switched memory B cells, n (%)	5.3 (2-21)	1.5 (1-2)
IgA (g/L)	3.7 ± 1.8	0.1 (0.05-0.24)	Albumin (g/dL)	3.9 ± 0.6	3.5 (3.2-3.7)
IgE (IU/mL)	24 (15-349)	18	Total Protein (g/dL)	7.1 ± 0.7	5 (4.7-5.3)
ALP (U/L)	106 (42-241)	219 (188-250)	INR	1.2 (1.1-1.4)	1.4 (1.2-1.6)
AST (U/L)	24.5 (13-61)	133 (34-233)	Platelet count (×10 ³ /μL)	127 (76-432)	174 (121-227)
ALT (U/L)	18.5 (11-40)	71 (26-116)	Lymphocyte (mm ³)	0.9 (0.6-2.5)	1.9 (1.8-2)

Data are shown as means±standard deviation or median (min-max) or n (%). CVID=common variable immunodeficiency, BMI=body mass index, MELD= Model for End-Stage Liver Disease, Ig=immunoglobulin, ALP= alkaline phosphatase, AST= aspartate aminotransferase, ALT= alanine transaminase, GGT= gamma-glutamyl transferase, INR=international normalized ration.

Normal values - AST=0 to 41 U/L, ALT=0 to 40 U/L, ALP=40 to 110 U/L, GGT=0 to 45 U/L, Albumin=3.5 to 5.2 g/dl, INR=0.8 to 1.2.

sence of a history of recurrent infections, the clinical and laboratory findings, including absent isohemagglutinins and/or poor response to vaccines, led to the diagnosis of CVID. IVIG treatment was started every three weeks.

The patient's liver biopsy was re-evaluated for CVID-related liver involvement. The biopsy results revealed nodular regenerative patterns in the liver sinusoids, accompanied by infiltration of CD4⁺ T helper cells, CD8⁺ cytotoxic T lymphocytes.

DISCUSSION

Numerous studies have examined the specific clinical and histopathological aspects of liver involvement in CVID [2, 7, 10]. However, the relationship between cryptogenic cirrhosis and CVID in the adult population remains insufficiently explored. In our study, CVID was identified in 6.7% of patients with cryptogenic cirrhosis.

In a retrospective analysis of patients with CVID, approximately 10% were reported to have non-infectious liver disease [11]. This study highlighted that liver involvement in CVID can present across a wide spectrum, ranging from isolated alkaline phosphatase (ALP) elevations to cirrhosis. Another study reported persistent abnormalities in liver function tests (LFTs) in 44% of patients with CVID [10]. Nodular regenerative hyperplasia (NRH) is commonly observed in patients with CVID and may lead to conditions such as cirrhosis, chronic cholestasis, or non-cirrhotic portal hypertension. Studies have reported the incidence of NRH in CVID to range between 32% and 84% [12, 13]. Mechanisms of liver involvement in CVID include microvascular disturbances caused by microthrombosis, periportal lymphocytic infiltration, and chronic disruption of blood flow due to CD8⁺ T cell activity. Additionally, impaired intestinal barrier function, leading to microbial translocation and autoimmune processes, such as seronegative autoimmune hepatitis, may contribute to liver damage. These mechanisms are critical in developing NRH associated with CVID [14]. Most CVID patients with liver involvement are reported to exhibit an inverted CD4/CD8 ratio [2, 7, 12]. In the biopsy of Case 2 included in our study, an increase in CD8⁺ cytotoxic T lymphocytes

was observed, consistent with the literature. Additionally, an inverted CD4/CD8 ratio was detected in both cases.

Liver disease in CVID can result from various causes, including infections, autoimmune reactions, or neoplastic conditions. These causes include hepatitis B and C infections, autoimmune hepatitis, primary biliary cholangitis, sclerosing cholangitis, and B-cell lymphomas [2]. Liver involvement is a determining factor in the outcome and prognosis of CVID patients; mortality is higher in those with liver disease compared to those without liver involvement [14]. In CVID patients with hypogammaglobulinemia, specific autoantibody levels are often low or undetectable, complicating the diagnosis of certain liver diseases. This frequently makes liver biopsy necessary. If autoimmune hepatitis is suspected, a biopsy should be performed even if AMA, ASMA, and LKM tests are negative [15, 16]. Additionally, liver biopsy is recommended in CVID patients who exhibit a significant (more than twice the upper limit of the range) unexplained elevation in one or more liver enzymes persisting for more than six months [15]. Also in particular the diagnosis of PBC which presents with elevated alkaline phosphatase and relies on the anti-mitochondrial antibodies (AMA) for diagnosis, should be considered despite negative AMA testing in CVID [6].

CVID can present with symptoms affecting multiple organ systems, and due to low awareness, delays in diagnosis may occur. In 5-10% of patients, a history of frequent infections may be absent, and these patients are more likely to present with inflammatory or autoimmune complications [4]. In our study, Case 2 had no history of recurrent infections, and the patient's initial presentation was with signs of liver failure. While investigating the etiology of liver cirrhosis in this case, a low total protein/albumin ratio was noted, raising suspicion for immunoglobulin deficiency. The patient, with observed immunoglobulin deficiency, was diagnosed with CVID following immunological evaluations conducted at our clinic. In the other case, the patient was referred to our clinic due to a history of frequent recurrent infections, and CVID was diagnosed.

Cryptogenic cirrhosis is defined as cases of liver cirrhosis in which the definitive cause cannot be identified despite comprehensive clinical, laboratory, and

histological evaluations. It is essentially a diagnosis of exclusion. To reach this diagnosis, the patient must have negative viral infection markers (HBsAg, HBV-DNA, anti-HCV, HCV-RNA), no history of parenteral blood exposure, alcohol use, or hepatotoxic drug exposure, normal metabolic parameters (ceruloplasmin, alpha-1 antitrypsin, ferritin levels), and negative autoimmune markers (ANA, AMA, anti-LKM-1). Over the past 40 years, with the accumulation of knowledge regarding liver diseases and advancements in technology, the definition of "cryptogenic cirrhosis" has changed, and a significant reduction in its prevalence has been observed [17]. MAFLD is considered a significant cause of chronic liver disease in the Western world, and it has been suggested that many cases of cryptogenic cirrhosis may be attributed to MAFLD. This view is based on the higher frequency of risk factors such as type 2 diabetes (DM), obesity, and metabolic syndrome in cryptogenic cirrhosis patients. Therefore, in our study, patients with type 2 diabetes and obesity (body mass index [BMI] ≥ 30) were excluded to minimize the possibility of MAFLD-related cryptogenic cirrhosis.

The observation of a close relationship between CVID and Immune Thrombocytopenia (ITP) has led to the inclusion of CVID screening in the diagnostic process and its incorporation into clinical guidelines, marking a significant development [18]. This highlights the critical role of immunodeficiencies in ruling out secondary causes and emphasizes the necessity of comprehensive evaluations to achieve an accurate diagnosis. Similarly, the findings of our study indicate that CVID can be observed in 6.7% of patients with cryptogenic cirrhosis, suggesting a potential relationship between these two conditions. To our knowledge, this is the first study to address the relationship between CVID and cryptogenic cirrhosis. Larger-scale and multicenter studies will contribute to a better understanding of the potential link between cryptogenic cirrhosis and CVID.

Limitations

Our study has certain limitations. First, the small sample size and selection bias may affect the reliability of the findings. Second, the study was conducted in a single center. These factors make it challenging to provide robust evidence regarding the prevalence of CVID in cryptogenic cirrhosis.

CONCLUSION

Determining the underlying causes of chronic liver diseases is essential, as this information can directly shape treatment and follow-up processes. Initiating appropriate treatment at an early stage may prevent the progression to cirrhosis, and, in some cases, the etiology may play a decisive role in evaluating eligibility for liver transplantation. Therefore, we recommend conducting CVID screening in patients diagnosed with cryptogenic cirrhosis and initiating necessary treatments accordingly.

Ethical Statement

Ethics committee approval was received for this study from the Ethics Committee of Necmettin Erbakan University Meram Medical Faculty, who approved this study protocol (17.03.2023/4251). The study followed the guidelines and principles of the Declaration of Helsinki.

Authors' Contribution

Study Conception: RE, MB, ŞA; Study Design: FÇ, FSA; Supervision: RE, MB, TA; Funding: EY, TA; Materials: MK, MEG; Data Collection and/or Processing: MK, FSA; Statistical Analysis and/or Data Interpretation: RE, FÇ; Literature Review: FSA, EY; Manuscript Preparation: RE and Critical Review: ŞA, MB.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Association between disease activity and HALP score in ankylosing spondylitis patients

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ABSTRACT

Objectives: The goal of this research was to assess HALP score (Hemoglobin, Albumin, Lymphocyte, Platelet) as a potential indicator of disease activity among patients with Ankylosing Spondylitis (AS).

Methods: Data from 260 individuals (130 AS patients and 130 healthy controls) were retrospectively reviewed. Clinical and demographic information was collected, and the AS group was divided into remission and active disease subgroups for comparison.

Results: In contrast to the group of healthy controls, AS patients had a lower HALP score ($P < 0.001$). The HALP score was notably lower in the active patient group than in the remission group ($P = 0.025$). The HALP score and the erythrocyte sedimentation rate were found to be negatively correlated ($r = -0.307$, $P < 0.001$). Additionally, significant negative correlations were identified between the HALP score and the following parameters: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ($r = -0.208$, $P = 0.017$), Bath Ankylosing Spondylitis Functional Index (BASFI) ($r = -0.195$, $P = 0.026$), Ankylosing Spondylitis Disease Activity Score using C-reactive protein (ASDAS-CRP) ($r = -0.199$, $P = 0.024$), and Visual Analog Scale ($r = -0.229$, $P = 0.009$). The optimal HALP score cut-off for determining disease activity was established as ≤ 0.56 (AUC: 0.619, 95% CI: 0.518-0.721, sensitivity: 80.00%, specificity: 40.00%).

Conclusions: This study found that the HALP score was lower in active AS patients compared to those in remission. Therefore, the HALP score may serve as a potential marker for assessing disease activity in AS patients.

Keywords: Inflammation marker, HALP score, ankylosing spondylitis

Ankylosing spondylitis (AS) is a chronic, progressive inflammatory disorder that primarily affects the axial skeleton, leading to spondylitis and sacroiliitis, but it can also involve peripheral arthritis, enthesitis, dactylitis, anterior uveitis, aortic insufficiency, atherosclerosis, osteoporosis, and subclinical intestinal inflammation [1]. AS has a prevalence of approximately 1 in 200 individuals in the

general population, with its onset typically occurring before the age of 45 [2]. It also occurs due to systemic inflammation in AS and causes irreversible damage to the joints, dysfunction and decreased mobility of the patient. When left untreated, AS can cause significant functional decline, loss of work capacity, and a deterioration in quality of life. Thus, early detection of disease activity and accurate prediction of long-term

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prognosis are paramount for effective clinical management [1, 3]. Ankylosing Spondylitis Disease Activity Score-CRP (ASDAS-CRP), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and ASDAS-ESR are the current activity indices used to evaluate disease activity in AS. In addition to the CRP or ESR score, this indices also includes four other self-reported items: back pain, peripheral pain or swelling, length of morning stiffness, and patient global assessment of disease activity [4]. Though ESR and CRP are routinely used as indicators of rheumatic disease activity, these markers exhibit low sensitivity and specificity. In AS patients, both ESR and CRP are normal in approximately half of the patients despite having active sacroiliitis, especially in the absence of peripheral arthritis. [5-7]. ASDAS-CRP and ASDAS-ESR activity indices are dependent on ESR and CRP, do not reflect disease activity sufficiently in cases of low CRP, ESR is affected by factors such as age and gender, and clinical and these parameters must be brought together for accurate measurement. BASDAI includes parameters such as pain, fatigue, joint swelling and limited movement perceived by patients. Therefore, it causes subjective responses and difficulty in application [4, 5]. Therefore, there is a need for reliable biomarkers that can reflect disease activity more accurately.

The HALP (hemoglobin, albumin, lymphocyte, platelet) score, which includes these markers, is calculated with the formula $\text{serum albumin (g/L)} \times \text{hemoglobin (g/L)} \times \text{lymphocyte count (/L)} \div \text{platelet count (/L)}$ [8, 9]. Inflammation-related markers such as CRP, leukocytes, platelets, ferritin and albumin often change their values in diseases with systemic chronic inflammation such as cancer and AS. Many studies have been conducted showing that the HALP score can predict the prognosis of various types of cancer [8, 10]. In a study conducted on anti-neutrophil cytoplasmic antibody-associated vasculitis (ANCA), the HALP score was suggested as a new index to evaluate disease activity. [11-13]. It is important to determine disease activity in AS with systemic inflammation. To our knowledge, there is no previous study examining the relationship between HALP score and disease activity.

The aim of this study was to examine the relationship between disease activity and HALP score in AS patients.

METHODS

Participants

There were 130 AS patients recorded retrospectively in the Rheumatology Clinic of Recep Tayyip Erdoğan University Faculty of Medicine between July 2019 and August 2024. Patients were diagnosed with AS considering the classification guidelines established by the International Working Group of the Assessment of Spondyloarthritis [14]. 130 healthy individuals with normal clinical and laboratory parameters, matched for age, gender and BMI, were included in the study in our outpatient clinic.

Exclusion Criteria

Patients with blood diseases that would affect hematological parameters, liver diseases, kidney diseases such as glomerulonephritis, acute and/or chronic infections, gastrointestinal diseases that would cause protein loss, other rheumatological diseases, pregnancy, diabetes mellitus, and patients with insufficient information were eliminated from the research. Exclusion criteria were established based on clinical, laboratory and imaging findings.

Disease Activity

Visual Analog Scale (VAS): In the clinical setting, VAS is the assessment of pain intensity on a scale from 0 to 10 on a line. 0 represents no pain, and 10 represents the most severe pain level. Patients recorded the intensity of the pain they experienced on this line. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI): An index evaluates the illness activity of AS. It consists of 6 questions in total and evaluates the severity of level of disease's activity on a 0-10 scale. Bath Ankylosing Spondylitis Functional Index (BASFI): An index evaluates functional capacity in individuals with AS. It consists of 10 questions and evaluates the degree of physical function impairment between 0 and 10. Ankylosing Spondylitis Disease Activity Score using C-reactive protein (ASDAS-CRP): It is a score that measures illness activity in patients with AS and also includes CRP levels. It shows illness activity with a score between 0 and 10. The 6-item Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is used to assess disease activity based on fatigue, spine pain, joint pain/swelling, localized pain

Table 1. Comparison of AS patients' laboratory, clinical, drug-use, and demographic characteristics with those of the healthy group

Variables	Healthy Group (n=130)	AS (n=130)	Cohen's d	P value
Age (year)	40.54 ± 9.81	39.82 ± 10.24	0.072	0.566
BMI (kg/m ²)	28.37 (17.19 - 43.71)	27.34 (16.07 - 43.28)	0.187	0.134
Sex, n (%)				-
Female	70 (53.8)	70 (53.8)	0.000	1.000
Male	60 (46.2)	60 (46.2)		
Family History	-	53 (40.8)	-	-
Duration of illness (year)	-	7.77 ± 5.5	-	-
Alcohol use	2 (1.5)	8 (6.2)	0.242	0.103
Smoking	35 (26.9)	52 (40)	0.280	0.035
Peripheral Arthritis	-	25 (19.2)	-	-
Anterior uveitis	-	18 (13.8)	-	-
Dactylitis	-	1 (0.8)	-	-
Enthesitis	-	34 (26.2)	-	-
Sacroiliitis	-	92 (70.8)	-	-
Medications, n (%)				
NSAID	-	55 (42.3)	-	-
Anti-TNF	-	73 (56.2)		
Anti IL-17	-	2 (1.5)		
Laboratory parameters				
WBC (×10 ³ /μL)	6.550 (3.680-11.900)	7.816 (4.090-15.600)	0.812	<0.001
Neutrophils (×10 ³ /μL)	3.59 (1.78-8.62)	4.92 (2.13-11.39)	0.851	<0.001
Lymphocytes (×10 ³ /μL)	2.12 (1.05-5.36)	2.2 (1.02-4.34)	0.200	0.108
Monocytes (×10 ³ /μL)	0.39 (0.2-0.85)	0.51 (0.11-0.92)	0.854	<0.001
HGB (g/dL)	14 (7.5-17.5)	13 (10-17)	0.511	<0.001
PLT (×10 ³ /μL)	256 (133-416)	298 (192-627)	0.862	<0.001
NLR	1.69 (0.52-5.16)	2.18 (0.78-7.75)	0.573	<0.001
PLR	119.72 (55.41-246.67)	136.68 (65.67-401.83)	0.411	0.001
CRP (mg/L)	2 (0.230)	6 (0.3-94)	1.168	<0.001
ESR (mm/h)	7 (2-40)	12 (2-62)	0.584	<0.001
Alb (g/dL)	4.6 (4-5.5)	4.5 (3.3-39)	0.437	0.001
HALP score	0.55 (0.22-1.21)	0.44 (0.14-5.42)	0.577	<0.001
HLA B27	-	79 (60.8)	-	-
ASDAS-CRP	-	2.37±0.92		
BASDAI	-	4.96±2.05		
BASFI	-	3.79±2.41		
VAS	-	6.27±2.67		

Data are shown as mean±standard deviation or median (range) or n (%). AS=Ankylosing Spondylitis, BMI=Body mass index, NSAID=Nonsteroidal anti-inflammatory drugs, Anti-TNF=Anti-tumor necrosis factor, IL-17=Interleukin-17, WBC=White blood cell, PLT=Platelet, NLR=Neutrophil to lymphocyte ratio, PLR=Platelet to lymphocyte ratio, HGB=hemoglobin, CRP=C-reactive protein, ESR=Erythrocyte sedimentation rate, Alb=Albumin, HALP score=hemoglobin (g/dL) × albumin (g/dL) × lymphocyte (10³/μL) / Platelet (10³/μL), HLA B27=Human leukocyte antigen-B27, ASDAS-CRP=Ankylosing Spondylitis Disease Activity Score, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI=Bath Ankylosing Spondylitis Functional Index, VAS=Visual Pain Score.

Table 2. Clinical, demographic, and laboratory parameter comparisons between the AS patient population in remission and the active group

Variables	Remission AS (n=45)	Active AS (n=85)	Cohen's d	P value
Age (year)	40.67±10.58	39.38±10.09	0.125	0.496
BMI (kg/m ²)	26.95±4.66	27.96±5.82	0.192	0.313
Sex, n (%)				
Female	18 (40)	52 (61.2)	0.265	0.034
Male	27 (60)	33 (38.8)		
Family History	17 (37.8)	36 (42.4)	0.040	0.751
Duration of illness (year)	6 (2-21)	6 (1-26)	0.031	0.800
Alcohol use	3 (6.7)	5 (5.9)	0.000	1.000
Smoking	18 (40)	34 (40)	0.000	1.000
Peripheral Arthritis	8 (17.8)	17 (20)	0.038	0.943
Anterior uveitis	4 (8.9)	14 (16.5)	0.148	0.356
Dactylitis	1 (2.2)	0 (0)	-	-
Enthesitis	13 (28.9)	21 (24.7)	0.064	0.759
Sacroiliitis	44 (97.8)	80 (94.6)	0.290	0.141
Medications, n (%)				
NSAID	13 (28.9)	42 (49.4)	0.326	0.023
Anti-TNF	32 (71.1)	41 (48.2)		
Anti IL-17	0 (0)	2 (2.4)		
Laboratory parameters				
WBC (×10 ³ /μL)	7.700 (4.090-11.860)	8.170 (4.870-15.600)	0.108	0.386
Neutrophils (×10 ³ /μL)	4.63 (2.13-7.97)	5 (2.8-11.39)	0.233	0.062
Lymphocytes (×10 ³ /μL)	2.31 (1.29-3.9)	2.17 (1.02-4.34)	0.138	0.267
Monocytes (×10 ³ /μL)	0.53 ± 0.17	0.53 ± 0.16	0.004	0.972
HGB (g/dL)	13.9 (11-17)	13 (10-16)	0.146	0.240
PLT (×10 ³ /μL)	291 (199-627)	301 (192-547)	0.225	0.071
NLR	1.96 (0.78-4.69)	2.28 (1.07-7.75)	0.307	0.015
PLR	128.28 (72.57-264.74)	139.54 (65.67-401.83)	0.261	0.037
ESR (mm/h)	12 (2-51)	12 (2-62)	0.088	0.477
CRP (mg/L)	6 (0.3-60.8)	6 (0.4-94)	0.109	0.381
Alb (g/dL)	4.4 (3.7-39)	4.5 (3.3-5.2)	0.050	0.689
HALP score	0.51 (0.23-5.42)	0.42 (0.14-1.01)	0.280	0.025
ASDAS-CRP	1.3 (0.8-2.2)	2.9 (1.2-5.1)	1.258	<0.001
BASDAI	3.2 (0.2-3.9)	5.7 (4 -10)	1.426	<0.001
BASFI	2 (0-7.3)	4.3 (0.2-9.8)	0.653	<0.001
VAS	4 (0-8)	8 (1-10)	1.052	<0.001

Data are shown as mean±standard deviation or median (range) or n (%). AS=Ankylosing Spondylitis, BMI=Body mass index, NSAID=Nonsteroidal anti-inflammatory drugs, Anti-TNF=Anti-tumor necrosis factor, IL-17=Interleukin-17, WBC=White blood cell, PLT=Platelet, NLR=Neutrophil to lymphocyte ratio, PLR=Platelet to lymphocyte ratio, HGB=hemoglobin, CRP=C-reactive protein, ESR=Erythrocyte sedimentation rate, Alb=Albumin, HALP score=hemoglobin (g/dL) × albumin (g/dL) × lymphocyte (10³/μL) / Platelet (10³/μL), HLA B27=Human leukocyte antigen-B27, ASDAS-CRP=Ankylosing Spondylitis Disease Activity Score, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI=Bath Ankylosing Spondylitis Functional Index, VAS=Visual Pain Score.

areas, morning stiffness length, and morning stiffness intensity. Higher total scores indicate increased disease activity. The score ranges from 0 to 10. BASDAI scores ≥ 4 indicate active disease. Patients classified as in remission were those with BASDAI < 4 , and patients classified as having active disease were those with BASDAI ≥ 4 [4, 15].

Data Collection

Gender, age, body mass index (BMI), habits, the duration of the disease, clinic, medications used, hemoglobin, white blood cell, lymphocyte, neutrophil, platelet, neutrophil to lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), albumin, ESR, CRP, VAS, BASDAI and ASDAS-CRP scores of the individuals included in the study were recorded. The HALP score was determined utilizing the formula the following: hemoglobin (g/L) $\times$ lymphocyte count ($10^3/\mu\text{L}$) $\times$ serum albumin (g/L) / platelet count ($10^3/\mu\text{L}$) [8].

Statistical Analysis

Data analysis was conducted using IBM SPSS 26 software. The Kolmogorov-Smirnov and Shapiro-Wilk tests were applied to assess the normality of the data. For normally distributed data, group comparisons were performed using an independent two-sample t-test, while the Mann-Whitney U test was utilized for non-normally distributed data. Categorical data were compared between groups using the Pearson chi-square test and Fisher's exact test. Effect sizes were

presented with Cohen's d (Cohen, 1988), which was developed for proportions tests (Rosenthal & DiMatteo, 2001, p. 71; comp. Elis, 2010, P. 28) and difference tests. The relationship between inflammation scores that were not normally distributed within the patient group was examined using Spearman's rho correlation coefficient. The diagnostic adequacy of BASFI, VAS and ASDAS-CRP scores for BASDAI level 4 and above (active disease) within the patient group was evaluated using the receiver operating characteristic curve (ROC) analysis. For continuous variables, the results are shown as mean $\pm$ standard deviation and median (range); for categorical variables, they are shown as frequency (%). The significance level for the study was determined to be less than 0.05.

RESULTS

The study included a total of 260 participants, comprising 130 individuals diagnosed with AS (age range: 19-68 years, mean age: 39.82 ± 10.24 years) and 130 healthy controls (age range: 19-68 years, mean age: 40.54 ± 9.81 years). No statistically significant differences were found between the AS patients and healthy control groups regarding age, BMI, gender, alcohol consumption, and lymphocyte count ($P > 0.05$). A comparison between the AS and healthy groups revealed statistically significant differences in smoking status ($P = 0.035$), WBC ($P < 0.001$), neutrophil ($P < 0.001$), monocyte ($P < 0.001$), platelet ($P < 0.001$), CRP ($P < 0.001$), ESR ($P < 0.001$), Albumin ($P = 0.001$), NLR ($P < 0.001$), PLR ($P = 0.001$) and HALP score values ($P < 0.001$) (Table 1).

AS patients were divided into two groups based on BASDAI score: 45 patients in the remission group (score < 4) and 85 patients in the active group (score ≥ 4). Gender ($P = 0.034$), medication use ($P = 0.023$), NLR ($p = 0.015$), PLR ($P = 0.037$), HALP score ($P = 0.025$), ASDAS-CRP ($P < 0.001$), BASDAI ($P < 0.001$) and BASFI ($P < 0.001$) results were statistically significantly higher in the active group than in the remission AS group (Table 2).

There was a negative significant correlation between HALP score and BASDAI (Spearman correlation coefficient (r): -0.208, $P = 0.017$), BASFI (r: -0.195, $P = 0.026$), VAS (r: -0.229, $p = 0.009$), ASDAS-

Table 3. Relationship between HALP score and BASDAI, BASFI, VAS, ASDAS-CRP, CRP and ESR in AS patients

	HALP Score	
	r	P value
BASDAI	-0.208	0.017
BASFI	-0.195	0.026
VAS	-0.229	0.009
ASDAS-CRP	-0.199	0.024
CRP (mg/L)	-0.015	0.863
ESR (mm/h)	-0.307	<0.001

AS=Ankylosing Spondylitis, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI=Bath Ankylosing Spondylitis Functional Index, VAS=Visual Pain Score, HALP score=hemoglobin (g/dL) $\times$ albumin (g/dL) $\times$ lymphocyte ($10^3/\mu\text{L}$) / Platelet ($10^3/\mu\text{L}$), ASDAS-CRP=Ankylosing Spondylitis Disease Activity Score, CRP=C-reactive protein, ESR=Erythrocyte sedimentation rate, r=Spearman's rho correlation coefficient.

Table 4. Receiver operating characteristic curves analysing of the BASFI, VAS, ASDAS CRP, HALP score, NLR, and PLR

	AUC (%95 CI)	P value	Cutt-off	Sensitivity	Specificity
BASFI	0.779 (0.697-0.862)	<0.001	≥ 2.9	76.47%	64.44%
VAS	0.901 (0.849-0.953)	<0.001	≥ 7.0	74.12%	88.64%
ASDAS-CRP	0.958 (0.927-0.989)	<0.001	≥ 2.3	84.71%	100.00%
HALP score	0.619 (0.518-0.721)	0.025	≤ 0.56	80.00%	40.00%
NLR	0.622 (0.516-0.728)	0.023	≥ 11.7	92.94%	28.89%
PLR	0.603 (0.501-0.705)	0.056	-		

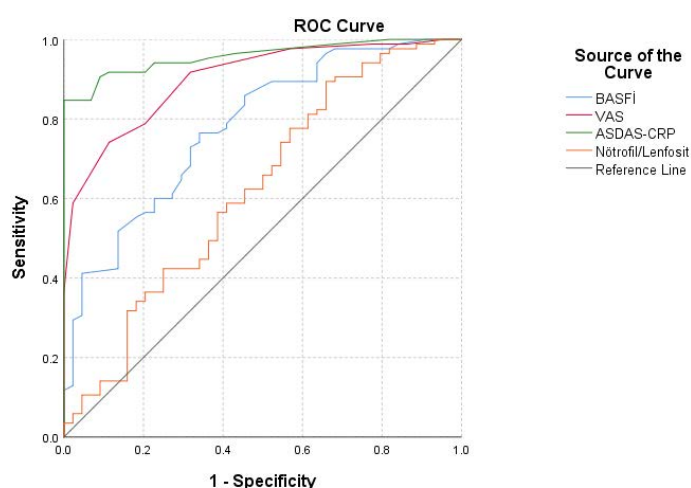
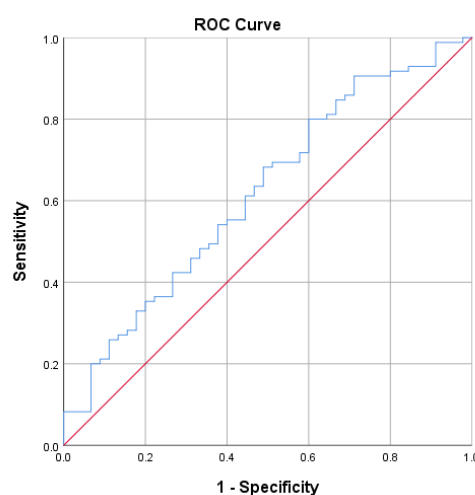
BASFI=Bath Ankylosing Spondylitis Functional Index, VAS=Visual Pain Score, ASDAS-CRP=Ankylosing Spondylitis Disease Activity Score, HALP score=hemoglobin (g/dL) $\times$ albumin (g/dL) $\times$ lymphocyte ($10^3/\mu\text{L}$) / Platelet ($10^3/\mu\text{L}$), NLR=Neutrophil to lymphocyte ratio, PLR=Platelet to lymphocyte ratio.

CRP ($r = -0.199$, $P = 0.024$) and ESR ($r = -0.307$, $P < 0.001$). No negative significant correlation was found between HALP score and CRP ($P > 0.863$). In other words, as HALP score decreased, disease activities and pain scores increased (Table 3).

When the activities of AS patients were evaluated on the receiver operating characteristic curve (ROC), the area under the curve (AUC) was 0.779 [95% confidence interval (CI): 0.697-0.862] for BASFI, 0.901 (95% CI: 0.849-0.953) for VAS, 0.958 (95% CI: 0.927-0.989) for ASDAS-CRP, 0.619 (95% CI: 0.518-0.721) for HALP score, and 0.622 (95% CI: 0.516-0.728) for NLR. The HALP score Cut-off value in assessing disease activity was found to be ≤ 0.56 (sensitivity 80.00%, specificity 40.00%). ROC analyses are shown in Table 4 (Figs. 1 and 2).

DISCUSSION

CRP, ESR, BASDAI, ASDAS CRP and VAS are routinely used as recommended by the guidelines for disease activity, functional status and pain score in AS patients [16, 17]. In this research, a significant association was found between HALP score and ESR, BASDAI, ASDAS CRP, BASFI and VAS. This result showed us that HALP score could be a new marker in the follow-up of disease activity in AS patients. However, no significant relationship was found between CRP and HALP score. CRP is a general biomarker indicating the presence of inflammation in the body and is particularly elevated in acute inflammatory conditions. In chronic inflammatory diseases such as anky-

**Fig. 1.** ROC curve of BASFI, VAS, ASDAS-CRP and NLR values.**Fig. 2.** ROC curve of HALP score.

losing spondylitis, CRP levels may be variable because the severity of inflammation may fluctuate over time. The clinical features and inflammation levels of AS patients may vary from person to person. In some patients, the systemic effects of inflammation may cause significant changes in blood parameters, while in others, they may have lesser effects [18]. In fact, although CRP and ESR are widely used in studies to evaluate the presence of inflammation, acute phase proteins are not specific and especially in patients with non-radiographic axial SpA, the sensitivity of acute phase proteins, which are mostly within normal limits, is low [19, 20].

The HALP score, which evaluates hemoglobin, albumin, lymphocyte and platelet values together, has recently been investigated as an important tool in disease diagnosis and prognosis. This score reflects systemic inflammation, nutrition, impaired immune response and tendency to clot. In addition, since it is easy to calculate, it can be used in diseases with severe inflammation [21, 22]. It has been reported that low HALP score may be an indicator of disease prognosis, chronic systemic inflammation and disease activity in inflammatory conditions such as rheumatoid arthritis [23], anti-neutrophilic cytoplasmic antibody-associated vasculitis [9], stroke [24] and chronic obstructive pulmonary disease [25]. The relationship between the HALP score presented in these studies and AS, an inflammatory disease, is similar to the literature.

In the case of systemic inflammation, hemoglobin and platelets increase, while albumin and lymphocytes decrease. Inflammatory cytokines promote the activation of neutrophils and their accumulation through chemotaxis, leading to a decrease in the number of lymphocytes and albumin in the circulation [26]. Interleukin (IL)-1 β and tumor necrosis factor (TNF)- α suppress erythropoietin release from the kidney. In addition, IL-6 increases hepcidin production from the liver. Hepcidin reduces iron absorption from the intestine and reduces iron release from macrophages, leading to decreased hemoglobin production, which in turn causes anemia of chronic disease in patients [12, 27]. In this research, a significant relationship was found between the healthy group and the components of the HALP score other than lymphocyte values (hemoglobin, neutrophil, albumin, platelet), similar to the literature. However, there was a significant relationship between the active AS and remission groups in terms

of HALP score. This result makes it important to assess the components of the HALP score together rather than using them for disease activity.

In our study, we found negative correlations between the HALP score and various disease activity indices, but the strength of these correlations was weak. The response of each of the parameters including the HALP score to inflammation, long-term disease activity in AS, and treatment received may be due to the poor correlation between disease activity indices and the HALP score.

The increase in neutrophil count in AS patients is associated with an increase in the differentiation and maturation of blood stem cells under the influence of various cytokines, such as TNF- α and IL-6 [28]. The increase in platelet count has been associated with factors such as thrombin, histamine, TNF- α , and IL-12. Again, anemia and a decrease in albumin may occur due to inflammation [29]. One study found that platelet, neutrophil, lymphocyte, NLR and PLR counts were markers of systemic inflammation in AS [30]. Another study reported that NLR ratio could be a significant biomarker in rheumatoid arthritis and AS patients [31]. In this study, similar to the literature, there was a significant relationship between AS patients and healthy group, active AS and remission group in terms of NLR and PLR.

NLR and PLR are generally used as simple, economical and quickly calculated biomarkers, but the HALP score may provide a more comprehensive assessment as it includes more parameters. ASDAS-CRP is known as a more specific indicator of inflammation and generally shows a stronger diagnostic accuracy [17, 30]. In order to better understand the potential clinical benefits of HALP score, more studies are needed to perform a comparative analysis with these indices and to understand the role of each in assessing disease activity. Additionally, the HALP score may allow for a broader perspective on inflammation and overall health status, thus helping to monitor patients' response to treatment or aid in treatment planning.

In our study, there was a significant difference in smoking status between the healthy group and the AS group. In the study conducted by Nam *et al.* [32], it was reported that AS smoking caused an increase in disease activity and clinical progression of the disease. In addition, smoking affects hematological parameters by increasing platelet and hemoglobin levels and de-

creasing lymphocyte levels [33]. It may affect disease activity similar to the literature in our study and appears to be a confounding factor. However, the high rate of smoking in the patient and healthy groups in society may be a positive aspect of the study in terms of reflecting the real life results.

Limitations

Limited sample size may affect generalizability due to single center and retrospective findings. The accuracy of measurement tools and data collection techniques used in the study may also be a limiting factor. In particular, subjective assessments and surveys may create uncertainty about the accuracy of some responses. Due to the retrospective design of our study, larger prospective studies are needed to confirm the limitations of the HALP score, such as its modest diagnostic performance, and for its clinical use.

CONCLUSION

HALP score was lower in patients with active AS than in patients in remission. It showed a negative significant correlation with disease activity scores and HALP score may be a potential marker that can be easily applied to assess disease activity in AS patients.

Ethical Statement

Ethical approval was obtained from the Recep Tayyip University Non-Interventional Clinical Research Ethics Committee (Approval date:18.07.2024 and no:195). The study was carried out in accordance with the Declaration of Helsinki

Authors' Contribution

Study Conception: OC; Study Design: OC; Supervision: OC; Funding: N/A; Materials: OC; Data Collection and/or Processing: OC; Statistical Analysis and/or Data Interpretation: OC; Literature Review: OC; Manuscript Preparation: OC and Critical Review: OC.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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Totally implantable venous access devices: A fifteen-year single-center experience

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ABSTRACT

Objectives: Totally implantable venous access devices (TIVADs) are frequently used in cancer patients, offering significant comfort and advantages. This study aims to evaluate the outcomes of patients who underwent port catheter placement.

Methods: Data from 3,774 patients who underwent venous port catheter placement between 2007 and 2022 were reviewed. Demographic information, primary diagnoses, port placement locations, number of punctures, complications, and reasons for removal were recorded.

Results: The median age of the patients was 54 years (range: 18-86 years). Catheters were placed on the right side in 3,667 patients (97.2%). The most commonly used vessel was the right subclavian vein, accessed in 2,494 patients (66.1%). Complication rates were observed as follows: femoral vein (40%), brachial vein (20%), subclavian vein (12.1%), internal jugular vein (9.9%), and external jugular vein (6.5%). The complication rate following a single puncture was 7.4%, compared to 16.1% for multiple punctures, showing a significant increase with the number of punctures ($P=0.03$). The most common early complication in 142 (3.8%) patients was arterial puncture with bleeding or hematoma, while the most common late complication was catheter infection of 1.4% ($n=54$).

Conclusions: Venous port catheter placement is generally safe, with the right subclavian vein being the most commonly used site. Ultrasound-guided placement reduces complications, which are more frequent with multiple punctures and left-side placements. Early complications like arterial puncture were more common, while late complications were primarily catheter infection.

Keywords: Totally implantable venous access devices, port catheter, subclavian vein

Cancer continues to be increasingly prevalent worldwide and in our country, and according to 2018 data, the cancer incidence in Turkey is 48.6 per hundred thousand [1]. These patients require a suitable intravenous route for many procedures such as getting rid of the irritating effect of the cytotoxic agents used in treating peripheral vessels, blood trans-

fusion, and infection treatment. This pathway should be easily accessible and safe at the same time. Totally implantable venous access devices (TIVAD), or ports, have been used in the treatment of oncological patients since 1982 [2] when they were first used. These devices are preferred because they are long-lasting, easy to maintain, provide high patient comfort, and are

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cost-effective in the long term [3]. It offers significant advantages in managing chemotherapy, blood transfusion, fluid therapy, and other intravenous applications by providing vascular access safely and effectively [4]. However, as with any medical intervention, the use of a venous port catheter (VPC) carries potential risks, and it is important to understand and manage these risks properly.

This study is crucial for evaluating the effectiveness of VPC in cancer patients and understanding the possible risks and complications during the placement and use processes. Our aim is to retrospectively examine the prospectively collected data of patients who had port catheters inserted by a team experienced in cancer treatment and to share the long-term results in light of the literature.

METHODS

The data of 4,739 patients who received treatment for cancer and underwent VPC between 2007 and 2022 in Istanbul University Institute of Oncology, Oncological Surgery Unit were retrospectively analyzed through the file and electronic database. A total of 3,774 patients were included in the study after excluding 12 patients under the age of 18, 212 patients with missing data, 328 patients who died in less than a year, 226 patients who could not communicate, and 187 patients who had a port inserted using the open method.

Demographic information, diagnoses, anatomical location of the port catheter, total number of venous access, arterial puncture, and early and late complications were recorded. The successful procedure was defined as the catheter being in the appropriate anatomical position in the radiological evaluation, blood coming out with aspiration, and the infusion is performed without any problems. Successful venous puncture was defined as the venous blood coming out easily when the vein was entered percutaneously with a syringe. The total number of punctures was recorded.

Complications during catheter insertion were determined as events (allergy, methemoglobinemia) against the local anesthetic drug, arterial puncture and associated hematoma, bleeding, persistent cardiac arrhythmia, and pneumo-hemothorax detected in post-procedure control imaging. Early complications were wound infection, wound dehiscence, pneumothorax

(Px), malposition, catheter dysfunction, arrhythmia, methemoglobinemia due to local anesthesia, and late complications were catheter infection, deep vein thrombosis (DVT), catheter occlusion, migration, skin necrosis, and malfunction. Complications seen within 30 days after port catheter placement were evaluated as early complications and complications seen afterward were evaluated as late complications. All results were evaluated by comparing them with the literature data.

Patient Preparation

Patients applied with a letter requesting the insertion of a venous port catheter, issued by the oncologist who performed their medical follow-up. All patients were evaluated before the procedure by a full-time anesthesiologist in our unit. Posterior-anterior (PA) chest X-ray, complete blood count, blood electrolytes, acute phase reactants, and coagulation factors were examined before and after the application. Attention was paid to ensuring that the platelet count was 50.000/mm³ and above, the hemoglobin level was preferably 9 g/dL and above, the coagulation factors were within normal limits, and there was no examination finding or laboratory value suggestive of acute infection. Patients with detected problems in their values were treated after the appropriate treatment given by their own physicians. Before the procedure, all patients were informed, and written informed consent was obtained. The ethics committee approval for the study was obtained from the Istanbul Faculty of Medicine Ethics Committee Unit on 03.09.2024 with number 2834775.

All procedures were performed in the operating room. A fasting period of at least 6 hours was requested before the procedure to provide general anesthesia against possible acute problems and when necessary. Patients were monitored by the anesthesia team, blood pressure and oxygen saturation were monitored, and peripheral vascular access was established. The electrocautery device plate was placed on the patient so that it was on the same side as the surgical site. Patients with cardiac pacemakers were identified before the procedure, and bipolar cautery was used throughout the procedure.

When necessary, skin shaving of the patients was performed using a machine in the operating room. The patients were positioned in the Trendelenburg position

at a 10-15-degree angle. In cases where visualization of the venous vessel by ultrasonography was difficult due to dehydration, a better image was achieved by administering a 1,000 cc saline infusion. The ultrasound device was positioned on the side where the procedure was not performed, ensuring that the physician could easily view it. When the catheter was planned to be inserted through the jugular vein, pillows were placed under the lower part of the neck and/or the interscapular area to achieve a 45-degree extension of the patient's neck. Since 2012, all procedures have been routinely performed under ultrasound guidance.

The area where the port catheter would be inserted was cleaned with povidone-iodine and then closed with a sterile drape. The ultrasound probe was covered with a sterile sheath. Since the application was relatively easier and more comfortable for the patient, the right subclavian vein was preferred primarily. In case of failure, the following vessels were preferred: left subclavian, right-left external or internal jugular vein, and right-left femoral vein. Especially in patients who underwent mastectomy due to breast cancer and whose treatment was ongoing, the contralateral subclavian vein was preferred, and in patients with bilateral mastectomy and especially if radiotherapy was to be given during treatment, the right-left jugular or femoral vein was preferred. Polysite (Perouse Laboratories, France), Celsite ST301 (Braun, FB Medical, France), and Bard (Bard Access Systems Inc., Salt Lake City, USA) brand products were used at various times as port catheters.

Placement of Port Catheter

A total of 15-20 cc of 2% prilocaine hydrochloride (Citanest, AstraZeneca, Istanbul, Turkey) was applied to the area where the catheter would be inserted and the reservoir would be placed, providing local anesthesia. Port placement under the guidance of anatomical signs without the use of ultrasound was defined as a "Conventional pathway". After visualizing the relevant vein using a 7.5 MHz superficial ultrasound probe (Toshiba Corp., Shimoishigami, Otawara-Shi, Tochigi-Ken, Japan), the vein was entered by aspirating the syringe with an 18G needle. The guidewire was passed through the needle and advanced through the superior vena cava into the right atrium. During this process, the arrhythmia detected on the monitor

was observed, and the catheter was retracted and left close to the junction of the vena cava and right atrium (Cava-atrial junction). The resolution of the arrhythmia indicated that the catheter tip was in the correct position (if no arrhythmia, abnormal position is suspected, or repositioning of the catheter is considered, the patient was taken to the Radiation Oncology unit's operating room, and the catheter was checked to be in the anatomically appropriate place by fluoroscopy). Then, an 8/9F dilator was placed over the guidewire, and under its guidance, a 7.5/8F port catheter was positioned. Two incisions were made, one for the catheter insertion site (small incision) and the other (larger incision) for the reservoir pocket. The catheter was tunneled subcutaneously from the smaller to the larger incision. The catheter was fixed at the cava-atrial junction at approximately 17-20 cm, depending on the patient's height and entry site.

The reservoir was placed in a prepared pocket in the upper part of the pectoralis major muscle, 2 cm distally to the puncture site, with a 2-4 cm skin incision. It was then connected and secured to the catheter. The presence of blood flow from the reservoir was checked, and it was flushed with 10 cc of saline. Until 2015, heparinized saline was used as the flushing solution, but since then, only saline has been used based on our study [5]. To prevent the reservoir from rotating, fixation stitches were placed on both sides using 3/0 Prolene. The subcutaneous tissue, skin, and puncture site were closed with 3/0 Monocryl sutures.

Post-procedure, a PA and lateral chest X-ray were performed for control purposes. Patients with catheter misplacement were transferred to another room with fluoroscopy, where the malposition was corrected. During the procedure, 1 gram of cefazolin sodium was used for prophylaxis, and based on our study from 2011, prophylaxis was not routinely performed afterward [6]. In high-risk patients such as those with neutropenia, prophylaxis was continued. Port catheters were placed by general surgeons (HK, SB, BK, BI), anesthesia specialists (IY), and plastic surgery specialists (SK), each of whom performed at least 50 port catheter placements per year.

Statistical Analysis

Normally distributed variables were given as mean and standard deviation, frequency and percentage, and the distribution of variables was checked

using the Kolmogorov-Smirnov test. Variables that did not show normal distribution were presented as median (min-max). Risk distribution was evaluated by logistic regression analysis. The chi-square test was used to compare independent groups with categorical variables. Data analysis was performed using the IBM SPSS Statistics for Windows, Version 19.0 (IBM-Corp., Armonk, NY, USA). A P-value ≤ 0.05 was accepted as statistically significant.

RESULTS

Patient Characteristics

The median age of the patients was 54 years (range: 18-86 years). Of the patients, 2,030 (53.8%) were male, and 1,744 (46.2%) were female. The mean body mass index (BMI) was 25.1 ± 5.1 kg/m². Higher BMI was not associated with an increased complication rate ($P=0.43$). Based on anesthesia evaluations, the majority of patients had an ASA II score of 54.4% ($n=2,053$). There was no significant difference between complications and ASA scores ($P=0.38$).

Of the patients, 1,298 (34.4%) were diagnosed with colorectal cancer, 1,023 (27.1%) with lung cancer, 419 (11.1%) with cancers of the upper gastrointestinal tract, 279 (7.4%) with cancers of the hepatopancreatobiliary system, and 245 (6.5%) with breast cancer. Patients' demographic findings are shown in Table 1.

Port Placement Locations

All but seven (0.19%) of the port catheters were placed for malignancy and chemotherapy treatment. A total of 132 (3.5%) procedures were performed under intravenous (IV) sedation combined with local anesthesia due to patient requests or medical conditions that were not suitable for local anesthesia alone, while the remaining procedures were performed under local anesthesia only. While the catheter was placed on the right in 3,667 (97.2%) patients, it was placed on the left side in 107 (2.8%) patients, which was statistically significant in terms of complications ($P=0.001$). The most preferred vein was the right subclavian vein in 2,494 (66.1%) patients. Right jugular interna was preferred in 961 (25.5%), right jugular externa in 196 (5.2%), right femoral in 11 (0.29%), and right brachial vein in five (0.13%) patients. Using anatomical mark-

ers, port catheters were placed in 45.4% ($n=1,714$) of the patients conventionally and in 54.6% ($n=2,060$) of the patients with ultrasound guidance. Antibiotic prophylaxis was administered to 2,061 (54.6%) patients, while it was not administered to 1,713 (45.4%) patients. Port flushing was predominantly performed with a normal saline (NS) + Heparin (100 U/mL) solution in 60.5% ($n=2,283$) patients, while it was performed with only NS in 39.5% ($n=1,491$) of patients (Table 1). During the follow-up, all patients were advised to come to our unit to have the port flushed with 10 cc NS after each use (medication, parenteral nutrition, blood collection, etc.) or every two months when not in use.

Complications

While 11.3% ($n=427$) of the patients had complications, 88.7% ($n=3,347$) in the whole patient group had no complications. The highest complication rates were seen after application from the femoral, brachial, subclavian and jugularis internal veins, respectively (40%, 20%, 12.1%, 9.9%). The least complication was observed after the procedures performed from the jugularis external vein with 14/215 (6.5%).

The number of successful procedures was 2,079 (55.1%) in a single puncture and 1,695 (44.9%) with more than one puncture. Additionally, the complication rate after a single puncture was 7.4%, while the rate was 16.2% in multiple punctures, and the frequency of complications increased significantly with the increase in the number of punctures ($P=0.03$).

While the complication rate was 12.4% when prophylactic antibiotics were not used during the procedure, it was 10.1% when used, but there was no statistical difference between antibiotic use and complication development ($P=0.64$).

When ultrasound was used during port insertion, the complication rate was 5.6%, while the complication rate after conventional insertion using anatomical markers was 18.1% and was statistically significant ($P=0.024$). In other words, the use of conventional route was one of the factors that increased the frequency of complications. However, flushing the port system with physiological serum instead of heparin solution after the procedure did not increase the risk of complications ($P=0.82$) (Table 1).

The early complication rate was 6.7% ($n=252$), while the late complication rate was 4.6% ($n=175$).

Table 1. Demographic information and port catheter procedure characteristics

n (%)	Overall 3.774 (100)	Complication (-) 3.347 (88.7)	Complication (+) 427 (11.3)	P value
Male, n (%)	2.030 (53.8)	1.785 (47.3)	245 (6.5)	0.37
Female, n (%)	1.744 (46.2)	1.562 (41.4)	182 (4.8)	
Age (years) (median, range)	54 (18- 86)	54 (18-83)	53 (20-86)	0.56
BMI (kg/m ²) (mean±SD)	25.1 (±5.1)	25.7 (±5.2)	24.3 (±5.4)	0.43
ASA I, n (%)	864 (22.9)	712 (18.8)	152 (4.1)	0.38
ASA II, n (%)	2.053 (54.4)	1.904 (50.5)	149 (3.9)	
ASA III, n (%)	857 (22.7)	731 (19.4)	126 (3.3)	
Colorectal Ca, n (%)	1.298 (34.4)	1.129 (30)	169 (4.4)	0.23
Lung Ca, n (%)	1.023 (27.1)	948 (25)	75 (2.1)	
Upper GIS Ca, n (%)	419 (11.1)	382 (10.1)	37 (1)	
Hepatopancreatobiliary Ca, n (%)	279 (7.4)	248 (6.6)	31 (0.8)	
Breast Ca, n (%)	245 (6.5)	210 (5.6)	35 (0.9)	
Hematological Ca, n (%)	230 (6.1)	198 (5.3)	32 (0.8)	
Gynecological Ca, n (%)	174 (4.6)	148 (3.9)	26 (0.7)	
Others, n (%)	106 (2.8)	84 (2.2)	22 (0.6)	
Right side, n (%)	3.667 (97.2)	3.281 (87)	386 (10.2)	0.001
Left side, n (%)	107 (2.8)	66 (1.7)	41 (1.1)	
Subclavian, n (%)	2.543 (67.4)	2.236 (59.3)	307 (8.1)	
Right	2.494 (66.1)	2.191 (58.1)	303 (8)	0.38
Left	49 (1.3)	45 (1.2)	4 (0.11)	
Internal Jugular, n (%)	996 (26.4)	897 (23.8)	99 (2.8)	
Right	961 (25.5)	868 (23)	93 (2.5)	0.017
Left	35 (0.93)	29 (0.77)	6 (0.16)	
External Jugular, n (%)	215 (5.7)	201 (5.3)	14 (0.4)	
Right	196 (5.2)	187 (4.9)	9 (0.23)	0.42
Left	19 (0.53)	14 (0.4)	5 (0.13)	
Femoral, n (%)	15 (0.39)	9 (0.23)	6 (0.16)	
Right	11 (0.29)	7 (0.18)	4 (0.11)	0.76
Left	4 (0.1)	2 (0.05)	2 (0.05)	
Brachial, n (%)	5 (0.13)	4 (0.11)	1 (0.02)	0.78
Number of Punctures, n (%)				
1	2.079 (55.1)	1.925 (51)	154 (4.1) *7,4	0.03
≥ 2	1.695 (44.9)	1.422 (37.7)	273 (7.2) *16,2	
Prophylactic Ab, none, n (%)	2.061 (54.6)	1.806 (47.9)	255 (6.7) *12,4	0.64
Prophylactic Ab, yes, n (%)	1.713 (45.4)	1.541 (40.8)	172 (4.6) *10,1	
Convantional method, n (%)	1.714 (45.4)	1.403 (37.2)	311 (8.2) *18.1	0.024
Ultrasound-Guided, n (%)	2.060 (54.6)	1.944 (51.5)	116 (3.1) *5,6	
Heparin + NS, n (%)	2.283 (60.5)	2.081 (55.2)	202 (5.3) *8,8	0.82
NS, n (%)	1.491 (39.5)	1.266 (33.5)	225 (6) *15.1	

SD=Standard Deviation, Ab=Antibiotic, BMI=Body mass index, USG=Ultrasonography, NS=Normal saline, Ca=Cancer, ASA=American society of anesthesiologists, *Complication rate within the group

Table 2. Early and late complications

n= 427 (11.3%)	Early Complications		P value	Late Complications		P value
	n= 252 (6.7%)			n= 175 (4.6%)		
	n	%		n	%	
Gender						
Male	144	57.1	0.12	90	51.6	0.38
Female	108	42.9		85	48.4	
Venous Access Method						
Conventional	155	61.5	0.004	78	44.7	0.16
Ultrasound-Guided	97	38.5		97	55.3	
Number of Punctures						
1	101	40.1	0.012	77	43.8	0.08
≥2	151	59.9		98	56.2	
Port Flushing Method						
Heparin +	110	43.5	0.07	82	47.1	0.18
Normal Saline	142	56.5		93	52.9	

Both early (57.1%) and late complications (51.6%) were higher in the male gender but were not statistically significant ($P=0.38$). In the procedures performed with the conventional method, early complications were observed at a higher rate than those performed with ultrasound guidance and were statistically significant ($P=0.004$), while there was no significant difference in terms of late complications ($P=0.16$). When evaluated according to the number of punctures, it was statistically significant that both early ($P=0.012$) and late complications ($P=0.08$) were seen as the number of punctures increased. There was no statistical difference between early ($P=0.07$) and late ($P=0.18$) complications in terms of port flushing method (Table 2).

The most common early complication, occurring in $n=142$ (3.8%), was arterial puncture with possible bleeding or hematoma due to the procedure. The common characteristic of these patients was that most were on anticoagulant therapy. Although no patient required surgery due to bleeding, port removal was performed in eight patients due to infection secondary to bleeding. The second most frequent early complication, seen in $n=46$ (1.2%) patients, was malposition, and revision was performed on the same day for all patients in whom this condition was detected. The least com-

mon early complication was methemoglobinemia with a rate of 0.08% ($n=3$). While one patient with this condition recovered with conservative follow-up, two patients were hospitalized for one day due to nausea and vomiting and a decrease in oxygen saturation in room air (<80 mmHg) and discharged with recovery. Pneumo and/or hemothorax were seen in 0.7% ($n=28$) of the patients. Since two of these patients had less than 5% pneumothorax, the mask was conservatively followed up with oxygen and bronchodilator treatment and discharged without any problems, while 26 patients were hospitalized with closed thoracic tube drainage. No complications developed during hospitalization and all patients were discharged without any problems. Permanent cardiac arrhythmia requiring procedural intervention developed in $n=12$ (0.3%) patients. Patients recovered without any problems with anti-arrhythmic treatment by the anesthesiologist without the need for catheter removal. Only one patient's arrhythmia could not be controlled with the treatment applied in the operating room and was admitted to the Cardiology Arrhythmia Intensive Care Unit and was followed up and discharged two days later without any problems.

The most common late complication was catheter infection of 1.4% ($n=54$). These patients were con-

Table 3. Causes and outcomes of complications

Complications	n	%	% Overall	Outcomes
Early Complications	252	100	6.7	
Arterial puncture +/- Hematoma	142	56.3	3.8	Eight patients' ports were removed*
Malposition	46	17.7	1.2	Revision was done on the same day
Pneumothorax +/- Hemothorax	28	11.1	0.7	Two patients were monitored 26 patients had chest tubes inserted
Arrhythmia (requiring intervention)	12	4.7	0.3	One patient was monitored in the intensive care unit for arrhythmia
Methemoglobinemia	3	1.3	0.08	One patient stayed in the hospital for one day
Other (Persistent pain, patient request, wound dehiscence)	21	8.3	0.6	Five ports were removed
Number of removed ports	13	5.6	0.34	
Late Complications	175	100	4.6	
Catheter infection	54	30.9	1.4	44 patients' port were removed
Deep vein thrombosis	48	27.4	1.3	All patients' ports were removed after antithrombotic treatment
Reservoir malrotation	29	16.5	0.8	21 patients had their port corrected surgically Eight patients had their port corrected manually
Malfunction	20	11.4	0.5	15 patients had their port removed.
Skin necrosis	14	8.1	0.4	Nine patients underwent wound debridement Five patients had their port removed**
Other*** (Seroma, wound dehiscence, migration)	10	5.7	0.3	Three patients had their port removed Seven patients' ports were revised
Number of removed ports	115	6.6	3.04	

*Due to infection secondary to bleeding

**Due to chemical burn and necrosis caused by chemotherapeutic drug extravasation

***Requiring intervention

sulted with infectious diseases. Catheters were removed in 44 patients who had pathogenic microorganism growth in blood cultures taken from the catheter and peripheral vein and who did not respond to treatment. In ten patients with no bacterial growth, who responded well to treatment or had no growth in two consecutive blood cultures after treatment, the catheter was not removed. DVT, a serious complication, was the second most common (n=48, 1.3%). The level of thrombosis was determined by Doppler ultrasonography and anti-thrombotic treatment was organized by the Cardiovascular Surgery Unit. After the treatment,

the catheters of all patients were removed. The third most common complication was reservoir malrotation (n=29, 0.8%). In 21 of these patients, a second procedure was performed to reposition the reservoir and it was observed that the reservoir was not fixed with sutures. The catheters of eight patients were manually corrected in the outpatient clinic. The least common complication was seroma, wound dehiscence, and catheter tip migration, which required intervention and were seen at a rate of 0.3%. Fourteen (0.4%) patients developed partial skin necrosis due to drug extravasation, and improvement was achieved with debridement

and dressings. However, catheter was removed in five patients due to secondary infection that did not respond to treatment (Table 3).

DISCUSSION

Complications occurred in 11.3% (n=427) of 3,774 patients who underwent permanent central venous port catheterization with a minimum follow-up period of one year. We found that age, gender, ASA score, body mass index, prophylactic antibiotic use, and use of physiological saline for port flushing did not increase the risk of complications, while using conventional methods instead of ultrasound during the procedure ($P=0.024$), performing procedures on the left side ($P=0.017$), and performing more than one puncture ($P=0.03$) were factors that increased complication rates.

Permanent central venous port catheters are widely used, especially in cancer patients who experience difficulty finding vascular access or require long-term intravenous treatment [7]. Although the use of these catheters offers several advantages, the implantation process and the post-implantation period can lead to some undesired situations. The use of ultrasound guidance during port insertion is likely to be beneficial in reducing complication rates [8].

The most common early complication in our study was arterial puncture and/or hematoma (n=142, 3.8%). This rate was consistent with the studies in the literature [9, 10]. Eight patients who developed a secondary infection due to hematoma, which did not respond to treatment, required port removal.

When deciding on the veins for port catheter placement, several factors must be considered. Different veins such as the subclavian, jugular, and cephalic veins each have distinct advantages and disadvantages. The selection of each vein type depends on the patient's general health status, surgical history, vascular anatomy, and intended use of the catheter [11]. The preference for the subclavian vein is typically due to its short distance to the vena cava and right atrium; however, potential complications such as the risk of pneumothorax must be considered. The jugular vein, on the other hand, follows a relatively straight path, which can make catheter placement easier. The risk of pneumothorax is not as high as that of the subclavian vein. During surgical intervention, if the neck region

is involved, the segment of the catheter passing through the subcutaneous tunnel may bulge over time and become visible with neck movements, potentially impacting the patient's quality of life. Although the risk of hemothorax and/or pneumothorax is reported in the literature to range from 1.5% to 4.7% [12-14] it is closely associated with the surgeon's level of experience. In our study, the pneumothorax rate (0.7%) was relatively lower than the literature, as the port catheter was placed by specialist physicians who performed at least 50 or more successful procedures per year. Another factor contributing to its low occurrence rate is that procedures have been performed with ultrasound guidance since 2012. In a recently published meta-analysis [15] evaluating 130 studies, it was reported that ultrasound-guided port placement reduced both arterial puncture (risk ratio [RR], 0.20; 95% credible interval [CrI], 0.09-0.44; 13.5 events vs. 68.8 events/1000 catheters) and pneumothorax (RR, 0.25; 95% CrI, 0.08-0.80; 2.4 events vs. 9.9 events/1000 catheters). The right subclavian vein was used as the primary vein choice due to patient comfort. If success was not achieved after several punctures, the right jugular vein was preferred instead of insisting. Three of the 28 patients who developed pneumothorax were followed conservatively because they had less than 5% P_x, while 26 patients were hospitalized with closed thoracic tube drainage and were discharged without any problems after hospitalization.

In our study, the port was localized toward the cava-atrial junction, which was confirmed by observing cardiac arrhythmia on the monitor. The catheter tip was retracted and fixed at the cava-atrial junction. Twelve patients with persistent arrhythmia (sinus tachycardia, ventricular extrasystole) were treated with lidocaine, beta blocker, or calcium channel blockers by the anesthesia team. Only one patient was taken to the Cardiology Arrhythmia Intensive Care Unit and monitored because the arrhythmia continued. If no arrhythmia was present, but there was uncertainty about the correct placement of the port, the issue was resolved by transferring the patient to the operating room with a fluoroscopy. The rate of arrhythmia was 0.3% and it was consistent with the studies in the literature [16].

The least common early complication was methemoglobinemia, observed in three patients (0.08%). Local anesthetic reactions occurred in one patient

(0.04%), characterized by reduced oxygen saturation (room air $sO_2=82-90$ mmHg), while another patient (0.04%) experienced nausea, vomiting, and cyanosis (room air $sO_2=78-86$ mmHg). In both patients, the maximum methemoglobin levels in blood gas analysis were measured as 10% and 12%. One patient was hospitalized and monitored with oxygen therapy; by the following day, the methemoglobin level had decreased to $<2\%$ and the patient was discharged. The other patient was discharged on the same day after an uneventful follow-up with oxygen therapy via mask. None of the patients required antidotes such as methylene blue.

Among the late complications, DVT was seen in 48 (1.3%) patients. Most of these patients had a history of extravasation during the administration of chemotherapy or failure to regularly flush the port after use. In addition, none of them had anti-coagulant agents in their routine treatment. Only four patients were using anti-aggregates. The port catheter was removed in all patients at the end of antithrombotic treatment. The rate of thrombosis was consistent with the literature [17-19]. In a group of 1,586 patients with breast cancer, catheter-related thrombosis was reported in 96 patients (6.1%). The authors indicated that the location of catheter placement ($P=0.004$), catheter size ($P<0.001$), and catheter dwell time ($P<0.001$) were significant factors associated with thrombotic occlusion [20].

In a study of 799 cancer patients, the rate of catheter-related infection was 2.1% [21]. In a recent study, the infection rate was reported to be 5.1%, with the rate of port catheter removal due to infection at 0.85% [22]. In our study, the infection rate was 1.4% ($n=54$) across the entire group. Among patients with bacterial growth in blood cultures, the catheter was removed in 44 cases based on the recommendation of infectious disease specialists. In contrast, catheter removal was not required in 10 patients without bacterial growth.

Reservoir malrotation was observed in 29 (0.8%) patients. The reasons for catheter complications, particularly in obese patients, were the wide opening of the reservoir pocket, the loss of subcutaneous fat in weight loss patients causing an enlargement of the pocket, and the failure of fixation stitches.

A less common complication, skin necrosis (0.4%), was primarily caused by extravasation of the

chemotherapeutic drug during administration. Additionally, in patients with a small distance between the reservoir and the skin, the port needle eroded the skin during reservoir access. These patients were treated with debridement and dressing, although the port had to be removed in five patients (0.1%).

Among the 427 patients who developed complications after PCVC insertion, 30.1% ($n=128$) required port removal. When considering the entire patient group, the rate of port removal was 3.4% ($n=128/3,774$), which aligns with findings in the literature.

Limitations

The limitations of our study include its retrospective design, single-center nature, and the absence of a control group.

CONCLUSION

A large sample size reduces the margin of error and increases the accuracy of estimates, thereby enhancing the reliability of the study findings. Furthermore, a study with sufficient power is crucial for generalizability, as it ensures that the results represent the target population. In this context, our study is one of the largest reported to date, focusing exclusively on cancer patients. The findings demonstrated that positioning the port on the left side, performing multiple punctures, and using conventional methods instead of ultrasound guidance significantly increased the risk of complications. Furthermore, when performed by experienced practitioners and followed by appropriate post-procedural care, venous port catheter placement under ultrasound guidance is a highly comfortable and safe procedure for cancer patients.

Ethics Statement

The ethics committee approval for the study was obtained from the Istanbul Faculty of Medicine Ethics Committee Unit on 03.09.2024 with number 2834775.

Authors' Contribution

Study Conception: BK; Study Design: BK; Supervision: BK; Funding: BI; Materials: BK; Data Collection and/or Processing: BK; Statistical Analysis and/or

Data Interpretation: BI; Literature Review: BI; Manuscript Preparation: BK and Critical Review: HK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Effect of binaural beats on pain, anxiety, and procedure tolerance in patients undergoing colonoscopy without sedation: A randomized controlled trial

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ABSTRACT

Objectives: This study aimed to investigate the effect of binaural beats on pain, anxiety, and tolerance during colonoscopy of patients without sedation.

Methods: This is a prospective, randomized, controlled, single-blind procedural study that included 92 Turkish patients who underwent colonoscopy. The patients were randomly divided into two groups: the binaural beat music group (n=46) and the control group (n=46). The binaural music group was subjected to music through headphones during the colonoscopy, while the control group was provided headphones without music. The anxiety levels were measured using a Visual Analog Scale for Anxiety (VAS-anxiety), while the pain levels were assessed using a Visual Analog Scale for Pain (VAS-pain). Hemodynamic changes, procedure tolerance, cecal insertion and withdrawal times, polyp detection, and patients' experiences related to colonoscopy were recorded. Likert scales, indicating procedure satisfaction, were also administered immediately after the colonoscopy.

Results: The music group demonstrated significantly lower anxiety scores compared to the control group, along with better tolerance scores, a higher willingness to repeat the procedure, and a significant preference to listen to the same music again for any upcoming unsedated colonoscopy procedures ($P<0.05$). No significant difference was observed between the groups in terms of pain experienced during the procedure, vital parameters, cecum insertion time, procedure time, and polyp detection rate ($P>0.05$).

Conclusions: For patients undergoing colonoscopy without being sedated, listening to music composed of binaural beats demonstrated a significant decrease in anxiety levels and improved patient tolerance during the procedure, presenting an alternative to sedative medications.

Keywords: Binaural beats, anxiety reduction, gastrointestinal endoscopy, sedation free procedures, non-pharmacological intervention

Colonoscopy remains the gold standard for both diagnosing and treating colorectal disorders. It is also considered the primary approach for detecting precancerous lesions and colorectal cancer [1].

However, the colonoscopy procedure itself can cause pain and discomfort, leading to anxiety for patients before the procedure. As a result, many at-risk patients tend to postpone undergoing colonoscopy [2]. Addi-

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tionally, anxiety and pain can decrease the patient's tolerance and satisfaction during the procedure. Endoscopists can use sedative drugs to reduce patient anxiety and discomfort to minimize any disruptions caused by sudden or involuntary movements during the procedure. However, due to rising labor costs and equipment needs, many centers struggle to provide anesthesia and sedation to all patients. Also, especially in older adults, sedatives may raise the risk of cardiovascular disease [3].

Music therapy has been proposed as a safe, cost-effective, non-pharmacological approach to alleviate anxiety and stress in patients undergoing various interventional procedures [4]. It has been shown that music therapy improves relaxation, reduces anxiety, and effectively distracts the patient from pain phobia [5]. Hence, utilizing music therapy as supportive management in addition to conventional therapy for pain and anxiety has been investigated in numerous disciplines, such as oncology [6], endocrinology [7], pediatrics [8], urology [9], and orthopedics [10].

Gerald Oster first introduced binaural beat music as a unique audio type fifty years ago. The effect of binaural beats is best perceived when listened to with headphones. When two sinusoidal tones of close but differing frequencies are independently delivered to each ear at a consistent intensity, a single illusory tone is perceived by the listener. This perceived tone has a frequency that matches the average of the two separate tones, and its amplitude modulates at a rate equal to the frequency difference between them [11]. The inferior colliculi and superior olivary nuclei in the brainstem are responsible for merging the auditory signals from each ear, leading to the initial perception of binaural beats. It then progresses as neural impulses traverse the reticular formation, ascending through the midbrain to reach the thalamus, auditory cortices, and additional cortical areas [12]. Numerous clinical studies have provided evidence supporting the efficacy of binaural beat interventions in mitigating pain and anxiety in diverse clinical settings [13].

Due to the excessive patient load in our clinic, the lack of appropriate restrooms for sedated patients, and insufficient anesthesia personnel, we face difficulties in performing colonoscopy procedures after sedating the patient. Therefore, we have been seeking alternative methods beyond anesthetic interventions to im-

prove colonoscopic procedure tolerance and patient satisfaction. Theta and delta-band frequencies have been demonstrated as useful in reducing anxiety and raising hypnotic susceptibility [14, 15]. In this study, we utilized binaural beats at 5 Hz theta frequencies to investigate their effects on colonoscopic pain, anxiety, and tolerance.

METHODS

Study Design

This was a prospective, randomized, single-blind, controlled trial in which the physician performing the procedure were blinded. The study was conducted in the colonoscopy unit of the Gastroenterology Clinics of Abdurrahman Yurtaslan Oncology and Training Research Hospital in Ankara, Turkey, between October 2023 and November 2023. The study protocol was granted ethical approval (Approval number and date: 2023-10/418).

Sample and Setting

G*Power software version 3.1 was employed to carry out an a priori sample size calculation. In the referenced study, the mean VAS Pain score was reported as 5.19 for the experimental group and 6.65 for the control group. Based on these VAS values, a sample size calculation was performed using the "Difference between two independent means" test with a two-tailed approach. With an effect size (d) of 0.60, 80% statistical power, and a 0.05 margin of error, it was determined that a minimum of 45 participants per group, totaling 90 individuals, would be required for the study [16].

The study initially enrolled 98 patients. However, six patients were subsequently excluded as they did not fulfill the specified eligibility criteria. Sex or underlying diseases were not considered specifically. However, patients with a history of prior colonoscopic procedures, had anxiety or panic disorders, epilepsy, hearing impairments, ear canal disorders, or unwilling to undergo the procedure while listening to music were excluded from the study. Hence, this study assessed 92 Turkish patients aged 18 to 70 years with colonoscopy appointments scheduled at the above-mentioned location.

Procedure

The patients arriving for colonoscopy procedures at the location of intervention were included in the study. Authorized research personnel contacted eligible participants, explained the study in detail, and obtained their consent to participate. Following the acquisition of consent, participants were randomly split into two groups through a block randomization sampling technique: the binaural beat (music) group (n=46) and the control group (n=46). The block size for randomization was determined by the researchers, followed by the computation of all possible allocation combinations for the block, of which a random block combination was selected to split the patients into groups. A block size of four involved the random assignment of two patients to the group and two to the intervention. This random block-choosing procedure was repeated until all patients were allocated to a group at random. This division was facilitated by a computerized randomization sequence created by an independent researcher not directly engaged in the study; individuals assigned through computer randomization were provided sealed envelopes until the allocation phase. These envelopes were unsealed solely upon the agreement of eligible participants to take part in the intervention and after obtaining informed consent. Patients and colonoscopy nurses were aware of the study groups, but the outcome assessors and gastroenterologist performing the procedure were blinded. The colonoscopy nurse accompanied the patients throughout the entire procedure. The vital parameters and anxiety levels (measured using the VAS-anxiety) of all patients were measured by the colonoscopy nurse immediately before the procedure, and their demographic information was recorded. Subsequently, the patients were prepared for the colonoscopy procedure. Both groups received an MP3

player (Meizu Slim 8GB MP3 Player, Meizu Technology Co Ltd, China) and in-ear stereo headphones. The music group was exposed to binaural beats (relaxing theta waves at 5 Hz, MusicMindMagic Production) during the colonoscopy, while the control group wore headphones without auditory stimulation. No music was played for the control group to evaluate only the effects of binaural beats precisely. To prevent any influence on the results, the procedures were conducted by a single gastroenterologist. The colonoscopy nurse used the Modified Gloucester Comfort Scale to document and assess patient comfort, including levels of tolerance and compliance throughout the procedure. Neither the nurse nor the physician spoke to the patients during the procedure. After the procedure's completion, the patients' headphones were removed, and they were transferred to the recovery unit. Their vital parameters, VAS-anxiety and VAS-pain scores, were measured and recorded again 5 minutes after the colonoscopic procedure. All elective colonoscopies were scheduled between 8:30 AM and 12:30 PM and performed by an experienced endoscopist who was unaware of the group assignments. The Fujinon EC-590WL4 colonoscope (Fujinon Inc, Tokyo, Japan) was used in the procedures. The colonoscopy nurse recorded the examination time for all patients who underwent the procedure. The observed polyps were removed during the withdrawal of the colonoscope.

Instruments

The Visual Analog Scale (VAS), created by Price *et al.* [17] in 1983, has been utilized to assess patients' subjective feelings of anxiety and pain. This scale features a 10-cm line that can be oriented vertically or horizontally, with the two ends indicating the highest and lowest levels of anxiety and pain (0: no anxiety/no pain, 10: extreme anxiety/ the most severe pain).

Table 1. Modified Gloucester comfort scale

Score	Scale	Description
1	No	No discomfort-resting comfortably throughout
2	Minimal	One or two episodes of mild discomfort, well tolerated
3	Mild	More than two episodes of discomfort, adequately tolerated
4	Moderate	Significant discomfort, experienced several times during the procedure
5	Severe	Extreme discomfort, experienced frequently during the procedure

The patients' self-reported levels of anxiety and pain were recorded on this scale by the colonoscopy nurse. This indicator serves as a dependable tool for evaluating anxiety and pain [17, 18].

The Modified Gloucester Comfort Scale is a tool used to evaluate patient tolerance and compliance throughout the procedure [19]. This scale assesses discomfort, characterized by coughing, retching, belching, and non-compliance, using a 5-point Likert scale, where 1 indicates no discomfort and 5 represents extreme discomfort during the procedure. (Table 1).

Post-procedure, patients responded to a series of questions designed to evaluate their satisfaction with the unsedated colonoscopy experience and their willingness to undergo the unsedated procedure again for health reasons (yes, maybe, or no). Additionally, the music group was queried with a three-option response (yes, not sure, or no) regarding whether the music enhanced relaxation and if they would be interested in listening to the same music in future procedures.

Statistical Analysis

Data was analyzed using IBM SPSS Statistics version 27. Measurements were taken from two groups

(music vs. control) at two different time points, encompassing diastolic and systolic blood pressure, heart rate, and VAS scores. Continuous variables were presented as mean±standard deviation or median (25%-75% interquartiles). Normal distribution was determined using the Kolmogorov-Smirnov test. Categorical data were analyzed using the Chi-square test, while continuous variables were evaluated with either the Student's t-test or the Mann-Whitney U test, depending on data distribution. Repeated measures ANOVA was conducted to evaluate the intervention's effects, examining the influence of group, time, and the interaction between group and time (group×time effect). Statistical significance was defined as $P < 0.05$.

RESULTS

Data were collected between October 2023 and November 2023, through which 98 patients were evaluated, with 6 excluded from the study due to not meeting the eligibility criteria. The rest of the 92 patients (46 in the music group, 46 in the control group, as originally assigned) included in the study under-

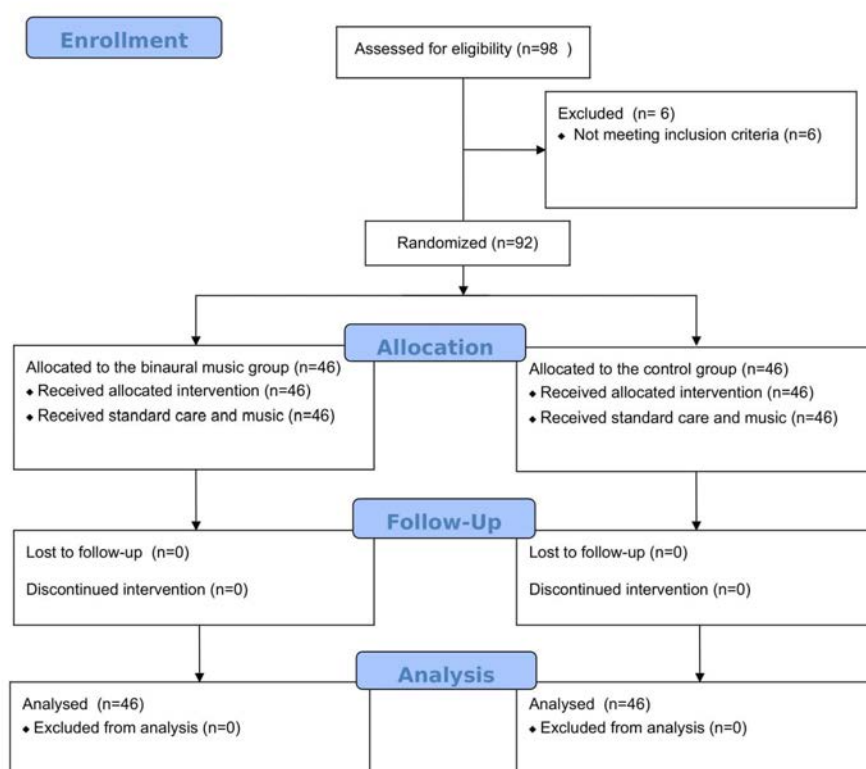


Fig. 1. CONSORT flowchart for participant flow.

went the procedure, and all colonoscopic interventions were successfully performed. The study was concluded when the target sample size was reached. With regard to the binaural music intervention, no subjects reported any discomfort (Fig. 1).

A summary of the demographics of patients and procedure related parameters has been presented in Table 2. Statistical analysis revealed no significant differences in age, sex, or education level, nor in the specific indications for colonoscopy ($P>0.05$), indicating

a similar demographic profile across both groups. Upon analysis of procedural parameters, no significant differences were observed between groups with respect to VAS pain scores, polyp rates, or procedure duration ($P>0.05$). Based on the Modified Gloucester Comfort Scale, the music group demonstrated significantly higher procedural tolerance compared to the control group ($P=0.020$).

Table 3 presents the changes in systolic and diastolic blood pressure, heart rate, and VAS-anxiety

Table 2. Baseline characteristics of patients and procedure related parameters

Characteristics	Music (n=46)	Control (n=46)	P value
Age(years)	49.17±10.83	53.54±13.11	0.085
Sex			
Female	16(34.8)	19(41.3)	0.519
Male	30(65.2)	27(58.7)	
Education level			
Elementary school	15(32.6)	19(41.3)	0.576
Secondary school	6(13)	7(15.2)	
High school	9(19.6)	10(21.7)	
University	16(34.8)	10(21.7)	
Colonoscopy indication			
Iron deficiency	8(17.4)	13(28.3)	0.699
Dyspepsia	7(15.2)	5(10.9)	
Symptoms (pain, flatulence)	5(10.9)	5(10.9)	
Chronic diarrhea	8(17.4)	4(8.7)	
Chronic constipation	4(8.7)	7(15.2)	
Rectal bleeding	6(13)	5(10.9)	
Cancer screening	8(17.4)	7(15.2)	
Diabetes mellitus	6(13)	9(19.6)	
VAS-pain	5.22 ± 2.53	5.65 ± 2.55	0.415
Procedure duration(minutes)	11.04 (10.47, 12.14)	11.24(10.69,12.94)	0.266
Patients with polyps	10 (21.7)	17 (37)	0.109
Modified gluocester comfort scale			
1	16 (34.8)	7 (15.2)	0.020
2	18 (39.1)	12 (26.1)	
3	6 (13)	12 (26.1)	
4	6 (13)	12 (26.1)	
5	0 (0)	3 (6.5)	

Values are presented as mean±standard deviation or median (25-75 inter-quartiles) or number (%). VAS, visual analog scale. Bold indices $P<0.05$

Table 3. Descriptive statistics and effects of intervention in control and music groups over time

Variables	Group	Before	After	P value
SBP(mmHg)	Music	148.93±23.88	147.26±22.75	T; F=1.353, P=0.248
	Control	147.02±15.35	144.07±17.58	G; F=0.473, P=0.493
				G×T; F=0.104, P=0.748
DBP(mmHg)	Music	89.98±11.68	93.09±13.07	T; F=0.007, P=0.934
	Control	90.28±11.51	92.54±10.02	G; F=1.912, P=0.170
				G×T; F=0.085, P=0.771
HR(beats/min)	Music	95.76±13.74	96.28±14.83	T; F=3.072, P=0.083
	Control	96.28±14.83	94.85±17.78	G; F=1.099, P=0.297
				G×T; F=1.746, P=0.190
VAS - anxiety	Music	6.67±2.09	2.03±1.56	T; F=267.363, P<0.001
	Control	6.54±2.32	3.41±2.03	G; F=2.797, P=0.098
				G×T; F=9.294, P=0.003

Values are presented as the mean±standard deviation. SBP=systolic blood pressure, DBP=diastolic blood pressure, HR=heart rate, VAS=visual analog scale, G=groups, T=time (before-after), G×T=group × time. Bold indicates P<0.05

scores before and after the procedure, as well as the interaction effect (group × time) between the groups. In the music group, the mean VAS-anxiety score showed a decrease of 4.64 points. The interaction effect for VAS-anxiety scores was statistically significant (group × time; F(1,90)=9.294, P=0.003). In contrast, no significant interaction effects were found for the other parameters (P>0.05).

Table 4 displays the patient satisfaction results.

The percentage of those in the music group expressing willingness to undergo the colonoscopic procedure again without sedation and those stating that the procedure went better than expected was significantly higher compared to the control group(P<0.05). Additionally, most patients in the music group expressed a desire to listen to the same music again if they required a sedation-free colonoscopic procedure in the future.

Table 4. Patient satisfaction

	Music (n=46)	Control (n=46)	P value
Willing to repeat the procedure			
Yes	35(76.1)	21(45.7)	0.010
Maybe	3(6.5)	9(19.6)	
No	8(17.4)	16(34.8)	
Patient experience			
Better than expected	36(78.3)	22(47.8)	0.009
As expected	5(10.9)	9(19.6)	
Worse than expected	5(10.9)	15(32.6)	
Would listen to the music again			
Yes	33(71.7)		
Not sure	6(13.0)		
No	7(15.2)		

Data are presented as number (%). Bold indicates P<0.05

DISCUSSION

Pain and distress are typical challenges in colonoscopy. Non-pharmacological approaches are essential to alleviate pain and distress in patients, reducing the need for increased sedative use. In this context, music plays a significant role in managing emotional states and promoting mind-body interactions, widely recognized for fostering relaxation in healthcare. In this context, various music genres have been employed to assess relaxation and tolerance in patients undergoing colonoscopy [4].

This prospective randomized single-blind controlled trial shows that when patients have a colonoscopy without sedation, adding binaural beats to their music significantly reduces their anxiety and increases their tolerance. The use of binaural beats is relatively new, and few publications are associated with its use during colonoscopy. Tani *et al.* [16] segregated patients undergoing unsedated colonoscopy into a music group (n=42) and a control group (n=48). They played binaural music (theta frequencies) from 5 minutes before starting the colonoscopy in the music group till the procedure was completed, while the control group did not receive the intervention. Measurements of anxiety and pain using the VAS scale and of patient satisfaction on a Likert scale revealed that the music group showed significantly higher levels of comfort and lower pain during the procedure [16]. Though no significant differences were observed between the music and control groups of our study in terms of pain during the procedure, the music group exhibited a significant reduction in post-procedural anxiety levels and a significant increase in procedure satisfaction. The willingness to repeat the procedure without sedation and the proportion of those in the music group who wished to listen to the same music if they were to undergo the procedure again were significantly higher.

In our study, the VAS-anxiety scores of both the music and control group patients before the colonoscopy procedure were similar and moderate. Being an invasive diagnostic intervention, sedation-free colonoscopy often induces anxiety in patients due to the accounts of excessively painful procedures they hear from others, the possibility of experiencing negative outcomes, or the information they gather from online research [2]. The moderate anxiety observed in

both groups before the procedure in our study is likely associated with the above-mentioned reasons. Despite the lower VAS-anxiety scores in both groups post-procedure, the reduction in anxiety in the music group was significantly greater. This result demonstrates the anxiety-reducing effect of binaural music associated with the procedure. Similar results have been obtained in studies where various types of music were applied during colonoscopy, confirming the anxiety-reducing effect of music therapy [20-22].

Several studies have been reported in existing literatures that assess the efficacy of music therapy in mitigating pain during colonoscopy procedures. Costa *et al.* [23] reported that offering a selection of blues, country, classic, swing, jazz, reggae, and instrumental music to the music group reduced sedation requirements and pain levels. In another study, Çelebi *et al.* [24] demonstrated that listening to Turkish classical music significantly lowered pain scores in the intervention group during colonoscopy. However, in studies where local and classical music were played for patients by Harikumar *et al.* [25] and classical music was played by Martindale *et al.* [26], no significant difference in pain during the procedure was found compared to the control group. Similarly, despite the satisfactory comfort scores during the procedure in our study, and the high willingness to undergo the procedure again, no significant difference was perceived in the maximum pain levels experienced during the procedure. Dabu-Bondoc *et al.* [27] and Kliempt *et al.* [28] conducted measurements on the anesthesia dosage administered to patients who were provided with intricate binaural beats music (Hemi-sync), encompassing multi-layered frequencies such as alpha, beta, delta, theta, and gamma during the interventional procedure. The findings of the study demonstrated that individuals in the intervention group, who listened to binaural beats, required significantly less analgesia compared to those in the control group, who did not receive any auditory stimulus. In our study, we attribute the lack of a significant decrease in pain scores to the music being only in the theta frequency. We think the good comfort score and the high desire to repeat the procedure to the anxiolytic and hypnotic effects of binaural music in the theta frequency [15].

In a meta-analysis conducted by Bechtold *et al.* [29] evaluating the impact of music therapy (classical, relaxing, variety radio station, variety per patient) on

procedure duration in patients undergoing colonoscopy, no significant differences in procedure duration were found in 6 studies. In contrast, a reduction in procedure duration was identified in only one study [29]. Procedure duration in colonoscopy varies with patient tolerance and factors such as colonic cleanliness, polyp detection, and the number of interventions. In our study, despite similar polyp detection rates and pain scores in both groups, no significant difference was observed in procedure duration and polyp detection rates. Although not statistically significant, we believe that the higher polyp detection rate observed in the control group in our study could be reversed in larger-scale patient studies.

Limitations

This study has certain limitations that deserve to be highlighted. This study was conducted on a small scale at a single center. This study's reliability and quality could be enhanced through a larger-scale, double-blind, multicenter trial. In addition, only binaural music in the theta frequency was used in the study. The effects of binaural music in other frequencies were not compared.

CONCLUSION

This randomized controlled trial demonstrated that binaural beat therapy effectively reduces anxiety and enhances tolerance during colonoscopy, as evidenced by lower VAS-anxiety scores and higher patient satisfaction. While it did not significantly impact physiological measures such as heart rate or blood pressure, its psychological benefits improved patient comfort and willingness to undergo future procedures without sedation. Binaural beats offer a promising, cost-effective, non-pharmacological alternative for enhancing patient experience during medical procedures. Further research is warranted to explore their anxiolytic and analgesic potential in colonoscopy and other interventions.

Ethical Statement

Ethical approval was obtained from the Health Sciences University Dr. Abdurrahman Yurtaslan Ankara Oncology Health Application and Research

Center Clinical Research Ethics Committee (Approval No: 2023-10/418).

Authors' Contribution

Study Conception: SD; Study Design: FPS; Supervision: SD; Funding: N/A; Materials: N/A; Data Collection and/or Processing: SD, SS; Statistical Analysis and/or Data Interpretation: SD; Literature Review: FPS, SS; Manuscript Preparation: SD and Critical Review: FDS, SS.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Differentiating types of breast cancer from digital mammography images with artificial intelligence methods

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ABSTRACT

Objectives: Breast cancer (BCA) is one of the world's most prevalent cancer and the top cause of mortality. For many decades, mammography has been used routinely for screening of early breast cancer and diagnosing symptomatic patients. The main purpose of this work is to investigate the usefulness of machine learning techniques using mammography images.

Methods: A total of 194 patients who underwent ultrasound examination after observing suspicious lesions on mammography images and were diagnosed with BCA by ultrasound-guided core needle biopsy were included in the study. A set of mammography images with complete cancer subtypes was used. A transfer learning-based computer vision method was adopted in this study. AlexNet was to extract the features and select the most significant features using a feature selection function. Our deep learning-based model attained more than 80% accuracy in classifying malignant and benign cancers. However, the employed deep learning model cannot classify subtypes accurately.

Results: Per the results, the commonly used image classification model is highly accurate in distinguishing malignant and benign changes, however unable to classify cancer subtypes.

Conclusions: In conclusion, machine learning can still not simulate conventional immunohistochemistry subtyping using tissue biopsy.

Keywords: Artificial intelligence, breast cancer, deep learning, mammography

Breast cancer (BCA) is the most common malignancy in women [1]. For this reason, screening programs have been developed for women for breast cancer and efforts are being made to detect cancer at an early stage [2]. The most effective, most frequently used and easily accessible method for screening breast cancer is mammography. Although the success of mammography in detecting breast can-

cer depends on breast density, its specificity varies between 75-90% [3, 4]. BCA tumor morphology is diverse and results from different markers in the intratumoral heterogeneity structure [5, 6]. Determining BCA types is very important in treatment planning. Although histopathological sampling is a minimally invasive procedure, it is very important to be able to diagnose and determine breast cancer types with non-

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invasive methods [7]. In recent years, artificial intelligence (AI) methods have been increasingly adapted to assist in cancer detection, reducing false negative or false positive findings, reducing recall rate, and at a more advanced level, assisting in identifying cancer subtypes [8]. There are studies investigating the detectability of tumoral lesions by analyzing digital mammographic images used in BCA screening with AI methods [9, 10]. There is also increasing interest in exploring the possibility of AI to assist in cancer subtyping and predicting treatment response [11, 12].

The aim of this study is to investigate the detectability of malignant breast lesions and BCA subtypes in mammography images using deep learning methods.

METHODS

This study is a cross-sectional study conducted by retrospective recruitment of patients who underwent mammography in a tertiary center between 2017 and 2021. The study was carried out according to the Declaration of Helsinki and local ethics committee approval was obtained.

Table 1. Characteristic of the BCA included in the selected patient dataset.

	Data
Age (years)	42.22±11.25
Breast Density, n (%)	
C	102 (52.6%)
D	92 (47.4%)
Breast cancer molecular subtypes, n (%)	
Luminal A	72 (37.1%)
Luminal B HER –	40 (20.6%)
Luminal B HER +	54 (27.8%)
HER+	18 (9.3%)
Triple negative	10 (5.2%)
Breast Cancer Types, n (%)	
Invasive ductal carcinoma	182 (93.8%)
Invasive lobular carcinoma	12 (6.2%)

Data are shown as mean± standard deviation or n (%).
HER2=Human epidermal growth factor receptor 2

Study Population

Patients with breast density C and D presenting BIRADS 4A-4B-4C and 5 lesions on mammography images according to ACR BIRADS (Breast Imaging-Reporting and Data System) were recruited. Patients with inconclusive tissue biopsy or benign lesions were excluded. A total of 194 patients who underwent ultrasound examination by observing suspicious lesions on mammography images and were diagnosed with BCA by ultrasound-guided core needle biopsy were included.

The presence of estrogen receptors (ER), progesterone receptor (PR), human epidermal growth factor (HER2) gene expression, and Ki-67 immunohistochemical staining were obtained from the pathological evaluation results of each patient and was presented in Table 1.

Identification and Classification of Tumoral Subtypes

The presence of tumoral ER, PR, HER2, and immunohistochemical staining with Ki-67 as proliferation marker and epidermal growth factor (EGF) play a role in determining BCA subtypes [5]. BCA was divided into subtypes according to its molecular properties.

Molecular subtypes of invasive breast tumors are divided into 4 basic groups: 1- Luminal A like: ER-positive (+) PR+ HER2 negative (-) and Ki-67 index <15%, Luminal B like: This group is divided into two: Luminal B like (HER2 -) ER+ HER2- and at least one; P- or weak Ki-67:>30%, Luminal B like (HER 2 +): ER: +, HER2: overexpressed or amplified, Ki-67: any result, PR: any result, 3) HER 2 +: ER-, PR:-, HER2: overexpressed or amplified, 4) Triple-negative: ER+, PR+, Ki-67: negative [13].

Artificial Intelligence Method

Dataset

This dataset had 806 mammography images with two categories. These categories were named Malignant Group and Control Group. A total of 382 images belonged to malignant and there were 424 images in the normal category. These images were stored in JPEG format. Images of 382 lesions in the malignant group were categorized according to their subtypes. Craniocaudal (CC) and Mediolateraloblique (MLO) images of the breast with the detected lesion were ob-

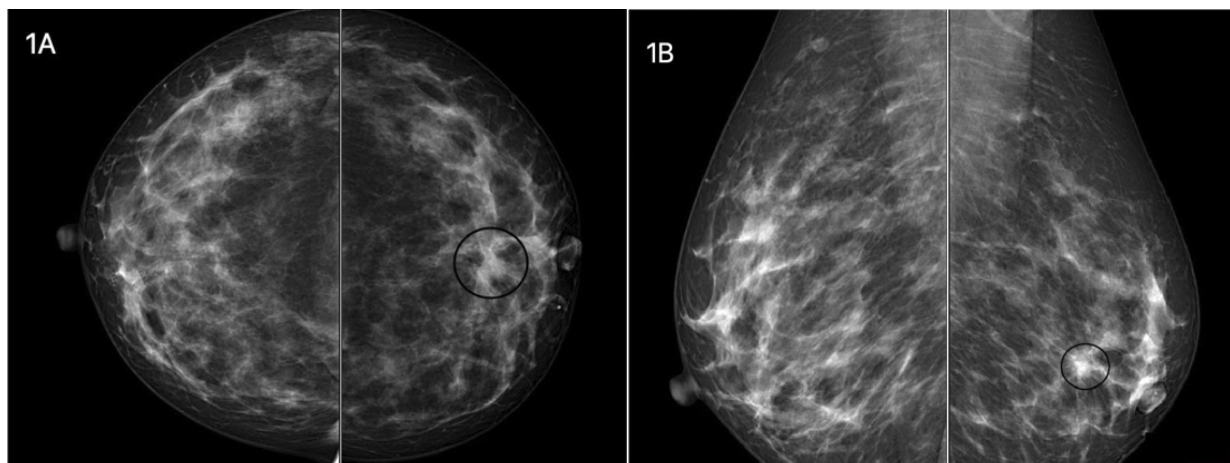


Fig. 1. Mammary images. (a) CC mammogram of a 12×10 mm, irregularly shaped, spiculated contoured mass lesion in the retroareolar area of the left breast (circle) in a 52-year-old female patient. (b) MLO mammogram of a 12×10 mm, irregularly shaped, spiculated contoured mass lesion in the retroareolar area of the left breast (circle) in a 52-year-old female patient.

tained from 188 patients and 6 patients in whom the lesion could be detected only in CC mammograms. Mammography images are presented in Fig. 1.

First Aim

The proposed model has four sections and these

sections are breast image segmentation (breast area localization), deep feature extraction using pre-trained AlexNet, NCA-based feature selection, and classification with Cubic SVM classifier. An overview of the proposed intelligent AlexNet-NCA-SVM-based model is shown in Fig. 2.

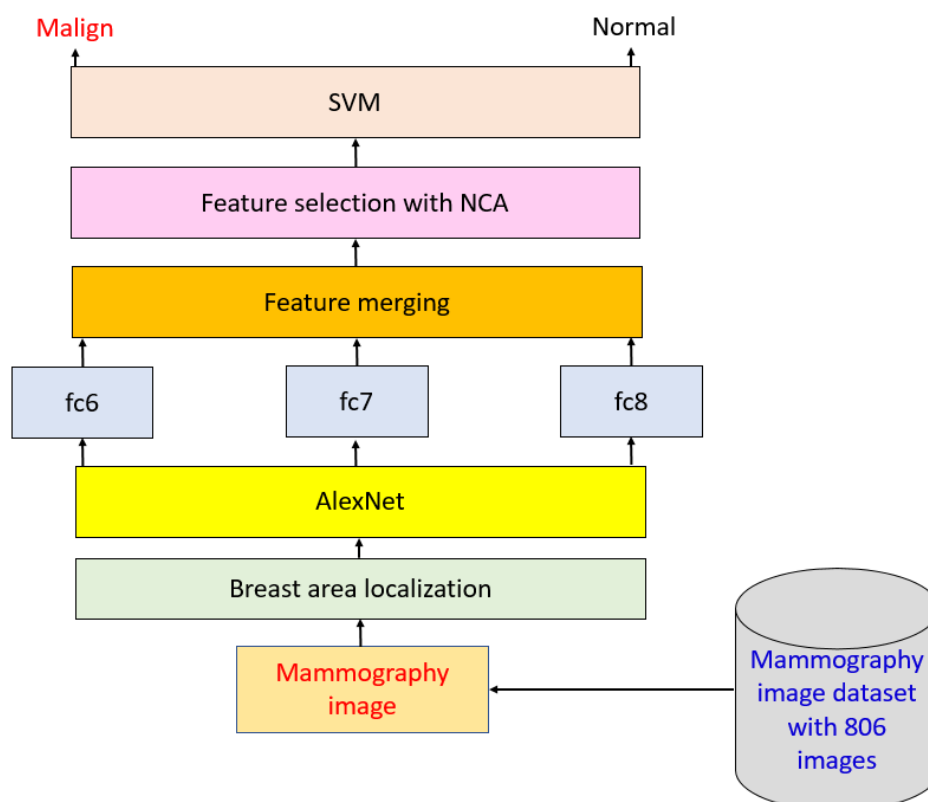


Fig. 2. Overview of the proposed AlexNet-NCA-SVM based breast cancer detection model. .

The steps of the presented model are given as follows.

Step 1: Load the mammography image dataset.

Step 2: Read each mammography image.

Step 3: Segment the breast using binary image conversion.

Step 4: Apply pre-trained AlexNet [14] on these images. The used AlexNet was trained on the ImageNet [15] dataset and the ImageNet dataset contains a few million images with 1000 classes. We transferred this information (optimized weights) to solve our BCA detection problem.

Step 5: The used pre-trained AlexNet has three fully connected layers and the names of them are fc6, fc7, and fc8. By using the fc6, fc7, and fc8, 4096, 4096, and 1000 features are generated from an image respectively.

$$f^1 = fc6(M) \quad (1)$$

$$f^2 = fc7(M) \quad (2)$$

$$f^3 = fc8(M) \quad (3)$$

In Equations (1)-(3), we used three deep feature creation functions and these functions are $fc6(.)$, $fc7(.)$ and $fc8(.)$. These functions are called names of the fully connected layers. By employing these function, first (f^1), second (f^2) and third (f^3) feature vectors with a length of 4096, 4096 and 1000 are generated.

Step 6: Merge the generated features and obtain $4096+4096+1000=9192$ features.

$$X = \text{merge}(f^1, f^2, f^3) \quad (4)$$

Herein, $\text{merge}(...)$ is concatenation function and X defines merged feature vector with a length of 9192.

Step 7: Select the most informative 1000 features from the generated 9192 features deploying NCA.

NCA is a feature selection version of the k nearest neighbor (kNN) and uses the distance metric (Manhattan distance) to calculate the weights of the features. The most valuable features are selected using weight values. The big weight values assign discriminative features and small weight values denote redundant features. We selected the top 1000 features by using indexes of the weights.

Step 8: Classify the best 1000 features deploying the SVM classifier. The attributes of the used SVM are; Kernel: 3rd degree polynomial (Cubic), Box-constraint: 2, Standardize: True, and Validation: 10-fold CV.

Second Aim

Deep learning is the flagship of machine learning and various automated diagnosis models. In this work, we have used a deep learning model to classify the mammogram according to tumor subtype. To classify our images, DarkNet53 [15] which is a widely preferred computer vision model in the literature. These categories are: (1) Luminal B HER2+, (2) HER 2+, (3) Luminal A, (4) Luminal B, HER-, (5) Control Group, and (6) Triple Negative Subtype.

RESULTS

Detection of BCA with Deep Learning Method

In this study, MATLAB 2020a programming environment and Classification Learner Toolbox have been used and the results were calculated. In the collected dataset, there are 382 “Malignant” and 424 “Normal” mammography images, and the proposed AlexNet-

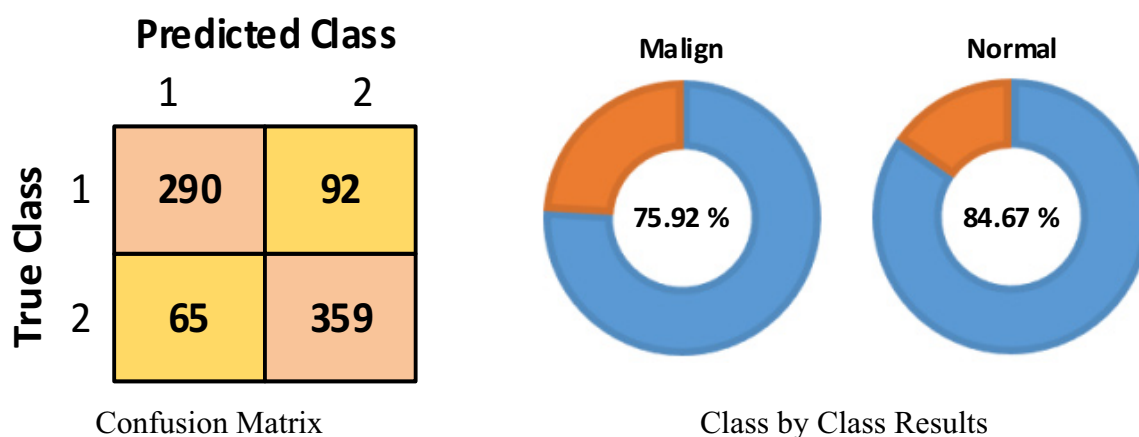


Fig. 3. Confusion matrix and class-wise results of the proposed AlexNet-NCA-SVM based model using Cubic SVM classifier.

Table 2. Accuracy, sensitivity, specificity, geometric mean, balanced accuracy, precision and F1-score results of our proposal

Parameters	Results (%)
Accuracy	80.52
Sensitivity	75.92
Specificity	84.67
Geometric mean	80.17
Balanced Accuracy	80.29
Precision	79.60
F1-score	82.06

F1 Score is the harmonic mean of Precision and Recall scores. It calculated in AI.

NCA-SVM model was developed. Cubic SVM is chosen as a classifier. The calculated confusion matrix and class-wise results are also shown in Fig. 3.

As seen in Figure 3, 75.92% accuracy for "Malign class" and 84.67% accuracy for "Normal class" were calculated. Accuracy, Sensitivity, Specificity, Geometric mean, Balanced Accuracy, Precision, and F1-Score values were calculated by running 1000 iterations of the Cubic SVM classifier, and the calculated best results are listed in Table 2 [16-18].

The results calculated in Fig. 3 were obtained by performing a 10-Fold CV [19]. The calculated fold-wise accuracy results are shown in Fig. 4.

Fig. 4 denotes that, the highest result was obtained with fold-7 and the lowest result with fold-3 in the calculated fold-wise accuracies. The cubic SVM algorithm was used to classify the calculated features in the proposed method. The reason why this classifier is preferred is that it achieves higher performance results than other used classifiers. 12 classifiers have been used for classification and they are Fine Decision Tree (DT), Medium DT, Coarse DT, Linear Discriminant, Gaussian Naïve Bayes, Linear SVM, Cubic SVM, Quadratic SVM, Fine k nearest neighbor (KNN), Medium KNN, Cosine KNN, and Ensemble Boosted Trees [18]. The accuracy results calculated for 12 classifiers are shown in Fig. 5.

As can be seen in Fig. 5, Cubic SVM was preferred among these classifications with high accuracy. The calculated unit annulus rate (UAR) rates are calculated as 0.78 and 0.85 respectively for these groups. Therefore, the average UAR rate is equal to 81.50%. (Fig. 6).

The calculated UAR rates are calculated as 0.78 and 0.85 respectively. Therefore, the average UAR rate is equal to 81.50%.

Differentiation of Breast Cancer Subtypes with Deep Learning Methods

We could not obtain successful results on our dataset. By applying DarkNet53, the reckoned confusion matrix is denoted in Fig. 7. In this confusion ma-



Fig. 4. The calculated fold-wise accuracies employing Cubic SVM classifiers.

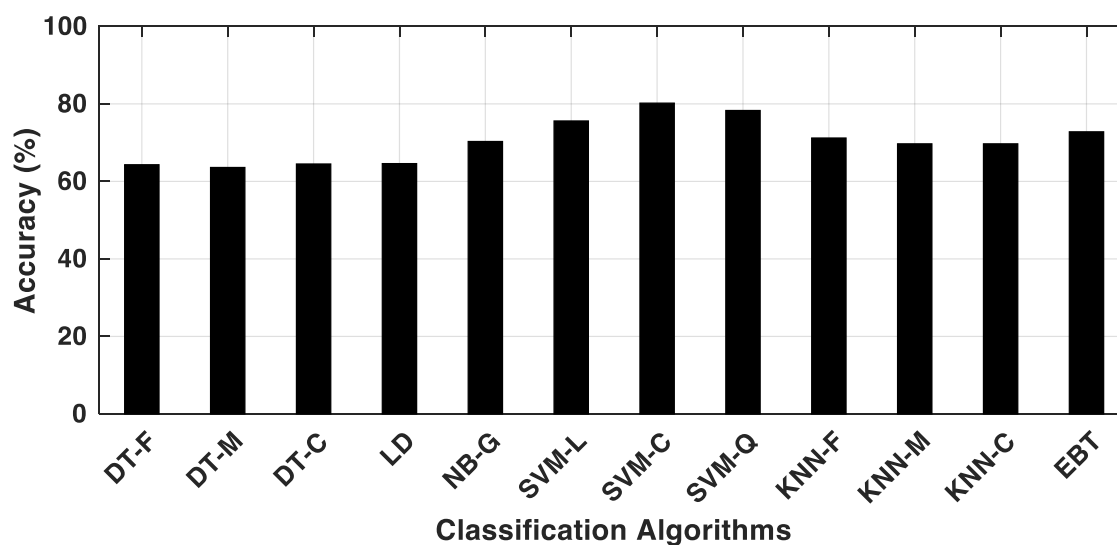


Fig. 5. The accuracy results calculated for Fine DT, Medium DT, Coarse DT, Linear Discriminant, Gaussian Naïve Bayes, Linear SVM, Cubic SVM, Quadratic SVM, Fine KNN, Medium KNN, Cosine KNN, and Ensemble Boosted Trees. DT=decision tree, KNN=k nearest neighbor.

trix, true positive rates (TPR) and false negative rates (FNR) have been shown using blue and pink color tones. According to this matrix, 49.49% classification accuracy has been calculated (Fig. 7).

Moreover, the class-wise area under curves (AUC) has been reckoned and the results are illustrated in Fig. 8.

DISCUSSION

In this work, a set of mammograms with biopsy-proven cancer was collected and an automatic malignant lesion detection model was presented using transfer learning. By using transfer learning, the pre-

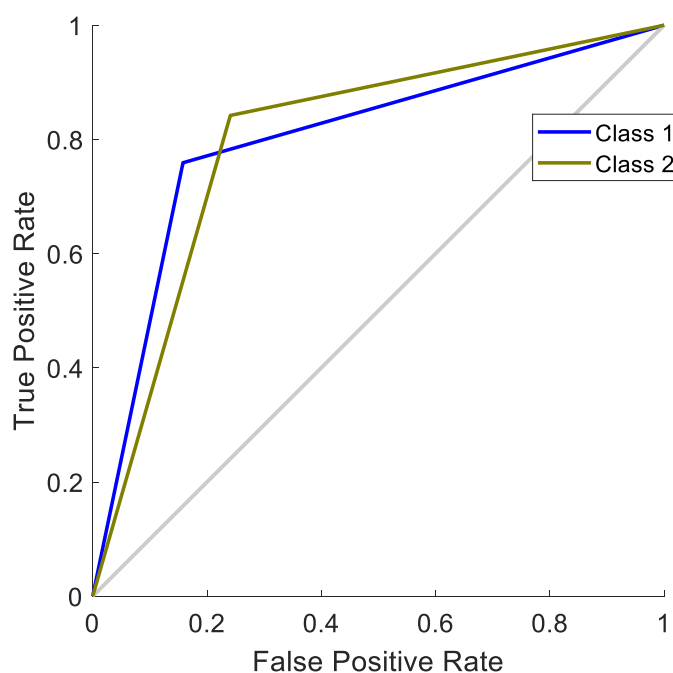


Fig. 6. These classes are named Normal (Class 1) and Malign (Class 2).

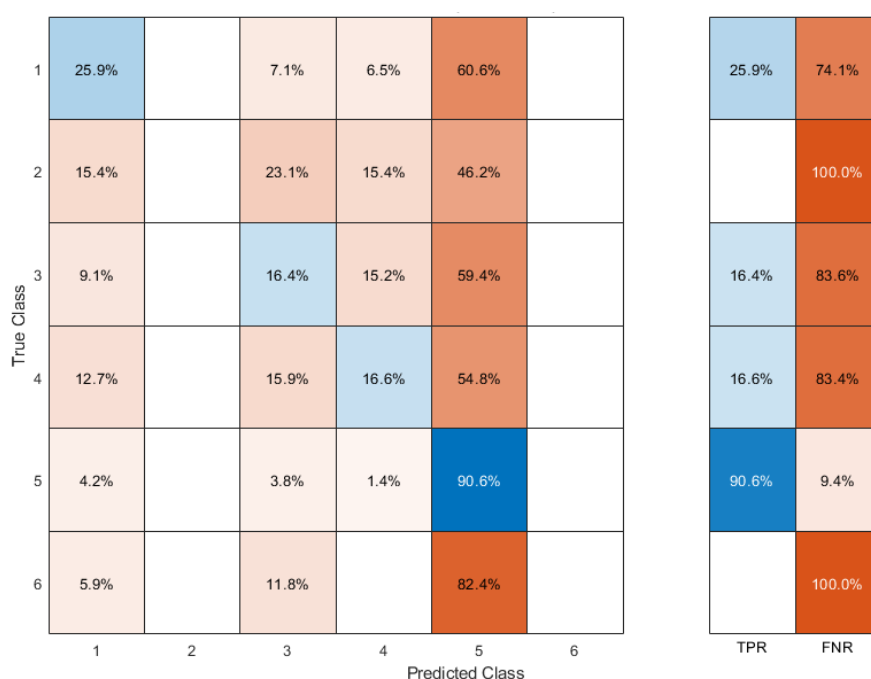


Fig. 7. Confusion matrix and class-wise results of the proposed AlexNet-NCA-SVM based model using Cubic SVM classifier for BCA subtypes.

trained networks have been used and the optimal weight has been used for feature extraction and there is no need to use back propagation. Therefore, we used AlexNet in transfer learning mode to extract deep features. All fully connected layers of the AlexNet have been utilized as feature generation functions and 9192 features are generated from each mammography image. NCA has chosen 1000 features and Cubic SVM has been used to classify these features. The presented AlexNet-NCA-SVM-based mammography classification method attained 80.52% classification accuracy, 75.92% sensitivity, and 84.67% specificity rates. In this view, our model is successful in detecting BCA images in the evaluation and varies depending on breast density.

Classification of mammographic images as benign and malignant is the most important step in the evaluation and varies depending on breast density [19]. In a multicenter study, the performance of screening mammograms in the evaluation of radiologists was investigated, and this sensitivity was reported as 73% and specificity as 96% in the initial evaluation [20]. This highlights the necessity of robust AI methods to assist radiologists in the initial evaluation. There are multiple studies on the use of AI methods in the eval-

uation of screening mammograms and their results are variable. In these studies, conducted by evaluating the images in screening mammograms by different radiologists and AI, it has been shown that AI contributes to the evaluation of mammographic images and increases the detection of breast cancer [21-23].

In this study, the effectiveness of the deep learning method was investigated in a dataset that included mammographic images of patients with C and D breast patterns with BCA detected and normal mammograms. According to the results of our study, the sensitivity and specificity of BCA detection by deep learning method in mammographic images of patients with dense breast patterns is very high. In other words, the use of artificial intelligence methods in the initial evaluation of screening mammography may increase the evaluation performance of radiologists, reduce reading time, and reduce recall rate.

In the curves in which the AI method was used to determine the pathological subtypes of BCA detected in mammography images, the AUC value was 0.75 in determining the HER2+ subtype, while the AUC value in the detection of other subtypes varied between 0.64-0.69. These low values may be due to the small number of patients in the groups, as well as the lack of

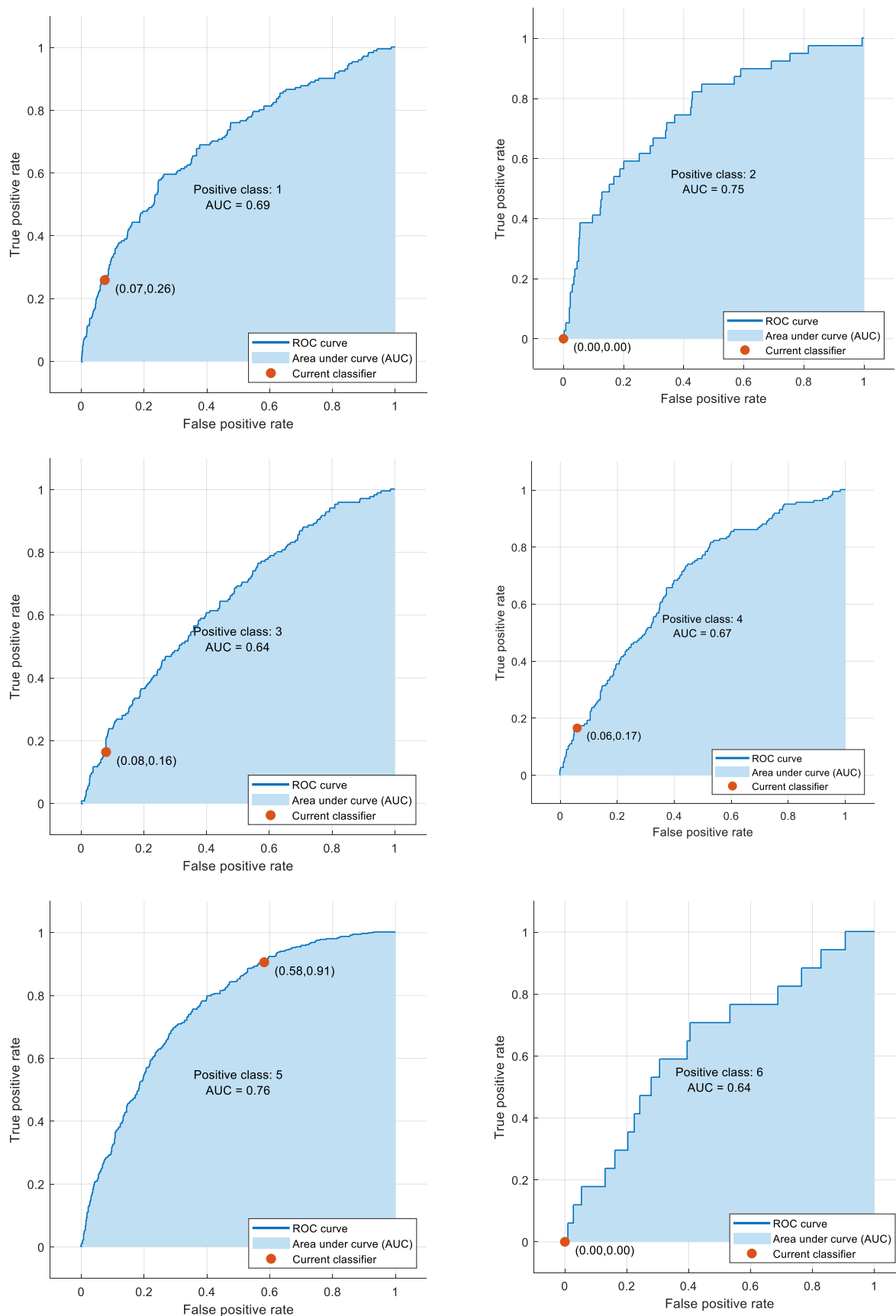


Fig. 8. ROC curves of BCA subtypes classes.

specific imaging characteristics of subtypes in mammographic imaging features. However, studies using larger databases can still be conducted to determine the effectiveness of AI methods in detecting the HER2+ subtype.

Limitations

There are some limitations of our study. First of all, this study is a single-center study, and evaluation was made using a single AI method. In addition, unlike other studies investigating the diagnostic effectiveness of AI in mammography, the evaluation performance of radiologists was not taken into account in this study. Based on the idea that radiologists can detect asymmetric breast tissue by comparing both breasts in the first reading, it was tried to determine the diagnosis rates of AI methods compared to normal breast tissue. This finding may have led to the detection of a lower rate compared to the higher AUC rates in other studies and may have made the detection of BCA subtypes unsuccessful. However, from another perspective, it may also represent a strong aspect of this study. Undoubtedly, the purpose of using AI methods in the evaluation of screening mammograms is to obtain positive results independent of radiologists, and to ensure that the radiologists waive their workforce in the initial evaluation.

CONCLUSION

The use of AI-based screening methods in the field of mammography can be used as auxiliary methods for radiologists by including them in the medical diagnosis stages. The most important concept in radiomics is to see beyond what a radiologist can see, and subsequently aid in diagnosing, reducing ‘missed’ lesions, and finally, assisting in treatment planning and prognostication. However, the detection of radiomic features of mammography with AI is insufficient, and its clinical use should be supported by studies with larger patient populations. Therefore, in future work, we aim to collect bigger mammography datasets to detect more classes of the BCA and new generation deep learning models can be proposed to detect type of the breast accurately. Although AI detection of mammographic features and classification of tumor subtyping

will not replace biopsies, it will have an important place in the diagnosis and treatment of breast cancer.

Ethical statement

The study was approved by Adıyaman University Non-Interventional Clinical Research Ethics Committee (Date: 26.10.2021, number: 08).

Authors' Contribution

Study Conception: EK; Study Design: EK, TT, ŞD; Supervision: EK, TT, ŞD; Materials: EK, HTB, MŞ; Data Collection and/or Processing: EK, MŞ; Statistical Analysis and/or Data Interpretation: EK, HTB, MŞ; Literature Review: EK, TT, ŞD; Manuscript Preparation: EK, TT, ŞD, OY and Critical Review: TT, OY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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Comparison of hypothermic and normothermic cardiopulmonary bypass in patients undergoing coronary artery bypass graft surgery

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ABSTRACT

Objectives: Coronary artery bypass graft (CABG) surgery operations accompanied by cardiopulmonary bypass (CPB) are the most prominent treatment options. One of the basic application principles of the CPB system is the protection of vital organs by reducing metabolic rate and oxygen consumption with hypothermia. In this study, we aimed to investigate the effects of normothermia and hypothermia applications on clinical outcomes in CABG operations performed with CPB.

Methods: This single-center study was planned retrospectively. Patients who underwent isolated CABG operation with CPB at Şanlıurfa Mehmet Akif İnan Training and Research Hospital between January 01, 2020, and January 01, 2022, were included. A total of 120 patients, 60 of whom underwent hypothermic and 60 normothermic cardiac bypass, were included in the study after applying the exclusion criteria.

Results: There was no difference between the groups in terms of age, gender, diabetes mellitus, hypertension, left ventricular ejection fraction, and body surface area characteristics ($P>0.05$). In the normothermia group, urea, creatinine, direct bilirubin, and lactate levels were significantly higher in the first postoperative day blood values ($P=0.003$, $P=0.04$, $P=0.028$, $P=0.005$, and $P<0.001$, respectively). Positive inotropic agent requirement and defibrillation requirement after cross-clamping were significantly higher in the hypothermia group ($P=0.006$ and $P=0.027$, respectively).

Conclusions: In CABG operations performed with CPB, normothermia and hypothermia applications may have beneficial effects on different clinical situations.

Keywords: Cardiopulmonary bypass, coronary artery bypass grafting, normothermia, hypothermia, postoperative term

Coronary artery disease (CAD) is the most common form of cardiovascular disease associated with high mortality and morbidity worldwide. Coronary artery bypass graft (CABG) surgery operations accompanied by cardiopulmonary bypass (CPB)

are the most prominent treatment options [1]. Cardiac surgery performed with CPB aims to have a bloodless and immobile surgical field. For this purpose, the functions of the heart and lungs are disabled, and the CPB system takes over these tasks. One of the basic

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application principles of this system is the protection of vital organs by reducing metabolic rate and oxygen consumption with hypothermia [2-4].

The principle of protection of other organs, especially the brain, by hypothermia is based on the Arrhenius equation. According to this equation, the reaction rate of chemicals is related to heat. The mechanism is the protection of cellular pH and adenosine triphosphate, delaying the pathological process following ischemia. [3-5] Thus, the metabolic needs of the body, especially critical organs such as the brain, kidney and heart, will be reduced. In addition, the risk of organ damage will decrease in cases where mean arterial pressure and perfusion are low [6-8].

Another method that can be applied in addition to hypothermia-based application is normothermic CPB. The main element of this method is that the patient's body temperature is kept within the normal temperature range during cardiac surgery and no intervention is made. It is stated that normothermic CPB reduces blood loss and decreases systemic vascular resistance, but causes cerebral venous oxygen desaturation in the first moments of perfusion [3, 8-10].

In this study, we aimed to investigate the effects of normothermia and hypothermia applications on clinical outcomes in CABG operations performed with CPB.

METHODS

This study was approved with the protocol dated 31/10/2022 and numbered HRÜ/22.21.05 of the Haran University Clinical Research Ethics Committee. In this study, which was planned retrospectively as a single center, patients between the ages of 20-85 who underwent isolated CABG operation with CPB at Şanlıurfa Mehmet Akif İnan Training and Research Hospital between January 01, 2020, and January 01, 2022, were included in the study. The patients who had undergone redo cardiac operations, emergency cases, those with a known history of lung disease, those with chronic renal failure, and those with a history of pneumonia were excluded from the study. A total of 120 patients, 60 of whom underwent hypothermic and 60 normothermic cardiac bypass, were included in the study after applying the exclusion criteria. Of the patients included in the study, those who underwent normothermic (36-37 oC) CPB were determined as Group

1, and those who underwent hypothermic (32 oC) CPB were determined as Group 2. Preoperative, intraoperative and postoperative data of the patients were obtained retrospectively from hospital records and patient files. Normothermic CPB is applied less frequently in our clinic. Therefore, when determining the sample size, when 60 patients were reached in the normothermic group, 60 patients were randomly selected from the hypothermia group within the same period using a computer program.

Collection of Research Data

Demographic data, identity information, age, gender, and smoking were determined and recorded. Their medical histories were analyzed in detail. The presence of hypertension, diabetes, and chronic obstructive pulmonary disease were recorded. In the study, the individual characteristics of the participants were height, weight, body surface area (BSA = Body surface area; surgical characteristics were perfusion flow rate (flow) (L/m²/min), aortic cross-clamp time, total perfusion time and coronary graft number; preoperatively and postoperatively on the 1st day. Among the biochemical data examined are glucose, urea, creatine, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, C-reactive protein (CRP); from electrolytes; sodium, potassium, calcium values and blood gas values. Lactate data and postoperative intra-aortic balloon pump (IABP) requirement, intraoperative+postoperative erythrocyte suspension (ES) transfusion, post-cross clamp defibrillation requirement, postoperative drainage amount, postoperative positive inotrope requirement, extubation duration, intensive care unit (ICU) length of stay data regarding duration of hospital stay were recorded.

Cardiopulmonary Bypass Method

The blood flow rates (Flow) of the patients included in this study during CPB were determined according to their body surface area (2.4 L/m²/min). The tubing set venous line diameter was used as 1/2-inch, and arterial line diameter was used as 3/8-inch. Arterial line pressures were kept between 150-180 mmHg on average during CPB. Active clotting time (ACT) was kept at 480 seconds and above by providing anticoagulation. 1200 mL balanced solution (Isolyte), 150 ml 20% mannitol, 5000 units heparin, and 2 g cefazolin were used as the primary solution. Normoth-

ermic blood cardioplegia solution was used in Group 1 and hypothermic blood cardioplegia solution was used in Group 2. Group 1 received normothermic (36-37 oC) CPB, and Group 2 received hypothermic (32 oC) CPB.

Statistical Analysis

Statistical evaluation was performed using the SPSS® 16.0 computer program. Means and standard deviations were calculated for continuous and ordinal data. Kolmogorov Smirnov test and Shapiro-Wilk test were used to evaluate normality distribution. Student

t-test and Mann-Whitney U tests were used to evaluate normal and non-normally distributed numerical data, respectively. Frequency and percentage analyses were performed for nominal data and the Chi-square test was used for comparison. P values less than 0.05 were considered statistically significant.

RESULTS

Demographic characteristics and preoperative blood values of the patients included in the study are given

Table 1. Demographic characteristics and preoperative blood values of the patients

Variables	Normothermia (n=60)	Hypothermia (n=60)	P value
Age (years)	62.88±9.17	61.70±9.52	0.553
Female gender, n (%)	25 (41.7)	27 (45)	0.479
Smoking, n (%)	15 (25)	23 (38.3)	0.116
Hypertension, n (%)	48 (80)	53 (88.3)	0.211
Diabetes mellitus, n (%)	15 (25)	12 (20)	0.512
COPD, n (%)	5 (8.3)	7 (11.6)	0.543
Height (cm)	162.70±8.87	164.60±9.33	0.873
Weight (kg)	80.70±12.61	77.11±12.47	0.818
Body surface area (m ²)	1.90±0.18	1.86±0.17	0.631
LVEF (%)	51.01±8.11	49.85±8.22	0.784
Glucose (mg/dL)	172.65±51.26	187.28±58.24	0.486
Urea (mg/dL)	44.09±18.37	41.26±14.62	0.329
Creatinine (mg/dL)	1.01±0.46	0.90±0.30	0.067
Albumin (g/L)	33.78±7.66	33.30±7.36	0.903
ALT (IU/L)	38.58±53.20	33.75±53.36	0.857
AST (IU/L)	77.88±153.89	72.44±154.16	0.956
Total bilirubin (mg/dL)	1.98±10.51	0.90±0.92	0.109
Direkt bilirubin (mg/dL)	0.28±0.25	0.26±0.56	0.074
Sodium (mEq/L)	140.70±4.07	140.10±3.62	0.181
Potassium (mEq/L)	4.38±0.44	4.35±0.42	0.653
Calcium (mg/dL)	9.12±6.66	9.26±6.62	0.953
CRP (mg/L)	6.56±4.7	6.22±3.6	0.724
Lactate (mmol/L)	1.63±1.04	1.78±1.11	0.424

Data are show as mean ± standard deviation or n (%). COPD=chronic obstructive pulmonary disease, LVEF=left ventricular ejection fraction, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CRP=C reactive protein

in Table 1. There was no difference between the groups in terms of age, gender, diabetes mellitus, hypertension, LVEF, and body surface area characteristics. In addition, the preoperative blood values of the study groups were similar ($P>0.05$).

Operative data such as flow, cross-clamp time, total perfusion time, and number of coronary bypasses were similar between the groups. In the normothermia group, urea, creatinine, ALT, direct bilirubin and lactate levels were significantly higher in the first postoperative day blood values ($P=0.003$, $P=0.04$, $P=0.028$, $P=0.005$, and $P<0.001$, respectively) (Table 2).

Perioperative clinical characteristics of the patient groups are given in Table 3. There was no statistically significant difference between the groups in terms of IABP requirement rates, red blood cell suspension requirement, postoperative drainage, extubation time,

ICU stay, and total hospital stay. Positive inotropic agent requirement and defibrillation requirement after cross-clamping were significantly higher in the hypothermia group ($P=0.006$ and $P=0.027$, respectively).

DISCUSSION

In CABG operations performed with cardiopulmonary bypass (CPB), intraoperative hypothermia is an integral part of CPB. Among the findings of this study, we found that intraoperative hypothermia has some advantages on postoperative clinical outcomes compared to intraoperative normothermia. We found that urea, creatinine, direct bilirubin and lactate levels were significantly lower in the hypothermia group. Also we showed that inotropic requirement and defibrillation

Table 2. Comparison of operative variables and postoperative first-day blood values of the patients

Variables	Normothermia (n=60)	Hypothermia (n=60)	P value
Glucose (mg/dL)	192.38±54.02	158.31±59.06	0.355
Urea (mg/dL)	44.66±17.37	34.43±9.53	0.003
Creatinine (mg/dL)	1.26±1.48	0.90±0.41	0.040
Albumin (g/L)	33.91±6.04	35.79±5.71	0.506
ALT (IU/L)	24.37±13.16	23.19±18.58	0.028
AST (IU/L)	51.72±38.21	39.70±48.13	0.873
Total Bilirubin (mg/dL)	1.15±1.06	0.94±0.86	0.066
Direkt Bilirubin (mg/dL)	0.56±0.61	0.30±0.51	0.005
Sodium (mEq/L)	140.00±3.41	139.38±2.99	0.207
Potassium (mEq/L)	4.37±0.45	4.49±0.38	0.317
Calcium (mg/dL)	8.31±0.81	8.37±0.73	0.527
CRP (mg/L)	69.17±65.44	44.94±46.20	0.362
Lactate (mmol/L)	1.86±1.40	1.39±0.51	<0.001
Flow (L/min)	4.55±0.39	4.47±0.41	0.881
X-Clamp time (minutes)	84.36±31.77	85.01±32.41	0.852
Total perfusion time (minutes)	111.53±33.93	109.98±35.41	0.621
CABG, n (%)			
Single	2 (3.3)	1 (1.7)	0.249
Double	19 (31.7)	17 (28.3)	
Triple	20 (33.3)	25 (41.7)	
Quatruple	19 (31.7)	17 (28.3)	

Data are show as mean±standard deviation or n (%). ALT=alanine aminotransferase, AST=aspartate aminotransferase, CRP=C reactive protein, CABG=coronary artery bypass graft

Table 3. Comparison of perioperative clinical outcomes of the patients

Variables	Normothermia (n=60)	Hypothermia (n=60)	P value
Need for Intracardiac defibrillation, n (%)	20 (33.3)	32 (53.3)	0.027
Positive inotropic requirement, n (%)	19 (31.7)	34 (56.7)	0.006
IABP requirement, n (%)	3 (5)	5 (8.3)	0.464
Erythrocyte suspension (Units)	1.38±1.20	1.33±1.24	0.818
Postoperative drainage (mL)	1110.00±308.74	1124.42±301.05	0.711
Extubation time (hours)	6.73±1.73	7.38±2.60	0.182
ICU stay time (hours)	31.26±7.95	33.25±8.48	0.628
Total hospital stay time (days)	8.28±2.59	8.10±2.54	0.743

Data are show as mean ± standard deviation or n (%). IABP=intra-aortic balloon pump, ICU=intensive care unit

rate were lower after cross-clamping in the normothermia group.

Among the advantages of intraoperative normothermia is the significantly lower need for defibrillation. However, when evaluated with a holistic approach, we think that this advantage of normothermia compared to hypothermia should be evaluated in a different category. For this reason, the reversibility principle of cardioplegia solutions used for myocardial protection and arrest in cardiac surgery and the selection of appropriate cardioplegia solutions can be considered as a solution at this point. In a study conducted by Cakir *et al.* [11] on this subject, it was stated that in patients who underwent isolated CABG with CPB, myocardial damage was less in normothermic (above 34°C) cardioplegia than in deep hypothermic (18-28°C) cardioplegia. In other words, it may be more useful to prefer mild hypothermic or normothermic cardioplegia solutions for myocardial protection, regardless of CPB temperature, or to evaluate myocardial protection temperature separately.

Kaplan *et al.* [12] investigated patients who underwent surgery under normothermia and hypothermia (intraoperative body temperature <34°C- ≥28°C) in terms of postoperative differences. In their study, they found that aortic cross-clamping time, CPB time, awakening and extubation times, ICU and hospital stay, drainage, mean serum lactate levels, arrhythmia rates, infection status, renal failure, neurological complications, myocardial infarction, inotrope, transfusion requirements, and mortality rates were similar be-

tween groups and stated that cardiac surgery could be performed safely at the patient's temperature without active cooling [12]. Ziyaeifard *et al.* [13] compared the effects of hypothermia and normothermia on cognitive functions after CABG surgery in their study. As a result of the study, it was found that cognitive impairment was lower in patients who underwent normothermic CPB during hospitalization after CABG surgery compared to those who underwent hypothermic CPB [13]. In cases of atrioventricular (AV) septal defect repair, Amer *et al.* [14] compared normothermic and mild hypothermic (32°C- 35°C) CPB. In their study, they reported higher liver enzymes, more inotropic support, and longer intubation time in the mild hypothermic group in the postoperative period. As a result, they concluded that normothermia during CPB provides better global tissue perfusion than hypothermia in elective surgeries for the repair of AV defects [14].

Bianco *et al.* [15] compared normothermia versus mild hypothermia (32°C-35°C) in patients undergoing cardiac surgery. They reported that postoperative renal failure and ICU stay were higher in patients who received mild hypothermia during CPB, but there was no difference in long-term survival between the two groups [15]. Boodhwani *et al.* [16] reported that re-warming had negative effects on renal function in patients who received mild hypothermia after CABG and that this should be avoided. In contrast, our study showed that there were negative results in renal parameters in the normothermic group compared to hypothermia. We believe that these differences may be

due to rapid rewarming or the time interval during rewarming and the sudden increase in temperature.

In the study by Yuksel *et al.* [17], normothermic and mild hypothermic CPB were compared in myocardial revascularization in patients with left ventricular dysfunction. In their study, they evaluated patients who underwent surgery under mild hypothermia (32°C) and normothermia ($\geq 35^\circ\text{C}$) in terms of defibrillation rates, other morbidity problems and mortality. As a result of their study, they stated that normothermia provided less defibrillation requirement after aortic cross-clamping in patients with left ventricular dysfunction, which could be interpreted as better myocardial protection. However, they also showed that normothermia did not have an advantageous effect on postoperative stroke, postoperative atrial fibrillation, renal failure, and mortality [17]. In parallel with this study, the need for defibrillation was less in the normothermia group in our study.

In a study, it was determined that cardiac index, systemic oxygen delivery, and consumption, duration of respiratory support, ICU, and hospital stay were similar in the postoperative period after normothermic and hypothermic CPB in patients undergoing combined valve surgery [18]. It has also been stated that hypothermic and normothermic CPB show similar clinical results in congenital and pediatric patients other than adult cardiac surgery [19]. In our study, the duration of respiratory support, ICU, and hospital stay were similar.

Regarding the stages of hypothermia, it is stated that mild hypothermia is more advantageous during CPB. It is stated that mild hypothermic CPB temperature provides better clinical results in terms of less inotropic support, less blood loss, less blood transfusion, better platelet count, shorter hospital stay, and less ventilation support compared to other hypothermic temperatures [2]. It is stated that moderate hypothermia (24°C) provides better protection of the intestinal barrier compared to deep hypothermia (18°C) during total circulatory arrest [20]. When the studies in the literature are examined, it is seen that normothermic and hypothermic CPB applications have different advantages over each other. In our study, we also concluded that the two methods have different advantages.

Limitations

The limitations of this study include the small number of cases undergoing normothermic cardiac bypass in the center where the study was conducted. In addition, the fact that only postoperative day 1 biochemical and blood gas parameters were taken into account in the evaluation is among the other limitations of the study. We believe that conducting similar studies in multicenters, with more patients and patient groups that have undergone different cardiac surgical operations will yield more comprehensive and general results.

CONCLUSION

In CABG surgery performed with CPB, the advantages of intraoperative hypothermia compared to intraoperative normothermia on the outcome are significantly lower levels of urea, creatinine, direct bilirubin, and lactate. The advantages of intraoperative normothermia are less defibrillation and inotropic requirements.

Ethical Statement

This study was approved with the protocol dated 31/10/2022 and numbered HRÜ/22.21.05 of the Haran University Clinical Research Ethics Committee.

Authors' Contribution

Study Conception: BA, ME; Study Design: BA, ME; Supervision: BA, ME, AKA, MA, SY; Funding: BA, ME, AKA, MA, SY; Materials: BA, ME, AKA, MA, SY; Data Collection and/or Processing: BA, ME, AKA, MA, SY; Statistical Analysis and/or Data Interpretation: BA, ME, AKA, MA, SY; Literature Review: BA, ME, AKA, MA, SY; Manuscript Preparation: BA, ME, AKA, MA, SY and Critical Review: BA, ME, AKA, MA, SY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The effects of a 6-week pilates exercises on quality of life, depression, and musculoskeletal disorders in menopausal women

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ABSTRACT

Objectives: This study examines the impact of a 6-week Pilates intervention on quality of life, depression, and musculoskeletal disorders in menopausal women.

Methods: The sample comprised 13 menopausal women with a mean age of 59.45 ± 11.52 years. Data collection was conducted using the World Health Organization Quality of Life-BREF (WHOQOL-BREF), the Beck Depression Inventory for Primary Care (BDI-PC), and the Cornell Musculoskeletal System Discomfort Questionnaire (CMSDQ). These instruments were administered at three intervals: baseline, following a 6-week non-intervention period, and after a subsequent 6-week Pilates program.

Results: Within the scope of the study findings, after 6 weeks of Pilates, there was a significant increase in the participants' quality of life scores in the physical and psychological health domains and a significant decrease in the BDI-PC total score (For physical health domains: $\eta^2=0.62$, $P<0.001$; for psychological health domains: $\eta^2=0.56$, $P<0.001$; for BDI-PC total score: $\eta^2=0.51$, $P<0.05$). However, no statistically significant difference was found in participants' quality of life scores in the social relations and environmental health domains and the CMSDQ total weighted score after 6 weeks of Pilates ($P>0.05$).

Conclusions: In conclusion, six weeks of Pilates exercises in menopausal women increases the quality of life within the framework of physical health and psychological health and reduces the depression level of these women. Therefore, to reduce the psychological problems that may occur in menopausal women and to improve their quality of life, they should be directed towards physical activities, especially Pilates. It is recommended to study the effect of Pilates performed for more than 6 weeks musculoskeletal disorders, environmental health and social relationships in this population.

Keywords: Physical activity, menopause, women, depression, musculoskeletal disorders, quality of life

Menopause is a "life change" period that occurs in women, usually between the ages of 45 and 55, with a decrease in estrogen levels, ovarian insufficiency, the end of the menstrual cycle, and the loss of reproductive functions [1, 2].

This decline is accompanied by several physiological and psychological changes. These changes lead to differences in reproductive health, bone density, muscle strength, and general health [3]. Particularly during menopause, women are more likely to experience

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health problems such as musculoskeletal disorders and chronic pain [4-6].

The quality of life of individuals can be affected by their physical health [7, 8]. Musculoskeletal disorders, which are common in women during menopause, lead to a decrease in their quality of life, limit their activities of daily living, and negatively affect their physical and psychological health [5, 9, 10]. Especially during this period, depression, which is a psychological health problem, is seen at a high rate [11]. In this context, physical and psychological health should be supported to protect and increase the quality of life in women during menopause [12]. Exercise plays an important role in this support [7, 13].

One type of exercise, Pilates, is an effective method for regulating musculoskeletal health and reducing symptoms of depression [14, 15]. Pilates, which is particularly inexpensive and has a wide variety of exercises, has a low risk of causing pain and increases the individual's postural balance, muscle flexibility, and strength [16, 17]. Aibar-Almazán *et al.* [18] found that a Pilates exercise program in postmenopausal women had beneficial effects on sleep quality, anxiety, depression, and fatigue. A study by Farzaneh *et al.* [19] suggested that Pilates training could improve mental and physical functioning and reduce depression (67%) and anxiety (53%). In patients with chronic low back pain, only Pilates exercises were found to be effective in reducing pain and depression [20, 21]. In a meta-analysis study, Pilates was found to affect pain control in people with fibromyalgia [22]. Pilates was also found to reduce pain and disability and improve the quality of life in women [23]. In addition, it was found to reduce depression and increase the quality of life in overweight and obese individuals [24]. This study aimed to investigate the effects of 6 weeks of Pilates exercise on quality of life, depression, and musculoskeletal disorders in menopausal women. The results of this study will contribute to the development of health policies to improve the quality of life of menopausal women and provide a scientific basis for the integration of health and exercise science.

METHODS

Research Design

This study is a quasi-experimental study with a 6-week intervention, with repeated measures in a single group.

Subjects

The study included 13 sedentary menopausal women. The average age of the participants was 59.45 ± 11.52 years, they had an average weight of 88.68 ± 11.14 kg and a height of 160.42 ± 5.07 cm. The criteria for inclusion and exclusion from the study are listed below.

Criteria for inclusion in the study;

- Being in menopause
- Being sedentary and not doing active exercise
- Not having a health problem that would prevent them from exercising
- Not having had a surgery that would affect the musculoskeletal system in the last year

Criteria for exclusion from the study;

- Voluntarily leaving the study
- Not following the procedures required by the study
- Arbitrarily disrupting the exercise schedule more than 2 times

Procedure

The study aims to determine the effects of 6 weeks of Pilates exercise on quality of life, depression, and musculoskeletal disorders in menopausal women. 15 participants were initially included in the study. However, two participants were excluded from the analysis because they did not participate regularly in the exercise program during the study. The study was conducted with 13 menopausal women. The participants were assessed using the Cornell Musculoskeletal Disorder Scale, the World Health Organisation Quality of Life-BREF (WHOQOL-BREF), and the Beck Depression Inventory for Primary Care. No intervention was then carried out for 6 weeks, and the tests were repeated a second time after the 6th week. After that, the participants did Pilates exercises 2 days a week for 6 weeks, and then their third test was taken.

Data Collection Tools

Participant Demographic Form

This form queried the participants' age, gender,

weight, height, whether they were in menopause, whether they exercised regularly, whether there was a condition that would prevent them from exercising, and whether they had undergone surgery that would affect their musculoskeletal system in the last year. Participants to be included in the study were determined based on the results of this form.

The World Health Organization Quality of Life - BREF (WHOQOL-BREF)

The World Health Organization Quality of Life - BREF (WHOQOL-BREF) was developed in 1988 [27] and its Turkish validity and reliability were performed by Eser *et al.* [28]. WHOQOL-BREF consists of 27 questions. WHOQOL-BREF measures individuals' quality of physical health (questions 3, 4, 10, 15, 16, 17, 18), quality of psychological health (questions 5, 6, 7, 11, 19, 26), quality of social relationships (questions 20, 21, 22), and quality of environmental health (questions 8, 9, 12, 13, 14, 23, 24, 25, 27). The scale has a 5-point Likert structure. The total score of each subheading was multiplied by 5 and evaluated out of 100 points. An increase in the score obtained from the scale indicates that the quality of life in the relevant category increases [29].

Beck Depression Inventory for Primary Care (BDI-PC)

The scale, developed by Beck *et al.* [25] in 1997, was adapted into Turkish by Aktürk *et al.* [26] in 2005. The scale screens for depression under seven headings using symptoms of sadness, pessimism, past failures, self-dislike, self-blame, loss of interest, and suicidal ideation or desire. Each heading includes a rating from zero to three. A total score of a minimum of zero and a maximum of 21 is obtained [26]. The analysis was conducted on the total score in the current study.

Cornell Musculoskeletal System Discomfort Questionnaire (CMSDQ)

The Cornell Musculoskeletal System Discomfort Questionnaire (CMSDQ) was developed by Cornell University and its Turkish validity and reliability were performed by Erdinç *et al.* [30]. The CMSDQ allows the assessment of 20 separate body regions (neck, right and left shoulder, back, right and left upper arm, waist, right and left forearm, right and left wrist, hip, right and left upper leg, right and left knee, right and

left lower leg, right and left foot). The frequency, severity, and work-interference status of pain, aching, or discomfort felt in these regions in the last 7 days are questioned. The weighted score for each body region is calculated by multiplying the scores it receives for pain frequency, severity, and work-interference status. The weighted score ranges between 0 and 90 for each body region. An increase in the score indicates that the frequency, severity, and effect of the pain on work increase [30, 31]. Total weighted score was used in this study.

Pilates Exercises

The Pilates exercise program was conducted twice a week for six weeks, with each session lasting 60 minutes and divided into three phases: a 10-minute warm-up, a 40-minute main exercise period, and a 10-minute cool-down. The warm-up phase included 4 minutes of low-intensity on-the-spot marching to gradually increase heart rate, followed by 6 minutes of dynamic and static stretching exercises targeting major muscle groups such as the hamstrings, quadriceps, and shoulders to improve flexibility and prepare the body for the main exercises. The main exercise period consisted of 3 main phases that changed every two weeks according to the difficulty level. During each phase, participants performed foundational Pilates movements, starting with 2 sets of 10 repetitions for each movement in the first week, which were increased to 2 sets of 15 repetitions from the second week onward to ensure gradual progression. The main Pilates exercise program is included in Table 1. The cool-down phase involved 4 minutes of low-intensity on-the-spot marching to lower the heart rate, followed by 6 minutes of static stretching focused on the muscles engaged during the main workout, such as the lower back, hamstrings, and shoulders, to promote relaxation and reduce muscle tension.

Ethical Consideration

Ethics committee permission for the study was received from Yalova University Ethics Committees Coordination on 01.10.2024 with protocol number 2024/227. Participants were informed about the study and filled out an informed consent form. Participants were included in the study on a voluntary basis. The current research is in accordance with the Declaration of Helsinki.

Table 1. Pilates exercises program

Weeks 1-2	Weeks 3-4	Weeks 5-6
Pelvic curl	Push Up	Arm abduction with band
Chest lift	Overhead shoulder openers	Standing flies with band
Side lying leg circles	Glute bridge leg lifts	Russian twist
Lateral lunges	Swan prep	Scissor crunches
	Child's pose	Kneeling arm and leg reach
	Plank jack	Cat-cow

Statistical Analysis

IBM SPSS Statistics 25.0 program was used in the application of the analyses and the evaluation of the data. Since the skewness and kurtosis values of the obtained data were between (-1.5) and (1.5), the data were normally distributed [32]. For this reason, parametric tests were preferred in data analysis. Descriptive statistics and ANOVA tests were used in the analysis of the data. The statistical significance level was determined as $P < 0.05$. The effect of the mean score difference between the variables was evaluated with the eta squared (η^2) value. The η^2 value range was considered as "0.01-small effect power, 0.06-medium effect power, 0.14 and above - large effect power" [33].

RESULTS

In Table 1, to examine the effect of pilates exercises, 3 different measurements were made to the same group and the differences between the measurements were examined with the Repeated Measures ANOVA test.

For the participants' quality of life scores in the Physical health domain, the Mauchly's test provided the assumption of sphericity ($X^2(2)=4.042$, $P=0.133$). A significant difference was found between the three different measurements ($F(2,22)=17.949$, $P<0.001$, $\eta^2=0.62$). When the source of the difference was examined with post hoc tests, it was found to be between the post-pilates measurement (65.77 ± 4.49) and the first measurement (54.46 ± 4.70) and the second measurement (57.14 ± 4.48) ($P<0.05$) (Table 2). The participants' quality of life scores in the Physical Health domain increased statistically significantly after Pilates ($P<0.05$).

Mauchly's test sphericity assumption was met for the participants' quality of life scores in the domain of psychological health ($X^2(2)=4.270$, $P=0.118$). There was a significant difference between three different measurements ($F(2,22)=13.888$, $P<0.001$, $\eta^2=0.558$). When the source of the difference was examined with post hoc tests, it was found to be between the post-pilates measurement (60.42 ± 4.37) and the first measurement (52.43 ± 3.75) and the second measurement (52.43 ± 3.92) ($P<0.05$) (Table 2). The participants' quality of life scores in the psychological health domain increased significantly after Pilates ($P<0.05$).

The Mauchly's test assumption of sphericity was violated for the participants' quality of life scores in the Social relationships domain ($X^2(2)=12.738$, $P=0.002$). For this reason, Greenhouse-Geisser correction was applied and no significant difference was found between the three different measurements ($F(1.16, 12.79)=3.951$, $P=0.063$, $\eta^2=0.264$) (Table 2). After Pilates, the participants' quality of life scores in the social relations area did not differ significantly ($P>0.05$).

Mauchly's test sphericity assumption was met for the participants' quality of life scores in the field of Environmental health ($X^2(2)=2.521$, $P=0.284$). No significant difference was found between the three different measurements ($F(2,22)=2.118$, $P=0.144$, $\eta^2=0.161$) (Table 2). No statistically significant difference was found in the participants' quality of life scores in the environmental health area after Pilates ($P>0.05$).

Mauchly's test assumption of sphericity is not provided for the participants' Beck Depression scores ($X^2(2)=10.462$, $P=0.005$). Therefore, Greenhouse-Geisser correction was applied. A significant difference was found between the three different

Table 2. Differences between the measurements made at 3 different times regarding the participants' quality of life, depression, musculoskeletal disorders

Scales/ Domains		Measurement	Mean	SD	F	P value	η ²	Post-hoc (Bonferroni)
WHOQOL-BREF	Physical health	First pre-pilates (1)	54.46	4.70	17.95	<0.001	0.62	3>1, P=0.002*; 3>2, P=0.005*
		Second pre-pilates (2)	57.14	4.48				
		Post-pilates (3)	65.77	4.49				
	Psychological health	First pre-pilates (1)	52.43	3.75	13.89	<0.001	0.56	3>1, P=0.008*; 3>2, P=0.004*
		Second pre-pilates (2)	52.43	3.92				
		Post-pilates (3)	60.42	4.37				
	Social relationships	First pre-pilates (1)	52.08	4.12	3.95	0.064	0.26	P>0.05
		Second pre-pilates (2)	52.78	4.63				
		Post-pilates (3)	59.72	4.68				
	Environmental health	First pre-pilates (1)	43.06	6.14	2.12	0.144	0.16	P>0.05
		Second pre-pilates (2)	41.20	6.21				
		Post-pilates (3)	45.14	5.07				
BDI-PC (total score)		First pre-pilates (1)	4.67	1.35	11.31	0.004	0.51	1>3, P=0.033*; 2>3, P=0.006*
		Second pre-pilates (2)	5.00	1.26				
		Post-pilates (3)	2.00	0.70				
CMSDQ (total score		First pre-pilates (1)	26.25	6.04	0.78	0.396	0.07	P>0.05
		Second pre-pilates (2)	26.67	5.94				
		Post-pilates (3)	44.58	18.91				

BDI-PC=Beck Depression Inventory for Primary Care, WHOQOL-BREF= The World Health Organisation Quality of Life – BREF, CMSDQ=Cornell Musculoskeletal System Discomfort Questionnaire, SD=standard deviation

*P<0.05

measurements ($F(1.21, 13.34)=11.31$, $P=0.004$, $\eta^2=0.507$). When the source of the difference was examined with post hoc tests, it was found to be between the post-pilates measurement (2.00 ± 0.69) and the first measurement (4.67 ± 1.35) and the second measurement (4.67 ± 1.35) ($P<0.05$) (Table 2). A significant decrease was found in the participants' depression scores after Pilates ($P<0.05$).

Mauchly's test assumption of sphericity is not provided for the participants' CMSDQ total weighted scores ($X^2(2)=52.564$, $P<0.001$). In this direction, Greenhouse-Geisser correction was made and no significant difference was found between the three dif-

ferent measurements ($F(1, 22)=0.780$, $P=0.396$, $\eta^2=0.066$) (Table 2). No statistically significant change was found in the participants' CMSDQ total weighted scores after Pilates ($P>0.05$).

DISCUSSION

This study investigated the effects of six weeks of Pilates on the physical and psychological quality of life of menopausal women. The results of the study show that Pilates exercises are effective in improving the physical and psychological quality of life of

menopausal women. Studies in the literature support the fact that Pilates increases muscle strength in menopausal women, provides physical and psychological fitness and improves quality of life [34]. Lee *et al.* [35] found that Pilates helps protect physical and mental health by improving body composition and hormonal balance in menopausal women. In addition, studies show that Pilates provides psychological well-being by reducing fatigue, which is common during this period [36]. Persaki *et al.* [37] found that it improved the quality of life in terms of general health and social functioning. However, in the current study, it was observed that 6 weeks of Pilates did not affect the social and environmental quality of life of the participants. This difference may have been observed because the Pilates exercises were performed for 16 weeks in the study by Persaki *et al.* [37]. In conclusion, Pilates can be used to improve the physical and psychological quality of life of menopausal women. However, Pilates should be done for more than 6 weeks to improve social and environmental quality of life. It is recommended that similar studies are carried out in the future to investigate the effects of Pilates over a longer period.

Another important finding of the current study is that six weeks of Pilates reduces depression in menopausal women. Pilates is already recommended to improve symptoms of depression and anxiety in women [14]. In fact, Pilates was found to be more effective than aerobic exercise in reducing symptoms of depression in women with fibromyalgia [38]. Pilates alone has been shown to reduce anxiety in patients with chronic low back pain [20]. Farzaneh *et al.* [19] found that eight weeks of Pilates reduced anxiety in menopausal women. Other studies in menopausal women found that eight weeks [39, 40] and twelve weeks [18] of Pilates were effective in reducing depression. The Pilates program used in the current study lasts 6 weeks. In line with this finding, it can be argued that 6 weeks of Pilates is effective in reducing depression levels and improving psychological health in menopausal women.

In the current study, it is an unexpected finding that six weeks of Pilates did not affect musculoskeletal disorders in menopausal women. Normally, physical activity and postural health are closely related, which affects the musculoskeletal system [41]. It has been reported in the literature that Pilates exercises gener-

ally alleviate musculoskeletal problems [20, 42-44]. However, in our study, 6 weeks of Pilates did not have a significant effect on musculoskeletal disorders. This may be due to the small number of participants and the short duration of the exercise, or it may be that people's existing conditions were too chronic to be improved by exercise. The fact that the chronic pain levels of the participants were not measured with the pain questionnaire is a shortcoming of the study. It is recommended that future studies investigate the effects of longer-term Pilates, include a larger number of participants, or investigate whether different types of exercise programs are effective in this regard.

Limitations

In the current study, the fact that the duration of the Pilates program was limited to 6 weeks may have caused it to not affect musculoskeletal disorders. In addition, the limited number of participants in the study to thirteen people prevents this effect from being observed and the results from being generalized. It is recommended that future studies be conducted with a larger number of participants and that the time-dependent effects of Pilates be investigated in more detail. In addition, Pilates should be compared with other forms of exercise in menopausal women to determine the most effective form of exercise.

CONCLUSION

In conclusion, this study showed that six weeks of Pilates exercise can improve physical and psychological quality of life and reduce depression in menopausal women but has no significant effect on social and environmental quality of life or musculoskeletal disorders. These findings emphasize the importance of exercise during menopause but show that exercise programs should be tailored to the needs of the individual. According to the results of the study, Pilates exercises can be preferred to improve the quality of life of menopausal women and prevent possible psychological problems. Countries should develop plans and strategies to improve the physical activity levels of menopausal women as part of their health policies to improve women's health. In this way, excessive health expenditure can be avoided, the welfare of individuals in the country can be increased and social peace can

be maintained. Health professionals and sports scientists have a major responsibility in this process.

Ethical statement

Ethics Committee Permission for the study was received from Yalova University Ethics Committees Coordination on 01.10.2024 with protocol number 2024/227.

Authors' Contribution

Study Conception: SAK; Study Design: SAK; Supervision: SAK; Funding: SAK; Materials: SAK; Data Collection and/or Processing: SAK; Statistical Analysis and/or Data Interpretation: SAK; Literature Review: SAK; Manuscript Preparation: SAK and Critical Review: SAK.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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Effects of unilateral and bilateral vertebroplasty on coronal balance

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ABSTRACT

Objectives: Percutaneous vertebroplasty is frequently used to treat osteoporotic vertebral compression fractures (OVCFs) due to its low surgical risks. In this study, we tried to determine the early and late effects of single-pedicle and double-pedicle PVPs on the coronal balance of the vertebrae.

Methods: This study evaluated 95 OVCF patients treated with PVP between 2008 and 2023. Of these patients, 36 were treated with bilateral and 59 with unilateral vertebroplasty. The Coronal Cobb angle, coronal segmental Cobb angle, and coronal balance of the vertebrae were measured in preoperative, early postoperative, and 6-month postoperative radiographs. The results were compared between the two groups and the effects of single or double pedicle procedure on these values were analyzed.

Results: Two study groups were formed, consisting of a total of 95 patients. The mean age was 69.1 years. Forty-nine patients were female and 46 were male. No significant difference was detected between the groups regarding gender and age. When the data obtained in the preoperative and early postoperative period in patients who underwent single and double pedicle vertebroplasty were evaluated, no statistically significant difference was obtained in coronal balance, Cobb angle, and segmentary Cobb angle measurements.

Conclusions: From the radiographic point of view in the long-term follow-up, we think that bilateral PVP provides an advantage over the unilateral approach in maintaining the coronal balance and stabilization of the coronal Cobb angle in patients with OVCF.

Keywords: Coronal balance at vertebra, percutaneous vertebroplasty, Cobb angle, coronal balance

Osteoporotic vertebral compression fractures (OVCF) are caused by high or low-energy trauma [1]. Pain in these patients is usually caused by instability. It is a pain that increases with movement and decreases with rest. The collapse of the OVCF may lead to spinal instability, scoliosis, and kyphotic deformity. Increasing the load-bearing capacity of the corpus, mobility, and restoration of sagittal and coronal balance are important [2, 3]. Minimally

invasive surgical interventions have been used to treat these patients by avoiding radical surgical procedures with high mortality. Percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP) have been increasingly used in recent decades. The risk of complications of this method is less compared to open surgical procedures [2]. There are numerous advantages including restoration of height, stabilization of the vertebral body, significant reduction of pain, early mobi-

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lization, and significant reduction of mortality [4, 5]. It is a great advantage to use in elderly patients with a high general anesthesia risk.

PVP was initially performed through bilateral pedicles. Some authors recommend performing the procedure through a single pedicle to shorten the duration of the long surgical procedure and reduce the radiation dose. This also reduces the cost of the operation and significantly decreases the complications of placing a second cannula, in short, the complications of vertebroplasty [6, 7].

It is observed that some OVCFs continue to align in the normal coronal and sagittal plane after PVP or PVK, while others cause distortions in the coronal and sagittal planes.

Although publications indicate that both PVPs significantly improve the clinical outcomes of patients, there are no clear studies on their effects on the stability of the vertebra [7]. Some studies show that both techniques of PVPs with single pedicle access or double pedicle access do not impair or even correct sagittal balance and do not cause a significant loss of lordosis [7, 8]. However, there are few studies on the effects of PVPs on the coronal balance of the vertebrae. In this study, we tried to determine the early and late effects of PVPs with single-pedicle and double-pedicle access on the coronal balance of the vertebrae.

METHODS

This study evaluated OVCF patients treated with PVP between 2008 and 2023. Patients with neurological

deficits, bone compression of the canal, obesity, severe cardiovascular diseases, cancer, regional infection, radiotherapy, and patients with insufficient documentation were excluded. Perop specimens for pathology were obtained from all patients. A total of 95 OVCF patients who met these criteria were included in the study. Of these patients, 36 were treated bilaterally and 59 with unilateral vertebroplasty. Coronal Cobb angle, coronal segmental Cobb angle, and coronal balance of the vertebra were measured in the radiographs taken before surgery, in the early postoperative period, and in the 6th month after surgery. We compared the results between both groups and tried to reveal the effects of single or double pedicle procedure on these values. This study was approved by the Erciyes University institutional ethics committee (2023-788).

Radiological Evaluation

90×35 cassettes called scoliosis cassettes and radiographs taken with the same device (Multifunctional Radiograph Unit Siemens-GERMANY) were used as standard. For coronal plan imaging, radiographs taken from 1.8 meters in the posterior-anterior direction with the patient's arms on both sides and standing were obtained. Cobb and coronal balance measurements were performed using the software in Picture Archiving and Communication Systems (PACS). The same neurosurgeon made all the measurements. Cobb angle measurements are used for coronal segmental Cobb angle and coronal Cobb angle, and the distance between the central mid-sacral line and the C7 plumb line is evaluated for coronal balance examination [9, 10] (Fig. 1).

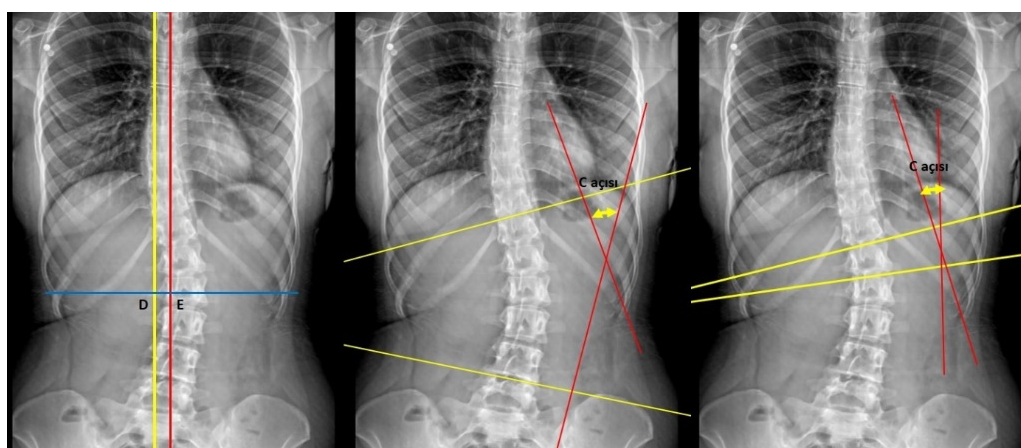


Fig. 1. (A) Coronal balance, (B) Cobb angle, and (C) Segmentary Cobb angle.

Surgical Methods

All interventions for PVP were performed in the operating rooms. Patients were placed in the prone position. Silicone pillows were placed under the chest and hips to correct the kyphosis. Vertebroplasty was performed percutaneously under C-arm control. All patients received prophylactic first-generation cephalosporin (Cefazolin) preoperatively. Local anesthesia and sedation were preferred for the procedure. Local anesthesia was performed with 1% lidocaine. General anesthesia was used in 7 cases where sedation failed and the patient did not communicate well. In patients undergoing unilateral VP procedure, the procedure was performed by entering 5 mm more laterally to deliver the bone cement to the centralized region. Polymethylmethacrylate (PMMA) bone cement (Berlin Germany) was used in all cases. Average 2-3.5 cc methylmethacrylate was used in bilateral VP, and 3.5-4 cc methylmethacrylate was used in unilateral VP. Patients were followed up during the operation. Possible complications were observed. Patients were mobilized with a corset 3 hours after the operation. The patients were discharged the same day after a control X-ray and, if necessary, a control computed tomography scan (according to the X-ray image). General anesthesia patients were discharged the next day under the same conditions [11].

Statistical Analysis

The data were analyzed using SPSS 22 software. Frequency, percentage, mean value, standard deviation, median value, and highest and lowest (min-max) values were used for descriptive statistics. Pearson Chi-square test was applied for statistical analysis of

categorical data. Shapiro Wilk test was used to check the suitability of the data for normal distribution. Since the independent groups of quantitative data did not conform to normal distribution, the Mann-Whitney U test was used in paired groups. The Wilcoxon test was used to determine whether there was a change in the quantitative values measured in the first and 6th month after surgery. The Pearson correlation coefficient was used to show the relationship between the variables. The statistical significance of the difference was accepted as $P < 0.05$.

RESULTS

Of the 95 patients enrolled in the study, 49 (51.6%) were female and 46 (48.4%) were male. The mean age of the patients was 69.1 ± 11.5 (range: 45-89) years. When the patients were categorized into two groups under 65 years and 65 years and over, 37 (38.9%) patients were under 65 years and 58 (61.1%) patients were 65 years and over. 59 patients (62.1%) were operated on unilaterally and 36 patients (37.9%) were operated on bilaterally. There was no significant correlation between the surgical operation group and the gender and age groups of the patients ($P > 0.05$) (Table 1).

When the data obtained in the preoperative and early postoperative period in patients who underwent single and double pedicle vertebroplasty were evaluated, no statistically significant difference was obtained in coronal balance, Cobb angle, and segmentary Cobb angle measurements, although there were partial changes in the measurement values in both groups ($P < 0.05$) (Table 2).

Table 1. Age and gender relationship with the surgical groups of the patients

Variables		All Patients		Patient Surgical Groups				P value
				Single Pedicle		Bilateral Pedicles		
		n	%	n	%*	n	%*	
Gender	Female	49	51.6	31	63.3	18	36.7	0.810
	Male	46	48.4	28	60.9	18	39.1	
Age Groups	65 years ↑	37	38.9	21	56.8	16	43.2	0.391
	65 years ↓	58	61.1	38	65.5	20	34.5	
All Patients		95	100.0	59	100.0	36	100.0	

*Percentage of rows was used. Pearson chi-square test was used.

Table 2. The preop, early postoperative, and 6th-month measurements of unilaterally/ bilaterally operated patients

Measurements	Single Pedicle		Bilateral Pedicles	
		P value		P value
Coronal Balance preop (mm)	2.5±1.9	<0.05	4.5±3.7	<0.05
Coronal Balance (early) mm	2.5±1.9		4.5±3.8	0.035
Coronal Balance (6. month) mm	4.0±3.0	<0.001	4.8±3.8	
Cobb Angle preop(°)	3.9±3.0	<0.05	5.9±4.9	<0.05
Cobb Angle (early) (°)	4.0±3.0		5.9±5.0	0.782
Cobb Angle (6. month) (°)	6.5±4.3	<0.001	6.0±5.1	
Segmentary Cobb Angle (preop) (°)	3.9±2.9	<0.05	6.0±5.1	<0.05
Segmentary Cobb Angle (early) (°)	4.0±3.0		6.0±5.2	0.796
Segmentary Cobb Angle (6. month) (°)	6.7±4.2	<0.001	6.0±5.1	

Data are shown as mean±standard deviation. Wilcoxon Signed Ranks Test was used.

When the data obtained in the early and late (mean 6 months) postoperative period in patients who underwent vertebroplasty from a single pedicle were evaluated. Coronal balance was measured as 2.5±1.9 in the early postoperative period and 4.0±3.0 in the 6th month and this change was statistically significant ($P<0.001$). Cobb angle was 4.0±3.0 in the early postoperative period and 6.5±4.3 at the 6th month and this change was statistically significant ($P<0.001$). Segmentary Cobb angle was 4.0±3.0 in the early postoperative period and 6.7±4.2 in the 6th month and the change was statistically significant ($P<0.001$) (Table 2).

When the data obtained in the early and late (mean 6 months) postoperative period in patients who under-

went double pedicle vertebroplasty were evaluated. Coronal balance was 4.5±3.8 in the early postoperative period and 4.8±3.8 in the 6th month and this change was statistically significant ($P=0.035$). Cobb angle was measured as 5.9±5.0 in the early postoperative period and 6.0±5.1 in the 6th month and the change was not statistically significant ($P=0.782$). Patients who underwent bilateral operations. Segmentary Cobb angle was 6.0±5.1 in the early postoperative period and 6.0±5.1 in the 6th month and the change was not statistically significant ($P=0.796$) (Table 2) (Figs. 2, 3 and 4).

When all patient groups (single and double pedicle interventions) were evaluated according to gender, preoperative, early postoperative, and 6th-month coro-

**Fig. 2.** CT view of cleft at osteoporotic vertebral compression fracture (OVCF).

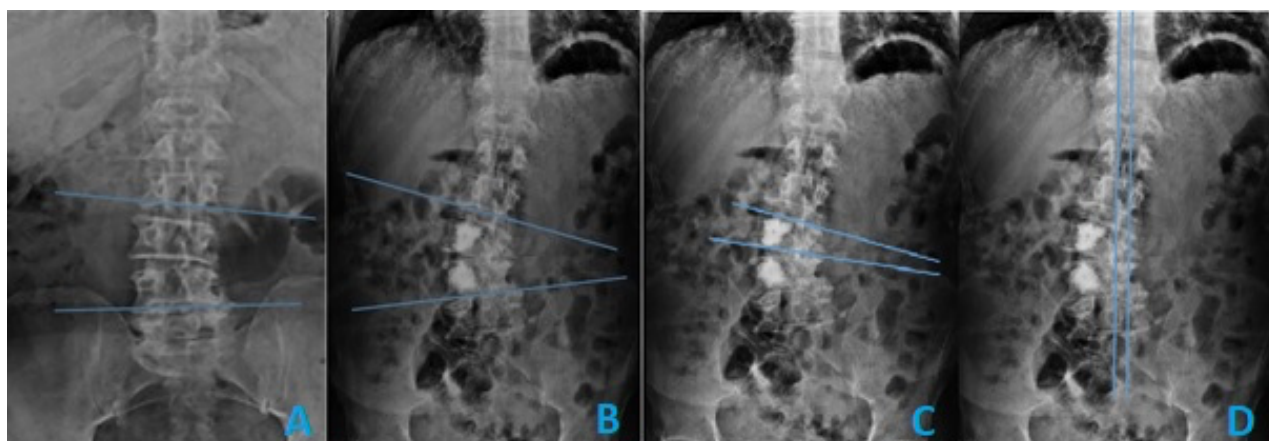


Fig. 3. (A) Preoperative Cobb, (B) Postoperative Cobb, (C) Postoperative segmentary Cobb, and (D) Postoperative coronal balance.

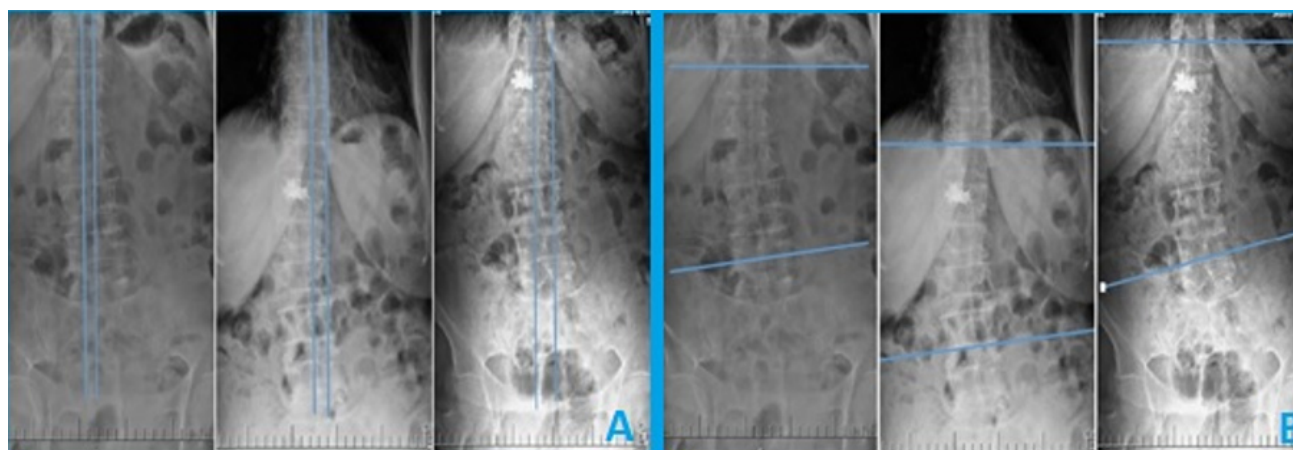


Fig. 4. (A) Preoperative/postoperative early/postop 6. month coronal balance and (B) Preoperative/postoperative early vs 6. month Cobb angle.

Table 3. Preoperative/postoperative measurements according to age groups

Measurements	Age groups		P value
	65 years ↓	65 years ↑	
Coronal balance preop (mm)	1.8±2.2	4.0±2.2	<0.001
Coronal balance (early) mm	1.9±2.6	4.1±2.8	<0.001
Coronal balance (6. month)	2.5±3.1	5.5±3.0	<0.001
Cobb angle preop(°)	2.6±3.1	5.8±3.1	<0.001
Cobb angle (early) (°)	2.8±3.6	5.9±3.7	<0.001
Cobb angle (6. month) (°)	4.1±3.7	7.8±4.6	<0.001
Segmentary Cobb angle (preop) (°)	2.7±3.2	5.6±2.9	<0.001
Segmentary Cobb angle (early) (°)	2.8±3.7	5.9±3.8	<0.001
Segmentary Cobb angle (6. month) (°)	4.2±3.8	7.8±4.5	<0.001

Data are shown as mean±standard deviation. Mann Whitney U Test was used.

nal balance, Cobb angle and segmental Cobb angle measurements did not differ significantly in both groups ($P>0.05$). When both groups were evaluated according to age, preoperative, early postoperative, and 6-month postoperative Cobb angle, segmental Cobb angle, and coronal balance measurements of patients aged 65 years and older were significantly higher ($P<0.001$). In both intervention groups, there was a positive correlation between age and Cobb angle, segmental Cobb angle, and coronal balance measurements in preoperative, early postoperative, and 6-month measurements ($P<0.05$) (Table 3) (Figs. 2, 3 and 4).

DISCUSSION

PVP is a much more successful treatment method than conservative treatment methods in treating treatment-resistant pain or acute pain in OVCF patients [11]. Moreover, when applied in multiple vertebral fractures, it has been reported to be effective and has similar results compared to single-level procedures in terms of healing, gaining mobility and pain relief [7, 12, 13]. Tohmen *et al.* [13] reported in their biomechanical tests on cadavers that unilateral or bilateral PKF did not affect the recovery of the vertebral corpus to its preoperative strength or stiffness.

In a study published in 2023, Tan *et al.* [8] showed that unilateral and bilateral PVP gave similar results in reducing pain complaints and maintaining the height of the vertebra, both models had a positive effect on the restoration of lordosis with no significant difference on sagittal balance. However bilateral PVP had advantages over unilateral PVP in stabilizing coronal balance. They reported that the loss of improvement in coronal balance was more pronounced in multilevel vertebroplasty. In this study, they also stated that balance changes are not only caused by the loss of height in the vertebral body but also by the adjacent segment and the intervertebral disc. Secondary scoliosis that may occur after surgery is caused by the effect of these factors.

In our study, there was a statistically significant loss of coronal correction in the measurements of patients who underwent unilateral PVP after 6 months of surgery, whereas no measurements were obtained to show loss of coronal balance in the measurements

of patients who underwent bilateral PVP. In addition, it was observed that coronal imbalance of the vertebrae after vertebroplasty was more common in patients over 65 years of age than in patients under 65 years of age. Cement distribution affects biomechanical balance [14]. It is recommended to place the bone cement symmetrically in the corpus during the PVP procedure [12, 15]. If the PVP is done through both pedicles, the stiffness of the spine increases on both sides of the corpus, but if this is done unilaterally and the cement is not evenly distributed and limited to only one side of the corpus, then only the side that is cemented will increase in stiffness and the other side will be weaker. This will create a biomechanical stress imbalance on the adjacent vertebrae. [15, 16]. This may explain the negative effect of unilateral PVP on coronal balance. The increased use of PVP in the treatment of OVCFs has led to more careful observation of the clefts in the vertebrae called clefts in OVCFs. Filling the clefts should be the primary goal in PVP. Patients with incomplete filling of the clefts are thought to achieve a return to preoperative baseline pain and deformity within 6 to 12 months [18]. Recent studies suggest that intervertebral clefts in OVCF affect the effects of PVP on clinical recovery and complications that may occur [18]. Therefore, it is necessary to detect intervertebral clefts during the treatment of patients with OVCF. MRI images are important here. Contrast MRI may show a hypointense area in a homogenous contrasting corpus or a hyperintense area in T1 and T2 sequences [19].

CONCLUSION

Patients with OVCF have significant clinical improvement as a result of PVP made of single or double pedicles. Pain is greatly reduced. Height improves significantly. However, from the radiographic point of view in the long-term follow-up, we think that bilateral PVP provides an advantage over the unilateral approach in maintaining the coronal balance and stabilization of the coronal Cobb angle in patients with OVCF, and that age over 65 years is a negative factor in terms of the coronal balance of the vertebrae after vertebroplasty. We believe that more long-term and numbered studies are also necessary.

Ethical statement

Ethics committee approval (number: 2023-788) was obtained from the from the Clinical Research Ethics Committee of Erciyes University.

Authors' Contribution

Study Conception: MM; Study Design: MM; Supervision: MM; Funding: MM; Materials: MM; Data Collection and/or Processing: MM; Statistical Analysis and/or Data Interpretation: MM; Literature Review: MM; Manuscript Preparation: MM, RKK and Critical Review: MM, RKK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Improvement in symptom severity, asthma control, and quality of life in pediatric patients with seasonal allergic rhinitis

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ABSTRACT

Objectives: To evaluate the allergic rhinitis (AR) symptoms, asthma control, and quality of life (QoL) outcomes following treatment in children with seasonal allergic rhinitis (SAR), with and without asthma.

Methods: Children diagnosed with SAR and presenting during the pollen season were included in the study. Symptom severity of SAR was assessed using the Total Nasal Symptom Score (TNSS), Total Ocular Symptom Score (TOSS), and Visual Analog Scale (VAS). Asthma control was measured using the Childhood Asthma Control Test (C-ACT), Asthma Control Test (ACT), and CARATkids. Quality of life (QoL) was evaluated using the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire. Data were collected at admission, the first month, and the second month of treatment.

Results: Fifty-five children aged 5-16 years with SAR were evaluated of whom twenty three (42%) had asthma. Sensitivities to grass, tree, and weed allergens were observed in 74.5%, 50.9%, and 80% of patients, respectively. During the study period, TNSS, TOSS, and VAS scores significantly decreased ($P<0.05$ for all). Significant improvements were also observed in CARATkids, C-ACT and ACT scores among SAR patients with asthma ($P<0.05$ for all). All domains of QoL score showed significant improvement ($P<0.001$ for all), and positively correlated with TNSS, TOSS, and VAS scores. In SAR patients with asthma, ACT and C-ACT scores demonstrated a positive correlation with QoL scores, while CARATkids scores showed a negative correlation.

Conclusions: Treatment for SAR in children significantly reduces symptom severity, improves asthma control, and enhances QoL. Effective management of SAR is crucial for alleviating the disease burden and improving patients' overall well-being.

Keywords: Allergic rhinitis, asthma, children, pollen, quality of life

Allergic rhinitis (AR) is a common chronic disease in children with an incidence rate reaching as high as 20% in some regions [1].

Seasonal allergic rhinitis (SAR) is triggered by airborne allergens such as grass, tree, and weed pollens, and is characterized by symptoms including nasal con-

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gestion, rhinorrhea, nasal itching, sneezing, ocular itching, and tearing. Furthermore, approximately, 30% of the patients with AR also suffer from asthma [2].

The symptoms of SAR can be especially challenging for children. They can experience disturbances in their daily activities, including reduced concentration in school, sleeping disturbances, and avoidance of physical exercise during peak allergy seasons, which can negatively impact social interactions with a noticeable decline in their quality of life (QoL) [3]. Limitations in outdoor activities may result in social withdrawal and emotional stress [4]. Academic performance is also frequently affected, as SAR symptoms can interfere with a child's ability to focus and learn effectively [5]. Sleep disturbances caused by nasal congestion and other symptoms also contribute to daytime tiredness and impaired cognitive function [6]. The emotional impact of SAR can be profound, as children may feel self-conscious about their symptoms, leading to anxiety, frustration, and difficulties in social situations.

Recognizing the profound impact of SAR on children's lives, this study aims to investigate the correlation between AR scores, asthma scores, and quality of life following treatment in pediatric patients with SAR.

METHODS

Patients aged 5-16 years diagnosed with SAR and presenting during the pollen season were included in the study. In this study, total nasal symptom score (TNSS), total ocular symptom score (TOSS), Visual analog scale (VAS), Childhood Asthma Control Test (C-ACT), Asthma Control Test (ACT), Control of Allergic Rhinitis, and Asthma Test for Children (CARATkids), and QoL scores in children diagnosed with SAR±asthma was evaluated by comparing their condition at admission, after the first month, and the second month of the treatment. Patients with missing data or comorbid chronic conditions were excluded from the study. The study was approved by the Clinical Research Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital.

Seasonal Allergic Rhinitis Scores

The total nasal symptom score was calculated as

the sum of four nasal symptom scores: nasal congestion, rhinorrhea, nasal itching, and sneezing, from 0 (none) to 3 (severe), with a maximum possible score of 12. Similarly, the Total Ocular Symptom Score was determined as the sum of three ocular symptoms (itching, redness, and tearing) on a 4-point scale, from 0 (none) to 3 (severe), with a maximum possible score of 9.

The patients marked their VAS scores, for objective measurement of the severity of AR, on a 10 cm scale, where 0 cm represented "bad" and 10 cm represented "good,". Consistent with previous studies, a VAS score greater than 6 indicates controlled disease [7, 8].

Asthma Control Measurements

All children with asthma and their parents filled in the Turkish version of the Childhood Asthma Control Test (C-ACT; 4–11 years old) or ACT (≥ 12 years old) [9-10]. The ACT score ranges between 5 and 25, with a score of less than 20 corresponding to uncontrolled asthma. The C-ACT score ranges from 0 to 27, and a score of <19 indicates uncontrolled asthma.

CARATkids

Children with both AR and asthma completed the Turkish version of CARATkids, a questionnaire, which assesses the control of both diseases (11). The CARATkids consist of 13 questions, of which the first 8 are answered by the children, and the remaining 5 are answered by their caregivers. Responses are based on the previous 4 weeks and answered as "Yes" or "No". A lower score indicates better disease control.

Quality of Life

The children completed the Turkish version of the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire, a validated 23-item tool designed to assess the physical, emotional, and social challenges experienced by children with rhinoconjunctivitis. This questionnaire provides both an overall score and subscale scores in five areas: nasal symptoms, eye symptoms, practical issues (e.g., rubbing the nose and eyes, blowing the nose, carrying tissues), other symptoms (e.g., thirst, irritability, fatigue), and activity limitations. Lower scores indicate better QoL.

Statistical Analysis

Statistical analyses were performed using the

SPSS version 22.0 statistical software package (IBM SPSS Statistics, Philadelphia, PA, USA). First normality tests for continuous variables were performed and as all of the continuous variables were distributed non-normally the results were given as median (interquartile range [IQR]). The χ^2 and Mann-Whitney U tests were used to compare nonparametric values. Statistical significance was defined as $P < 0.05$. The correlation between the scores was assessed through visual analysis using line graphs. Scores for variables were plotted over three-time points (baseline, 1st month, and 2nd month). In these plots, lines representing each variable that run parallel over time suggest a positive correlation between the variables, while lines that move in opposite directions or diverge indicate a negative correlation.

RESULTS

A total of 55 patients, comprising 22 females and 33 males, were included in the study. The median ages at

Table 1. Clinical and demographic characteristics of the patients

	n=55
Female, n (%)	22 (40)
Age at onset of AR symptom (year)	7 (5-10)
Age at AR diagnosis, (year)	9 (6-12)
Comorbid atopic diseases, n (%)	
Asthma	23 (41.8)
Food allergy	6 (10.9)
Drug allergy	2 (3.6)
Atopic dermatitis	12 (21.8)
Seasonal aeroallergen positivity, n (%)	
Grass	41 (74.5)
Tree	28 (50.9)
Weed	44 (80)
Perennial allergen sensitivity, n (%)	31 (56.4)
House dust mite	13 (23.6)
Mold	5 (9.1)
Pet dander	21 (38.2)

Data are shown as median (interquartile range) or n (%).
AR=Allergic rhinitis

Table 2. Comparison of total nasal symptom score (TNSS), total ocular symptom score (TOSS), and visual analog scale (VAS) scores at admission, and at the 1st and 2nd month of treatment in patients diagnosed with allergic rhinitis (AR)

	Total AR patients (n=55)			AR Patients with asthma (n=23)			AR Patients without asthma (n=32)		
	Admission	1 th month	2 nd month	Admission	1 th month	2 nd month	Admission	1 th month	2 nd month
TNSS	8 (6-9)	5 (3-8)	4 (2-5)	7 (6-9)	4 (3-8)	4 (3-6)	8 (6-9)	5.5 (3-7.8)	4 (1.3-5)
TOSS	5 (3-10)	3 (1-6)	1 (0-4)	5 (2-10)	2 (0-6)	0 (0-5)	5.5 (3-9)	3 (1-6)	1 (0-3.8)
VAS	6 (5-8)	4 (2-6)	2 (1-4)	7 (4-8)	4 (2-6)	2 (1-5)	6 (5-8)	4 (2-6)	2 (1-4)

Data are shown as median (interquartile range). AR=Allergic rhinitis

Table 3. Comparison of CARATkids and ACT scores at admission, and at the 1st and 2nd month of treatment in patients diagnosed with asthma and allergic rhinitis (AR)

	Admission	1 st month	2 nd month	P-value
CARATkids	8 (7-11)	5 (3-8)	3 (2-4)	<0.001
C-ACT (n=11)	18 (15.3-22)	22.5 (18-24)	24 (22.3-25.8)	0.001
ACT (n=12)	17 (8-21)	19 (18-20)	23 (22-25)	0.02

Data are shown as median (interquartile range). CARATkids=Control of Allergic Rhinitis, and Asthma Test for Children, C-ACT=Childhood Asthma Control Test, ACT=Asthma Control Test

the onset of AR symptoms were 7 years (range: 5-10), and the median age at diagnosis was 9 years (range: 6-12).

Among the patients, 42% had coexisting asthma, 21.8% had atopic dermatitis, and 11% had food allergies (Table 1). Sensitivities to seasonal allergens such as grass, tree, and weed were observed in 74.5%, 50.9%, and 80% of patients, respectively.

Sensitivities to perennial allergens were also recorded, with 23.6% reacting to house dust mites, 9.1% to mold, and 38.2% to pet dander.

At admission, 44 patients (80%) were given intranasal corticosteroids (Supplementary 1). Intraocular antihistamines were prescribed to 29 patients (53%), while 17 patients (30.9%) received systemic antihistamines. Additionally, leukotriene receptor antagonist (LTRA) therapy was given to 6 (10.9%) patients. Intranasal antihistamines were initiated in 3 patients

(5.5%), and combination therapy with LTRA and systemic antihistamines was given to 2 patients (3.6%).

The asthma treatments of the patients at admission were as follows: Inhaled corticosteroids (ICS) were started to 10 patients, combination therapy of ICS and long-acting-beta-agonist (LABA) started to eight patients, leukotriene receptor antagonists (LTRA) were started in three patients, combination therapy of ICS and LABA and LTRA was started to one patient (Supplementary 2). Two patients were instructed to use short-acting beta-agonists (SABA) as needed.

Nasal and Ocular Symptoms

During the treatment period, TNSS at admission in the asthma+AR group was 7 (6-9), which significantly decreased to 4 (3-8) in the first month, and remained at 4 (3-6) in the second month ($P=0.001$). Similarly, in the AR without asthma group, the TNSS

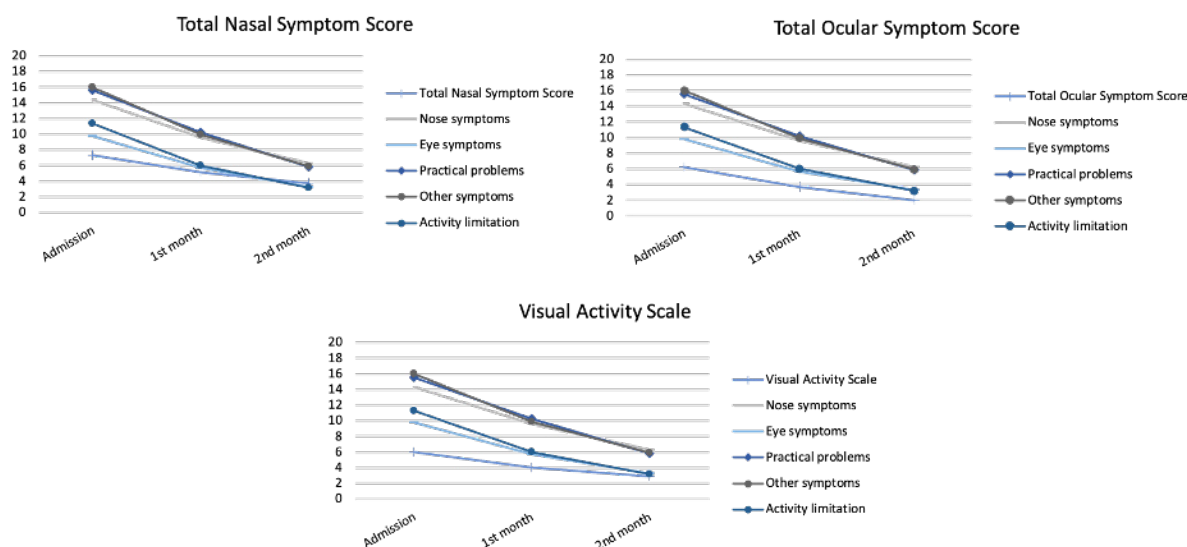


Fig. 1. Results of the test assessing the correlation of TOSS, TNSS, and VAS scores with quality of life over time (admission, 1st month, and 2nd month).

decreased from 8 (6-9) at admission to 5.5 (3-7.8) in the first month, and 4 (1.3-5) in the second month, respectively ($P<0.001$) (Table 2).

Total ocular symptom score for asthma+AR group decreased significantly from 5 (2-10) at admission to 2 (0-6) in the first month and 0 (0-5) in the second month ($P<0.001$). In the AR without asthma group, TOSS scores also decreased from 5.5 (3-9) at admission to 3 (1-6) in the first month and 1 (0-3.8) at the second month ($P<0.001$).

During the study period, the VAS scores decreased from 7 (4-8) at admission to 4 (2-6) in the first month and 2 (1-5) in the second month in the AR and asthma group ($P=0.004$). Similarly, in the AR without asthma group, the score improved from 6 (5-8) at admission to 4 (2-6) in the first month and 2 (1-4) in the second month ($P<0.001$).

CARATkids and Asthma Control Tests in AR+ Asthma Patients

The median CARATkids admission score of the patients with AR+asthma improved from 8 (7-11) to 5 (3-8) in the first month and 3 (2-4) in the second month ($P<0.001$) (Table 3). Similarly, C-ACT scores increased from 18 (15.3-22) at admission to 22.5 (18-24) in the first month, and 24 (22.3-25.8) in the second month ($P=0.001$). ACT scores also improved from 17 (8-21) at admission to 19 (18-20) at in the first month, and 23 (22-25) in the second month.

Quality of Life Scores

Significant improvements in QoL were observed across all domains (Fig. 1). The nose symptom score of QoL improved from 15 (12-18) at admission to 9 (5-14) IQR in the first month and 5 (2-10) in the second month ($P<0.001$). The eye symptom score of QoL decreased significantly from 9 (5-15) at admission to 3 (1-11) in the first month and further to 1 (0-5) in the second month ($P<0.001$). Practical issues scores improved from 16 (12-20) at admission to 9 (5-16) in the first month and 5 (2-10) in the second month ($P<0.001$). Similarly, other symptoms' scores of QoL showed a decrease from 16 (11-22) at admission to 9 (3-15) after one month and 5 (1-10) by the second month ($P<0.001$). Additionally, activity limitations score from 10 (6-17) at admission to 5 (1-10) in the first month and 2 (0-5) in the second month ($P<0.001$).

A positive correlation was found between QoL and

Table 4. Comparison of quality of life in patients diagnosed with allergic rhinitis (AR) at admission, and during the 1st and 2nd months of treatment.

	Total AR patients (n=55)			AR Patients with asthma (n=23)			AR Patients without asthma (n=32)		
	Admission	1 th month	2 nd month	Admission	1 th month	2 nd month	Admission	1 th month	2 nd month
Nose symptoms	15 (12-18)	9 (5-14)	5 (2-10)	15 (13-19)	8 (5-13)	7 (3-12)	15 (11.2-17.7)	10.5 (4.2-14.7)	4 (2-9)
Eye symptoms	9 (5-15)	3 (1-11)	1 (0-5)	9 (5-16)	2 (0-9)	1 (0-5)	9 (4.25-14.75)	3.5 (1.-12.)	1 (0-4)
Practical problems	16 (12-20)	9 (5-16)	5 (2-10)	17 (13-21)	11 (5-17)	6 (3-12)	15.5 (11-18)	9 (4.2-16)	3.5 (1-6.7)
Other symptoms	16 (11-22)	9 (3-15)	5 (1-10)	20 (12-24)	10 (3-21)	6 (1-13)	15 (9-19)	8.5 (3-14.7)	3 (0-9.5)
Activity limitation	10 (6-17)	5 (1-10)	2 (0-5)	14 (6-18)	6 (2-10)	3 (1-7)	10 (6-15)	4.5 (1-10.5)	2 (0-3)

Data are shown as median (interquartile range). AR=Allergic rhinitis

Table 5. Comparison of quality-of-life scores in allergic rhinitis patients with and without asthma

QoL domains	Admission			1 st month			2 nd month		
	Patients with AR and Asthma	AR Patients without asthma	P value	Patients with AR and Asthma	AR Patients without asthma	P value	Patients with AR and Asthma	AR Patients without asthma	P value
Nose symptoms	15 (13-19)	15 (11.2-17.7)	0.313	8 (5-13)	10.5 (4.2-14.7)	0.993	7 (3-12)	4 (2-9)	0.148
Eye symptoms	9 (5-16)	9 (4.25-14.75)	0.669	2 (0-9)	3.5 (1.-12.)	0.218	1 (0-5)	1 (0-4)	0.738
Practical problems	17 (13-21)	15.5 (11-18)	0.084	11 (5-17)	9(4.2-16)	0.732	6 (3-12)	3.5 (1-6.7)	0.087
Other symptoms	20 (12-24)	15 (9-19)	0.019	10 (3-21)	8.5 (3-14.7)	0.388	6 (1-13)	3 (0-9.5)	0.112
Activity limitation	14 (6-18)	10 (6-15)	0.166	6 (2-10)	4.5 (1-10.5)	0.406	3 (1-7)	2 (0-3)	0.080

Data are shown as median (interquartile range). AR=Allergic rhinitis

TNSS, TOSS, and VAS scores, with the largest reductions noted in patients with the most severely affected QoL at admission.

Improvement in QoL scores was observed in both the AR+asthma and AR-only groups (Table 4). Comparison of QoL scores of these groups did not show statistically significant differences in all domains but other symptoms (Table 5).

Furthermore, ACT and C-ACT scores positively correlated with QoL in AR+asthma patients, whereas CARATkids scores were showed a negative correlation (Fig. 2).

DISCUSSION

The treatment of SAR leads to significant improvements in nasal, ocular, and VAS scores. Several studies have reported a significant reduction in nasal and ocular symptom scores, as well as VAS scores following SAR therapy in children [12-14]. Consistent with these findings, our study demonstrated substantial improvements in nasal and ocular symptoms as well as VAS scores during the first two months of treatment.

Our results revealed significant improvements in TNSS, TOSS, and VAS scores throughout the treatment period, with a positive correlation with QoL scores. These findings indicate that the intervention effectively reduced symptom severity and improved QoL in patients with SAR. By the second month of treatment, patients experienced noticeable relief, particularly in nasal and ocular symptoms, which contributed to better daily functioning. Similar to our results, Devillier *et al.* reported that SAR treatment led to significant improvements in QoL in children, particularly alleviating nasal and ocular symptoms, which had a direct positive impact on daily activities and emotional well-being [12]. Wilson *et al.* [13] also reported that patients with SAR experienced an improved QoL after receiving intranasal corticosteroids.

When comparing SAR patients with and without asthma, there was no significant difference in nasal and ocular symptom scores, VAS, or QoL suggesting that appropriate treatment effectively managed symptoms and improved QoL, regardless of asthma status. It is well-established that patients diagnosed with both rhinitis and asthma often suffer from a more severe disease, which is more difficult and costly to manage

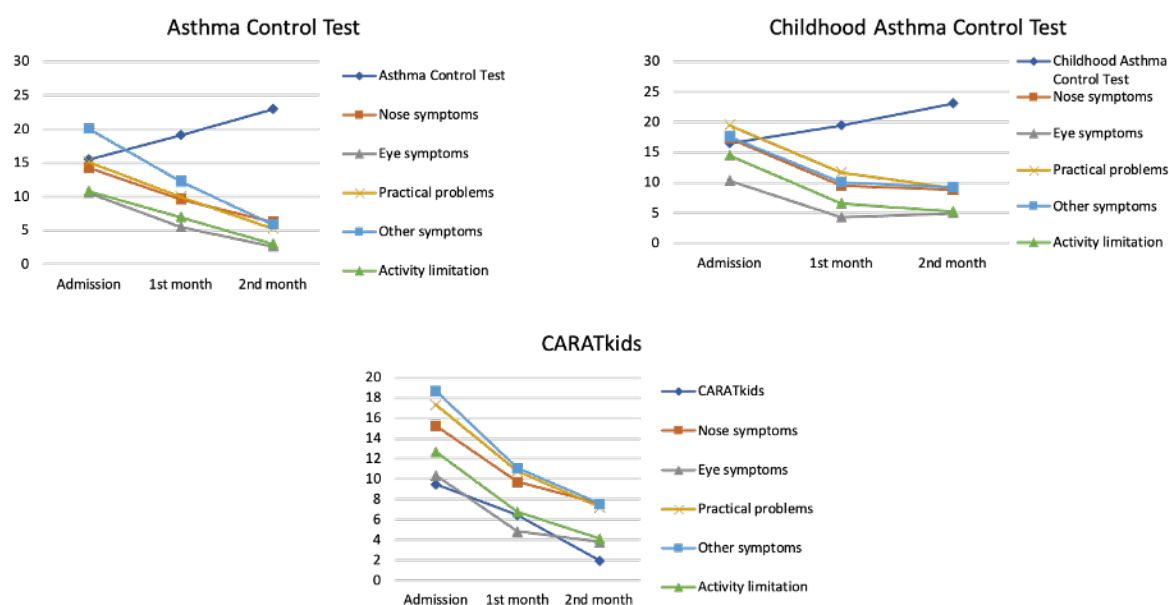


Fig. 2. Results of the test assessing the correlation of ACT, C-ACT, and CARATkids scores with quality of life over time (admission, 1st month, and 2nd month).).

than having only one of these conditions [14]. In contrast to our findings, Ginis *et al.* reported lower nasal symptom scores in SAR patients with asthma [15]. Price *et al.* [16] also concluded that SAR patients without comorbid asthma displayed greater improvements in VAS score and QoL scores after treatment compared to those with asthma. However, both groups showed significant improvements following treatment in our study. A possible explanation for this discrepancy could be the higher adherence to asthma medications during the COVID-19 pandemic, leading to better asthma control. Additionally, the relative sample size and better asthma control observed in our study may also account for the differences compared to other studies.

This study showed marked improvements in ACT, C-ACT, and CARATkids scores in the AR+asthma group, with a positive correlation with QoL scores across multiple domains, including nasal and ocular symptoms, practical challenges, and activity limitations. These findings underscore the effectiveness of combined AR and asthma treatment, demonstrating its ability not only to control asthma symptoms but also to enhance overall QoL in pediatric patients.

The strengths of this study include its comprehensive approach to evaluating both SAR and asthma control in a pediatric population. By utilizing validated instruments such as the CARATkids and C-ACT tests,

this study robustly assessed the impact of comorbid conditions on both disease control and QoL. However, several limitations must be acknowledged. The relatively small sample size may limit the generalizability of the findings, and the lack of a control group introduces potential biases in interpreting the results.

CONCLUSION

In summary, we conclude that treatment of SAR in children resulted in significant improvements in SAR and asthma symptom control, as well as QoL. Future studies with larger sample sizes and control groups are necessary to strengthen the evidence and evaluate long-term outcomes. Physicians should take into account the impact of AR on QoL, and implement safe and effective treatments to reduce the burden of the disease and to improve patient outcomes.

Ethics Committee Approval

The study was approved by the Clinical Research Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital (Date of Approval: 14.08.2004; Protocol No: 129).

Authors' Contribution

Study Conception: SÖ, ESA; Study Design: SÖ,

AEG, ESA; Supervision: SÖ ; Funding: ESA, HYB; Materials: HYB, AEG; Data Collection and/or Processing: HYB, EUS, ESA, AEG, AE; Statistical Analysis and/or Data Interpretation: ESA, SÖ; Literature Review: ESA, SÖ; Manuscript Preparation: ESA, SÖ and Critical Review: SÖ, EUS, AE, ESA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Analysis of incidental prostate acinar adenocarcinoma: a single-center retrospective study

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ABSTRACT

Objectives: Our study was conducted in a single center to evaluate the characteristics of prostate acinar adenocarcinoma.

Methods: A retrospective archive search was conducted between January 1, 2018 and September 1, 2024, and 900 prostate transurethral resection (TUR) and 127 open prostatectomy materials were examined. A total of 43 TUR and 9 open prostatectomy materials were found to have prostatic acinar adenocarcinoma.

Results: The ages of the patients were between 51-90. Gleason scores ranged from 3+3:6 to 5+5:10. In immunohistochemical analyses, Alpha methylacyl CoA racemase (AMACR) positivity and p63 negativity were prominent as characteristic findings. Lymphovascular invasion was rarely observed, while perineural invasion was detected more frequently.

Conclusions: The importance of histopathological and immunohistochemical features in determining the diagnostic and prognostic factors of prostate acinar adenocarcinoma was investigated in our study. This study may contribute to the literature on prostate cancer diagnostic and treatment strategies and may provide contributions for future research.

Keywords: Prostate acinar adenocarcinoma, Gleason score, Prostate specific antigen, immunohistochemistry

Prostate cancer, the most common cancer type in men worldwide, increases in frequency with age and is therefore a very serious public health problem [1]. Incidentally detected prostate cancer (IPC) is an important clinical problem encountered in patients undergoing transurethral resection of the prostate (TUR-P) due to benign prostatic hyperplasia (BPH). Recent studies have shown that IPC rates are approximately 10.1%, with clinically significant cases accounting for 20.2% [2]. Careful pathological examination remains crucial for accurate diagnosis as missed cases can lead to delayed treatment and poten-

tially worse outcomes [2, 5]

The detection rate has increased thanks to advanced diagnostic techniques and pathological examinations [3]. The observation of prostate cancer in 28.5% of patients with PSA below 4 ng/mL in our study emphasizes the importance of comprehensive screening approaches, as recent evidence suggests significant cancer detection rates even at low PSA values [4, 29]. Prostate Specific Antigen (PSA) testing is an important part of the diagnostic process in men at risk of prostate cancer [10]. Recent comprehensive reviews have demonstrated that careful pathological examina-

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tion remains crucial for accurate diagnosis [4]. The incidence of prostate cancer is high worldwide and is especially evident in developing countries [1].

Prostate acinar adenocarcinoma originates from the glandular structures of the prostate and is malignant. It constitutes approximately 95% of prostate cancers and its histopathological molecular features have important effects on diagnosis and prognosis [7]. According to the 2022 WHO Classification, proper pathological evaluation and classification are essential for treatment planning [9]. Current guidelines from major organizations provide comprehensive recommendations for disease management. The European Association of Urology guidelines recommend active surveillance and focal therapy options in certain cases [6], while the Advanced Prostate Cancer Consensus Conference has established standards for managing more advanced disease [8].

The use of multiparametric magnetic resonance imaging (mpMRI) along with PSA testing, rectal examination and histopathological examination methods has significantly increased diagnostic accuracy [14]. Standardized reporting systems, including detailed pathological parameters as described by Grignon [5], have improved communication between clinicians. Moreover, MRI-targeted biopsy has demonstrated superior accuracy over traditional methods, marking a significant step in prostate cancer diagnostics [11]. Many studies have shown that MRI-targeted biopsy has higher sensitivity and specificity than standard systematic biopsy for the detection of clinically significant prostate cancer [11, 14].

The Gleason scoring system remains the gold standard for histopathological evaluation. This system, further refined by the International Society of Urological Pathology (ISUP) consensus studies, has become integral in predicting clinical outcomes and tailoring patient-specific treatment plans [12, 13]. ISUP consensus studies have contributed to the development of the Grade Group system by improving the grading criteria, and this updated classification provides more accurate prognostic stratification and is more helpful in clinical decision making [12, 13].

Our study aims to provide a comprehensive analysis that bridges histopathological findings with prognostic implications, ultimately contributing to the advancement of personalized treatment approaches in prostate cancer management.

The aim of our study is to retrospectively examine the prostate acinar adenocarcinoma cases diagnosed by histopathological examination of tissue samples taken by TUR and open surgery and brought to our laboratory, to evaluate them in the light of current literature information and to help improve the medical processes of prostate acinar adenocarcinoma. Our study aims to provide a comprehensive analysis that bridges histopathological findings with prognostic implications, ultimately contributing to the advancement of personalized treatment approaches in prostate cancer management.

METHODS

Study Design and Ethical Approval

Our study was designed as a retrospective analysis and was approved by the Ethics Committee of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital (Approval No: 2024/301) and was conducted according to the principles of the Declaration of Helsinki. Data confidentiality was protected according to international research guidelines.

Patient Selection and Data Collection

Study Population

Patient selection followed the current European Association of Urology guidelines [6]. Active surveillance protocols were implemented based on established criteria for low-risk prostate cancer patients, as described in current literature [16]. Patients who underwent TUR or open prostatectomy in our hospital between January 1, 2018 and September 1, 2024 and were histopathologically diagnosed with prostate acinar adenocarcinoma were examined in our study.

Exclusion Criteria

Patients with insufficient clinical data were not included in the study.

Data Collection Process

Patients' demographic information, clinical characteristics, laboratory findings, and pathology reports were obtained from hospital medical records. Data quality was ensured by double-checking, following validated multiparametric data collection protocols [15].

Histopathological Evaluation

Tissue Processing and Staining

Histopathological specimens were processed following standardized protocols [5]. Tissue samples were fixed in 10% neutral buffered formalin for 24 hours, embedded in paraffin, sectioned at 4 μ m thickness, and stained with hematoxylin and eosin (H&E). All diagnoses were made according to the 2022 WHO Classification [9].

Microscopic Evaluation

Histopathological diagnosis and grading procedures were performed according to the World Health Organization classification [9]. The evaluation process followed established guidelines for prostate cancer pathology [5].

Gleason Scoring and Grade Group Determination

Gleason scoring and grade group determination were performed according to the current recommendations of the ISUP [12, 13]. This standardized approach ensures consistent reporting across all cases.

Tumor Percentage and Other Pathological Features

Tumor percentage was calculated and recorded for all samples individually. Pathological features such as perineural invasion and lymphovascular invasion were analyzed following current protocols [5].

Immunohistochemical Analysis

Immunohistochemical staining was performed using Ventana BenchMark ULTRA (Roche Diagnostics). AMACR, p63, and HMWCK expressions were evaluated following standardized pathological protocols [17]. Results were assessed using current semi-quantitative scoring systems that included staining intensity and percentage of positive cells.

Statistical Analysis

R statistical software (version 4.2.0, R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis. Descriptive statistics were presented as mean $\pm$ standard deviation for continuous variables and frequencies (percentages) for categorical variables. Correlations between continuous variables were assessed using Pearson's correlation coefficient. Chi-square test was used for categorical variables. $P < 0.05$ was considered statistically significant in all tests.

RESULTS

Demographic and Clinical Features

A total of 1027 patients were included in the study. The mean age was found to be 65.7 ± 8.3 years (45-89 years). In the age distribution, 18.2% of the patients were under 55 years of age, 52.6% were between 55-70 years of age, and 29.2% were over 70 years of age. The mean PSA value of the patients was found to be 12.4 ± 15.7 ng/mL (0.3-189 ng/mL). We categorized the values according to the current EAU guidelines. In this context, 28.5% of the patients were found to have PSA values < 4 ng/mL, 4-10 ng/mL (41.3%), 10-20 ng/mL (18.7%), and > 20 ng/mL (11.5%).

Histopathological Findings

Biopsy and Prostatectomy Specimens

Of the 1027 patients in our study, 900 (87.6%) underwent TUR and 127 (12.4%) underwent open prostatectomy. Prostatic acinar adenocarcinoma was detected in 43 (4.8%) of the TUR specimens and 9 (7.1%) of the open prostatectomy specimens.

Gleason Scores and Grade Groups

Gleason scores: The most common score was found to be $3+3=6$ (35.2%). This was followed by $3+4=7$ (28.7%), $4+3=7$ (18.1%), $4+4=8$ (9.6%), $4+5=9$ (5.8%) and $5+5=10$ (2.6%), respectively (Fig. 1).

Grade Group distribution: Grade Group 1 (35.2%), Grade Group 2 (28.7%), Grade Group 3 (18.1%), Grade Group 4 (9.6%) and Grade Group 5 (8.4%) were determined (see Fig. 1).

Tumor Percentage and Other Pathological Features

The mean tumor percentage was measured as $18.3 \pm 22.5\%$ (1-95%). A positive correlation was observed between tumor percentage and Gleason score ($r=0.62$, $P < 0.001$). Perineural invasion was detected in 42.7% of patients, while lymphovascular invasion was detected in 15.3%.

Immunohistochemical Findings

The immunohistochemical markers used in our study were AMACR, p63 and HMWCK, which are widely used in the diagnosis of prostate cancer. AMACR positivity was detected in 94.2% of patients in immunohistochemical analyses. p63 and HMWCK

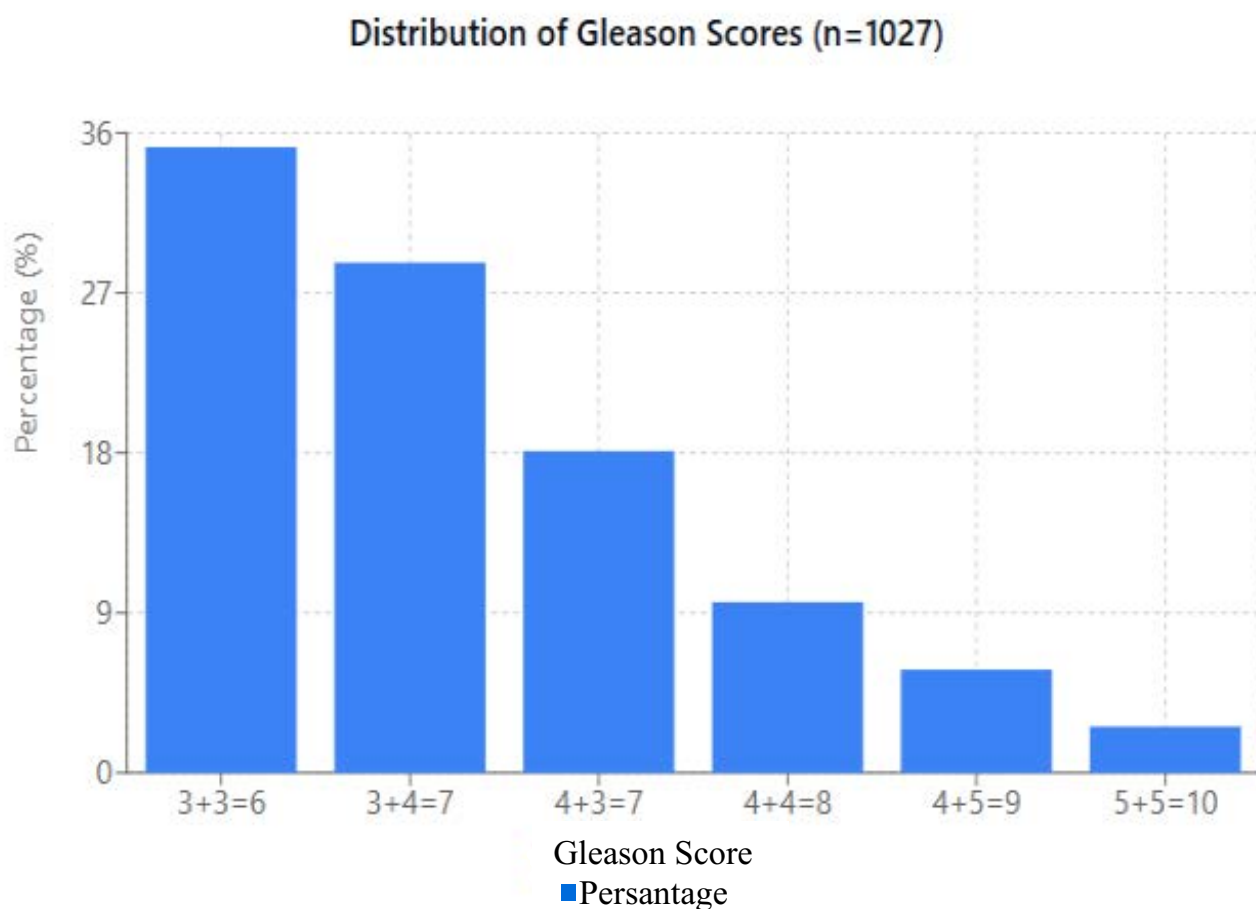


Fig. 1. Distribution of Gleason scores among study population (n=1027). The graph shows that Gleason score 3+3=6 was the most common (35.2%), followed by 3+4=7 (28.7%).

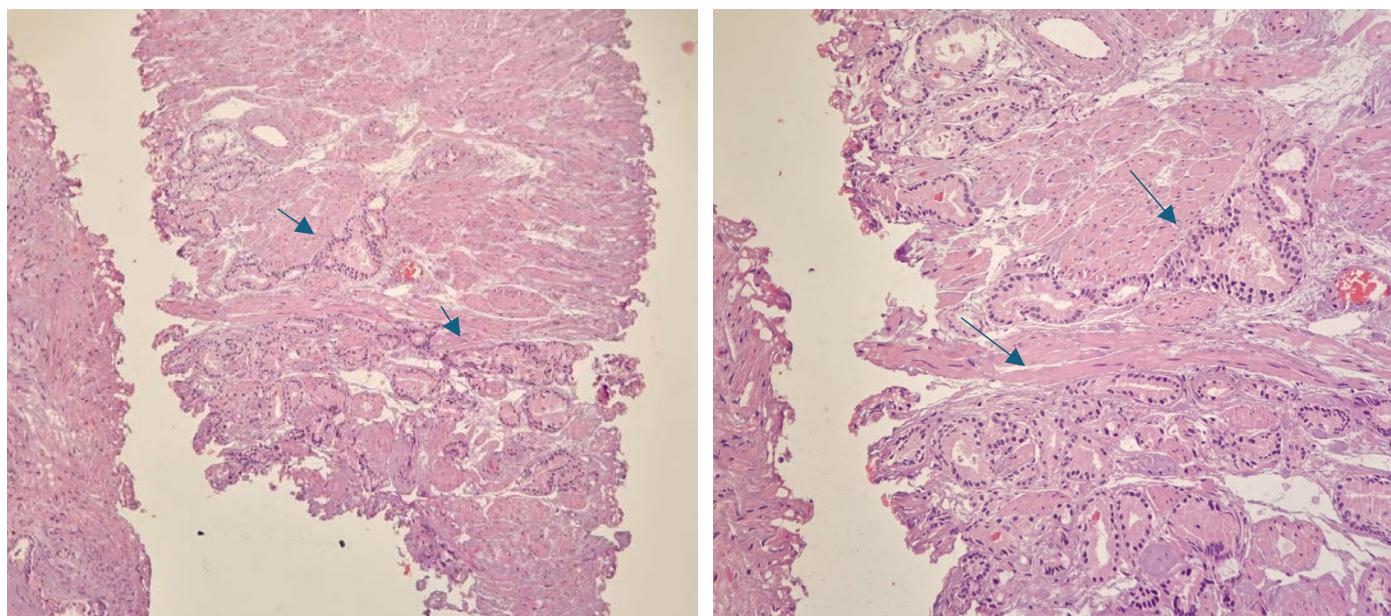


Fig. 2. Left: Acinar structures showing infiltrative growth pattern in prostate tissue are seen in TUR material H&E, ×100. Right: Small-medium sized, atypical glandular structures with uniform nuclear features are observed at higher magnification H&E, ×200.

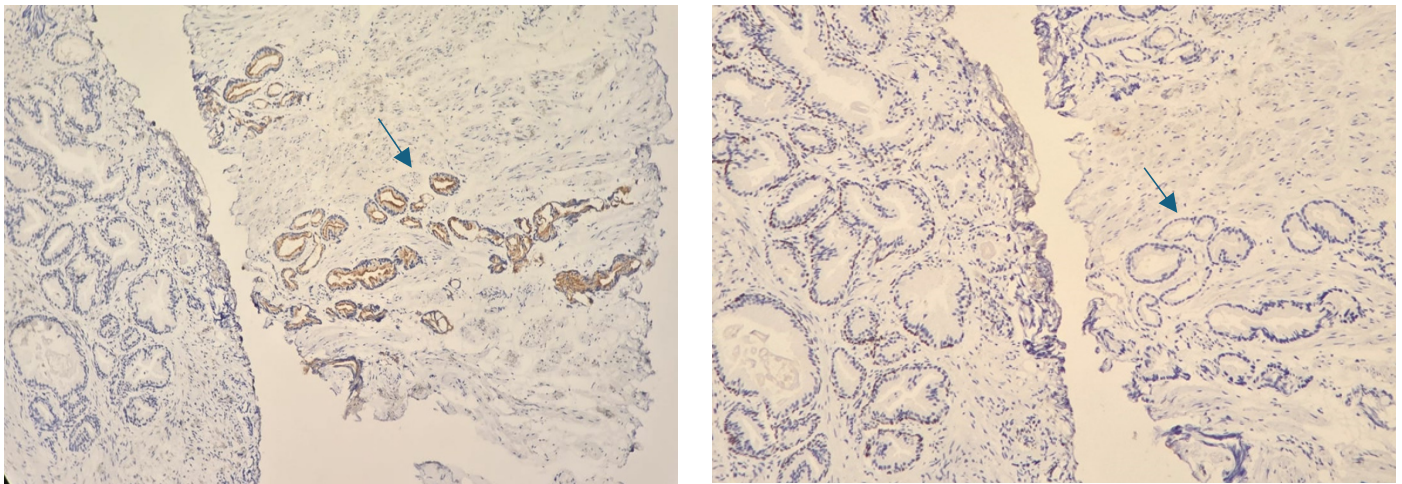


Fig. 3. Left: Brown staining is present in acinar adenocarcinoma foci with AMACR, while no staining is seen in adjacent normal glands (Immunohistochemistry, $\times 100$). Right: While no staining is seen in tumoral glands with P63, brown staining is observed in the basal layer of normal glands (Immunohistochemistry, $\times 200$). %).

negativity were observed in 97.8% and 96.5%, respectively (Figs. 2 and 3)

Clinicopathological Correlations

A significant positive correlation was found between PSA values and Gleason score ($r=0.54$,

$P<0.001$). In addition, the probability of high-grade (Grade Group 4-5) tumors was measured as 3.2 times higher in patients with PSA values >20 ng/mL compared to those with PSA values <10 ng/mL (95% CI: 2.1-4.8, $P<0.001$) (Fig. 4)



Fig. 4. Correlation between PSA levels and Grade Groups. The graph demonstrates a strong positive correlation between Grade Groups and mean PSA levels ($r=0.54$, $P<0.001$). Mean PSA values increased progressively from Grade Group 1 (4.2 ng/mL) to Grade Group 5 (19.2 ng/mL), indicating higher PSA levels are associated with higher Grade Groups.

DISCUSSION

Our study has extensively analyzed the characteristics of prostate acinar adenocarcinoma and evaluated them in the light of current literature. Long-term follow-up results show that the disease is stable in most patients under active surveillance [16, 24]. Our findings support and expand our current knowledge on the diagnosis, prognosis, and treatment approaches of prostate cancer [7].

Demographic and Clinical Features

Our study's age distribution findings (mean age 65.7±8.3 years) align with global cancer statistics [1]. Recent epidemiological studies have shown increasing incidence in developing countries [25, 26]. Our study is consistent with the threshold values recommended by current guidelines in terms of PSA values [6, 27]. The observation of prostate cancer in 28.5% of patients with PSA below 4 ng/mL in our study emphasizes the importance of comprehensive screening approaches, as recent evidence suggests significant cancer detection rates even at low PSA values [4, 29]. Current clinical practice guidelines emphasize this multidisciplinary approach to diagnosis and treatment [10, 23].

Histopathological Findings

Our Gleason scores and grade group distribution follow the current WHO Classification guidelines [9,20]. Recent updates in the WHO Classification system have refined our understanding of prostate cancer pathology [19]. Particularly, Grade Groups 1 and 2 (Gleason score ≤7) being the most common groups align with established reporting standards [5, 13]. The positive correlation we found between tumor percentage and Gleason score demonstrates the importance of tumor burden in prognosis [26,34]. Our perineural invasion and lymphovascular invasion results are consistent with recent pathological assessment guidelines [17, 35].

Advanced Diagnostic Approaches

Recent advances in prostate cancer diagnosis have introduced more precise methods [3, 11]. The use of multiparametric MRI has shown superior accuracy in detecting clinically significant prostate cancer [21, 22]. The integration of MRI-targeted biopsy has

demonstrated improved detection rates compared to conventional methods [14, 15]. These findings support the importance of advanced imaging techniques in diagnostic protocols [24].

Immunohistochemical Findings

Our results regarding AMACR, p63 and HMWCK confirm the sensitivity and specificity of these markers in the diagnosis of prostate cancer, as reported in current ISUP guidelines [12]. The high AMACR positivity and p63/HMWCK negativity rates align with established diagnostic criteria [31, 33]. Modern pathological techniques have improved our ability to accurately diagnose and classify prostate cancer [18].

Active Surveillance and Risk Management

Current guidelines support active surveillance for appropriate candidates [28,30]. The European Association of Urology position emphasizes careful patient selection and risk stratification [8, 32]. Recent studies have shown the importance of molecular and genetic factors in risk assessment [7, 19]. Standardized protocols for patient monitoring have been established through international consensus [16].

Main Findings and Clinical Significance

One of the most important results of our study is the validation of the prognostic value of the grade group system [12,13]. Recent advances in artificial intelligence applications in pathological diagnosis show promise for more accurate assessment [18]. The sensitivity and specificity of immunohistochemical markers in our study support current diagnostic protocols [17, 33]. New molecular markers and imaging techniques continue to emerge, potentially improving our diagnostic capabilities [15].

Recommendations for Clinical Applications

Based on our findings and current literature [6, 8], we recommend:

1. Integration of multiparametric MRI and targeted biopsy in diagnostic protocols [21, 22]
2. Standardized reporting following WHO guidelines [9, 20]
3. Risk-adapted follow-up strategies incorporating molecular markers [28, 34]
4. Regular pathological quality assessment and updates to diagnostic criteria [18, 35]

5. Development of precision diagnostic algorithms incorporating both molecular and imaging biomarkers for future research [18, 19]

6. Implementation of artificial intelligence-assisted pathological assessment protocols [18, 35]

7. Investigation of novel immunohistochemical markers for improved risk stratification [17, 33]

Limitations

Since it is a retrospective single-center study, its generalizability is limited. Some small tumors may have been missed in TUR-P samples, which may have underestimated the true prevalence of prostate cancer [2]. Lack of long-term follow-up data prevents us from obtaining clear results about the course of the disease and prognosis [31,32]. The evolving nature of diagnostic criteria and treatment protocols may also affect the interpretation of our results [27].

CONCLUSION

In conclusion, the results obtained in our study regarding prostate acinar adenocarcinoma may benefit the development of prostate cancer diagnostic approaches. While we tried to expand the current knowledge about prostatic acinar adenocarcinoma, which we tried to present in terms of the diagnosis of the disease, we also tried to reveal new questions and potential directions for future research. We believe that future studies examining our findings on a larger number of patient populations may provide significant advances in the diagnostic management of prostate cancer. Our study emphasizes the clinical importance of IPC and reveals the necessity of careful histopathological evaluation of TUR-P and open prostatectomy specimens. In light of our findings, we must state that our study shows that the risk of IPC increases especially in patients over 60 years of age and with PSA levels above 4 ng/mL. In light of the data we obtained, we can say that it would be very useful for future research to focus on long-term clinical outcomes and optimal management strategies in patients. Ultimately, this comprehensive analysis of prostate acinar adenocarcinoma not only enhances our understanding of the disease but also provides valuable insights for improving diagnostic accuracy, optimizing treatment strategies, and establishing more effective clinical protocols, thereby

contributing significantly to both the scientific literature and daily clinical practice in urological pathology.

Ethical statement

This research was approved by the Ethics Committee of Sancaktepe Prof. Dr. İlhan Varank Training and Research Hospital (Approval No: 2024/301) and was conducted and concluded in accordance with the ethical standards of the Declaration of Helsinki.

Authors' Contribution

Study Conception: BE, MY, MG, ÇDA, OS; Study Design: BE, MY, MG; Supervision: BE, MY, MG, ÇDA, OS; Funding: BE, ÇDA, OS; Materials: BE, MY, ÇDA, OS; Data Collection and/or Processing: BE, MY, MG, ÇDA, OS; Statistical Analysis and/or Data Interpretation: BE, MY, MG, ÇDA, OS; Literature Review: BE, MY, MG, ÇDA, OS; Manuscript Preparation: BE and Critical Review: BE, MY, MG, ÇDA, OS.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Exploring pediatric surgery dissertations: Focus areas and future directions

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ABSTRACT

Objectives: The aim of this study was to evaluate pediatric surgery dissertations included in the Higher Education Council dissertation database.

Methods: A search was conducted in Turkey's Higher Education Council dissertation database using the keyword "pediatric surgery" to identify all dissertations published in the database between 2019 and 2023. The evaluation focused on dissertation topics.

Results: A total of 120 dissertations were analyzed. The most common topics were related to the gastrointestinal system (n=37) and urology (n=30). Clinical studies showed an increasing trend over the years, rising from 53% in 2019 to 80% in 2022, before slightly decreasing to 72% in 2023. Experimental studies accounted for 47% of the studies in 2019 but declined to 20% in 2022, with a slight recovery to 28% in 2023 (P=0.242). Clinical studies dominated in most sections, particularly in traumatology (100%), thoracic surgery (86%), and general pediatric surgery (80%). Experimental studies had higher proportions in gynecology (60%) and urology (43%) (P=0.090). The most common topics were related to appendicitis (n=9), esophageal atresia (n=8), anorectal malformations (n=7), hypospadias (n=7), and testicular conditions (n=7). Dissertation top five topics accounted for 32% of all topics.

Conclusions: Pediatric surgery dissertations mainly centered on clinical studies, with a notable focus on gastrointestinal and urological topics. Appendicitis, esophageal atresia, and anorectal malformations were the most studied areas. Regenerative medicine was significantly underrepresented. Encouraging studies in regenerative medicine and multidisciplinary approaches could drive innovation and address gaps in pediatric surgery research.

Keywords: Pediatric surgery, Medical Specialization Board, thesis, dissertations

In Turkey, the Medical Specialization Board (TUK) is an official body responsible for setting and supervising the standards of medical specialization training [1]. Operating under the Ministry of Health, the board develops training curricula for specialization fields, evaluates the adequacy of training

institutions, and oversees the organization of specialization exams. TUK coordinates the Medical Specialization Examination (TUS) process, which places medical school graduates into specialization programs. Additionally, it conducts activities to accredit training programs, address the rights and responsibilities of

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specialization students, and improve the quality of training processes [2]. This TUK system aims to enhance the quality of medical education in Turkey and to train specialists in line with international standards.

In our country, approximately 30 pediatric surgery positions are offered during each term of the medical specialty examination, and an average of 20-30 pediatric surgeons receive their specialty certification each year [1-3]. The duration of training in each specialty varies, typically ranging from 3 to 5 years. The duration of pediatric surgery specialty training, however, is 5 years. According to the TUK regulation, every doctor specializing in medicine must write a dissertation at the end of the specialization period [1-3].

Not only in Turkey but also worldwide, and not only in pediatric surgery but across all medical specialties, every residency or specialty trainee must prepare a dissertation at the end of their training. Each trainee preparing this dissertation must have at least

one supervising advisor. This dissertation topic can be a clinical or experimental study.

The aim of this study was to evaluate pediatric surgery dissertations included in the Higher Education Council dissertation database.

METHODS

For this study, a search was conducted in Turkey's Higher Education Council dissertation database using the keyword "pediatric surgery" to identify all dissertations published in the database between 2019 and 2023 (5 years) [4]. The evaluation focused on the location and institution where the dissertation was conducted, the author, the title, whether the study was experimental or clinical, the subspecialty it involved, the organ it addressed, the topic of the study, and the methodology used. A flow chart is given in Fig. 1.

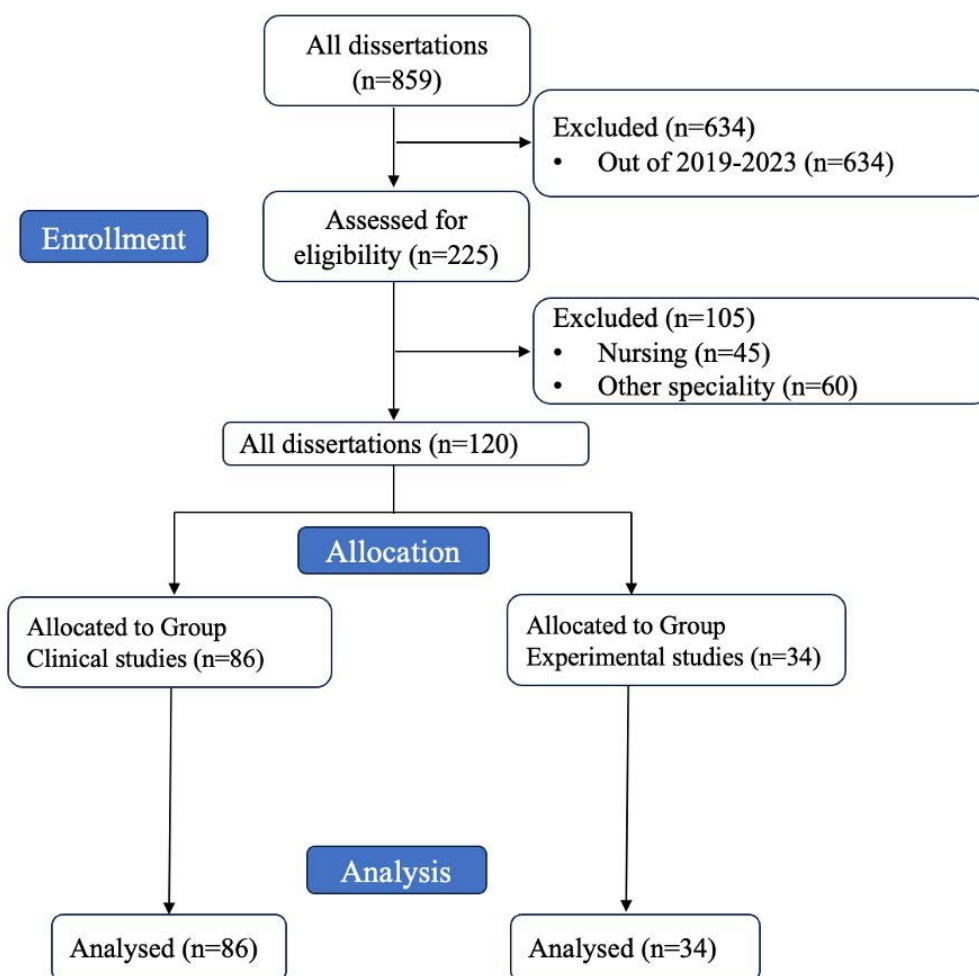


Fig. 1. Selection of dissertations.

Inclusion criteria

The dissertation must have been conducted by a pediatric surgery specialist and completed and polished in database between 2019 and 2023.

Exclusion criteria

Dissertations in the field of pediatric surgery nursing, those conducted by researchers specializing in disciplines other than pediatric surgery (even if related to pediatric surgery), and dissertations outside the specified years were excluded from the study.

This study was based on data obtained from the dissertations database and does not involve any human or animal subjects. Throughout the process, adherence to the Personal Data Protection Law was ensured.

Statistical Analysis

The data obtained from the database were coded into an Excel file. Statistical analyses were performed using Jamovi software. The data were expressed as frequencies and percentages. The chi-square test was used to compare categorical variables, with a significance level set at $P<0.05$. Relationships between the data were illustrated and analyzed using a Sankey diagram. A scatter plot was designed to address the cumulative percentage.

RESULTS

In this study, a total of 120 dissertations were analyzed between 2019 and 2023. The most common topics were related to the gastrointestinal system and urology (Table 1).

The distribution of dissertations by year revealed 17 cases in 2019, 19 cases in 2020, 29 cases in 2021, 30 cases in 2022, and 25 cases in 2023. The data demonstrated a consistent increase in the number of cases from 2019 to 2022, followed by a decline in 2023 (Fig. 2). The average number of dissertations per year was 24.

The analysis of studies by section revealed that the gastrointestinal system was the most researched area, with a total of 37 studies, accounting for the highest proportion of the dataset. Urology followed with 30 studies, demonstrating its significance as another major focus of research. Thoracic surgery and traumatology contributed to 14 and 12 studies, respectively,

Table 1. Total dissertations number

	Gastrointestinal	General pediatric surgery	Gynecology	Hepatobiliary	Oncology	Thoracic	Traumatology	Urology	Total
2019	5	0	2	0	2	2	1	5	17
2020	8	1	0	1	0	3	1	5	19
2021	8	4	1	2	0	3	5	6	29
2022	10	2	1	2	1	3	5	6	30
2023	6	3	1	3	1	3	0	8	25
Total	37	10	5	8	4	14	12	30	120

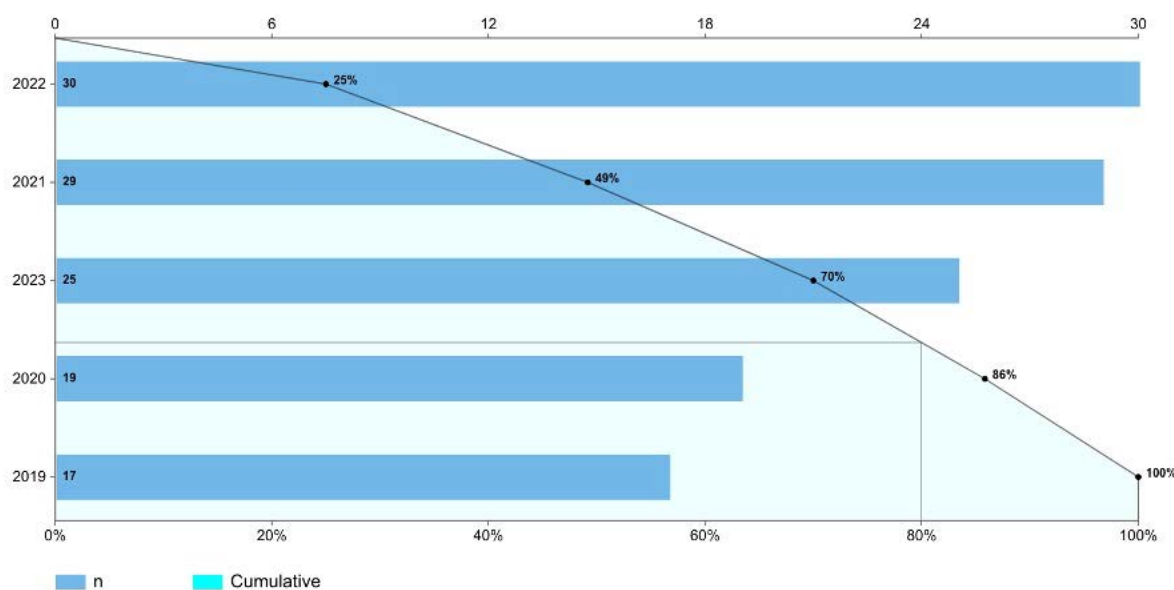


Fig. 2. Pareto chart for dissertations distribution by years.

highlighting their clinical and experimental relevance. General pediatric surgery and hepatobiliary studies had relatively fewer contributions, with 9 and 8 studies, respectively. Gynecology and oncology were less represented, with 5 and 4 studies, while the "Other" category included only a single study (Fig. 3).

Clinical studies showed an increasing trend over the years, rising from 53% in 2019 to 80% in 2022, before slightly decreasing to 72% in 2023. Experimental studies accounted for 47% of the studies in 2019 but declined to 20% in 2022, with a slight recovery to 28% in 2023. There was no statistically significant dif-

ference in the distribution of clinical and experimental studies across the years ($P=0.242$). The study types were also analyzed based on their focus area. Clinical studies dominated in most sections, particularly in traumatology (100%), thoracic surgery (86%), and general pediatric surgery (80%). Experimental studies had higher proportions in gynecology (60%) and urology (43%). However, the distribution of clinical and experimental studies across different sections was not statistically significant ($P=0.090$) (Table 2).

The relation between years, study types, and topics was presented as a Sankey diagram (Fig. 4).

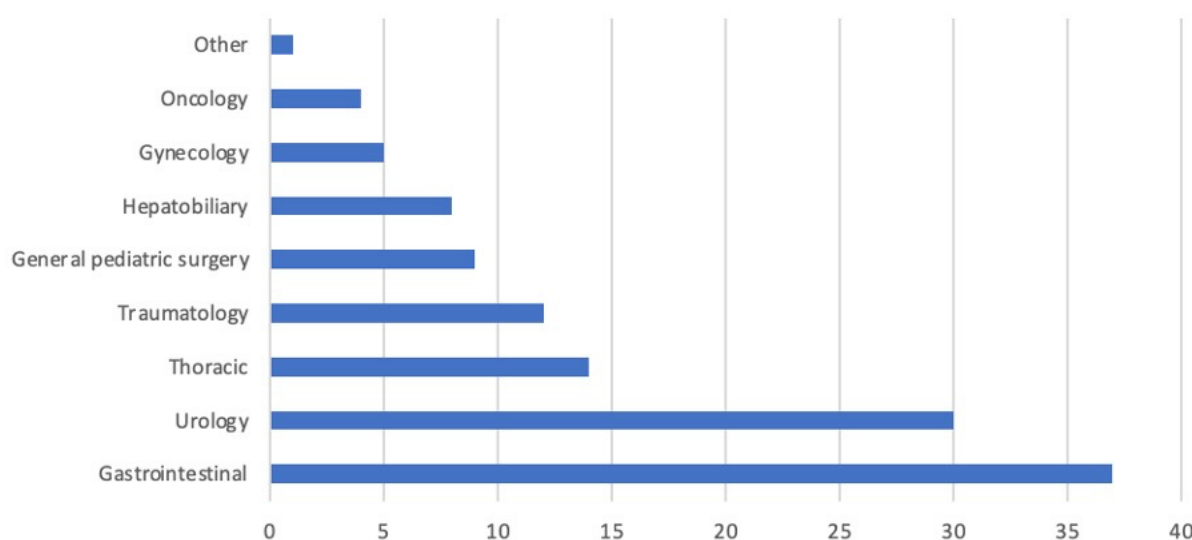


Fig. 3. Analysis of studies by section.

Table 2. Comparison of study type by years

	Clinical studies (n=86)	Experimental studies (n=34)	P value
Years, n (%)			0.242
2019	9 (53%)	8 (47%)	
2020	12 (63%)	7 (37%)	
2021	23 (79%)	6 (21%)	
2022	24 (80%)	6 (20%)	
2023	18 (72%)	7 (28%)	
Section / subspecialty, n (%)			0.090
Gastrointestinal system	26 (70%)	11 (30%)	
General pediatric surgery	8 (80%)	2 (20%)	
Gynecology	2 (40%)	3 (60%)	
Hepatobiliary	6 (75%)	2 (25%)	
Oncology	3 (75%)	1 (25%)	
Thoracic surgery	12 (86%)	2 (14%)	
Traumatology	12 (100%)	0 (0%)	
Urology	17 (57%)	13 (43%)	

Other: Topics related COVID-19

Among the dissertations, the most common topics were related to appendicitis (n=9), esophageal atresia (n=8), anorectal malformations (n=7), hypospadias (n=7), and testicular conditions (n=7). Dissertation's top five topics accounted for 32% of all topics. The

number of studies on other topics is provided in Table 3. In recent years, studies related to regenerative medicine have become particularly prominent in fields such as orthopedics, general surgery, and anesthesiology. However, in the field of Pediatric Surgery, among

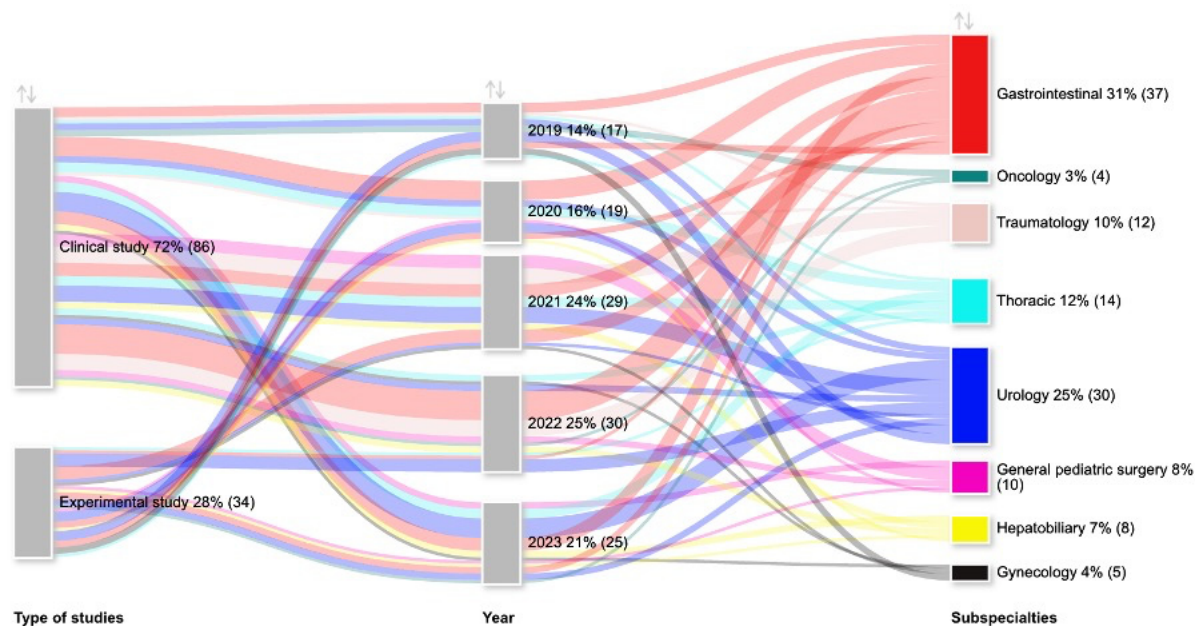


Fig. 4. Sankey diagram.

Table 3. Main topics

Topics	n
Appendicitis	9
Esophageal atresia/stricture	8
Anorectal malformations	7
Hypospadias/disorders of sex development	7
Testis	7
Hirschsprung disease	6
Abdominal/thoracic/urogenital traumas	5
Corrosive ingestion/esophagitis	5
Intussusception/volvulus	5
Lower urinary dysfunction/neuropathic bladder/urotherapy/bladder	5
Ovarian pathologies	5
Bowel ischemia/reperfusion /short bowel syndrome/bowel adhesion	4
Hydronephrosis/ureteropelvic and ureterovesical junction obstruction	4
Vesicoureteral reflux	4
Burns	3
Cholelithiasis/cholecystectomy	3
Circumcision/penile diseases	3
Necrotizing enterocolitis	3
Foreign body ingestion	2
Hypertrophic infantile pyloric stenosis	2
Inguinal hernia	2
Liver related fibrosis / damage	2
Pectus excavatum / carinatum	2
Sacroccygeal teratoma	2
Breast disorders	1
Congenital diaphragmatic hernia	1
Coronavirus disease	1
Enhanced recovery after surgery	1
Hepaticojejunostomy	1
Hepatoblastoma	1
Hydatid cyst	1
Intestinal atresia	1
Neuroblastoma	1
Portal hypertension	1
Pneumothorax	1
Thyroid disorders	1
Tracheostomy	1
Vascular access	1
Wound infections	1

the dissertations we reviewed, only two dissertations (2/120) in the last five years were related to regenerative medicine. One of these was published in 2023 (on stem cells), and the other in 2019 (on platelet-rich plasma) (Table 4). Both of dissertation studies were experimental. In the field of pediatric surgery, no dissertations have been conducted on regenerative medicine clinical studies.

DISCUSSION

This study analyzed pediatric surgery dissertations published between 2019 and 2023, highlighting trends in study types, topics, and subspecialties. Clinical studies were predominant, showing a consistent rise before a slight decline in the final year, while experimental studies followed an opposite trend. The gastrointestinal system emerged as the most researched area, followed by urology and thoracic surgery. Appendicitis, esophageal atresia, anorectal malformations, hypospadias, and testicular conditions were the most common topics, comprising nearly one-third of all dissertations. Regenerative medicine remained underrepresented, with only two experimental studies identified.

Güler [3] examined 238 pediatric surgery dissertations (2010-2021) to evaluate their contribution to the literature. Of these, 63 (26.5%) were published as articles, with experimental studies more likely accepted in Science Citations Index Expanded (SCI-E) journals. While clinical studies dominated, the publication rate declined in recent years. Dissertation topics remained static, reflecting limited adaptation to medical advancements. Aydın *et al.* [5] analyzed 49 pediatric surgery dissertations (1978-2010) from Cerrahpaşa Medical Faculty. Most focused on gastrointestinal (31) and urologic (16) topics, with experimental and clinical studies nearly balanced. Only 14 dissertations were presented nationally, and 14 were published (4 national, 10 international). Recommendations include earlier topic selection, financial support, and fostering multidisciplinary collaboration to improve dissertation quality and scientific impact. In our study, we were unable to analyze whether these dissertations were published, which can be considered a limitation of our work. Our findings are similar to those of Aydın *et al.* [5] in terms of the high number

Table 4. Topics related regenerative medicine

Title	Year
Do exosomes derived from adipose mesenchymal stem cells prevent ischemia-reperfusion injury after torsion-detorsion in rat testes?	2023
The effect of different bacteria contamination in adhesive intestinal obstruction and the role of 50% dextroz solution and PRP (platelet rich plasma) in preventing the postoperative peritoneal adhesions in rats	2019

of dissertations focused on the gastrointestinal system. Additionally, the number of experimental studies aligns closely with the findings of Güler *et al.* [3].

In Turkey, it is observed that both clinical and experimental studies are conducted in sufficient numbers. However, the data reveal that research in areas such as artificial intelligence and regenerative medicine is very limited. In recent years, there has been a significant increase in regenerative medicine articles published in the international literature [6-10]. Turkey must initiate regenerative medicine research, both experimentally and clinically, as part of residency dissertations. Several studies in this field are essential. Although the number of regenerative medicine articles focusing on pediatric cases is currently low, it is evident that these will see a geometric increase in the future, leading to substantial contributions to the field. The number of experimental and clinical studies related to regenerative medicine in pediatric surgery must be increased. The same applies to the field of tissue engineering. New studies could focus on conditions requiring tissue repair, such as esophageal atresia, hypospadias, bladder exstrophy, diaphragmatic hernia, airway malformations, gastroschisis, and omphalocele [11-16]. Early-career physicians entering their specialty training should consider selecting dissertation topics in these innovative fields. Each study conducted in these areas is likely to be considered "innovative," significantly increasing the probability of publication in prestigious SCI-E journals.

Similarly, as noted by Zani *et al.* [17] and Zani [18], the limited number of cases in pediatric surgery results in a scarcity of publications for many rare conditions. This poses a significant challenge in establishing guidelines for these rare diseases. Consequently, survey studies play a crucial role in addressing these gaps in pediatric surgery. Although some survey studies have been published as articles from Turkey [19-

23], none have been conducted as dissertations in the studied 5 years. Therefore, early-career physicians beginning their specialty training should consider this and select dissertation topics in this area to contribute to the literature.

Future Directions

Future research in pediatric surgery should focus on diversifying topics to include emerging fields such as regenerative medicine, stem cell research, tissue engineering, and artificial intelligence. Collaborative efforts between pediatric surgeons, researchers, and multidisciplinary teams can drive innovation and bridge gaps in underrepresented areas. Expanding clinical studies in regenerative medicine could offer significant advancements in patient outcomes. Additionally, promoting international collaborations and access to funding may help overcome resource limitations. Encouraging structured mentorship programs for dissertation preparation can enhance the quality of research. Establishing national research databases and integrating standardized metrics for evaluation will further support comprehensive and impactful studies in the field. The authors recommend conducting studies on stem cell, regenerative medicine and tissue engineering in the field of pediatric surgery which will be the future of pediatric surgery.

Limitations

This study has several limitations. First, it relied solely on data from the Higher Education Council database of Turkey, which may not include all dissertations in pediatric surgery during the specified period. Second, the analysis was restricted to dissertations published between 2019 and 2023, potentially overlooking trends or shifts in earlier or subsequent years. Third, categorization of topics and methodologies was based on available dissertation titles and abstracts,

which might have introduced subjective bias. Lastly, the study excluded nursing-related dissertations and those conducted by researchers outside pediatric surgery, limiting the scope and generalizability of the findings to broader interdisciplinary research.

CONCLUSION

Between 2019 and 2023, pediatric surgery dissertations mainly centered on clinical studies, with a notable focus on gastrointestinal and urological topics. Appendicitis, esophageal atresia, and anorectal malformations were the most studied areas. Regenerative medicine was significantly underrepresented, emphasizing the need for more diversified research. Encouraging studies in regenerative medicine and multidisciplinary approaches could drive innovation and address gaps in pediatric surgery research.

Ethical Statement

Administrative permission was received from the Esenyurt Necmi Kadioğlu State Hospital Management for this study (Date: 27.01.2025).

Authors' Contribution

Study Conception: MA, TOK; Study Design: MA, TOK; Supervision: MA, TOK; Funding: MA, TOK; Materials: MA, TOK; Data Collection and/or Processing: MA, TOK; Statistical Analysis and/or Data Interpretation: MA, TOK; Literature Review: MA, TOK; Manuscript Preparation: MA, TOK and Critical Review: MA, TOK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Ergonomics in surgery and work-related musculoskeletal disorders

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ABSTRACT

Objectives: Our study aimed to determine surgeons' work-related musculoskeletal disorders, physical workload, location of the disorder, frequency, characteristics, and effects on daily life. Furthermore, we aimed to draw attention to ergonomics education by investigating surgeons' opinions and attitudes regarding ergonomics.

Methods: Data were collected using survey forms from 37 surgeons who met the appropriate criteria. Sociodemographic characteristics, The Physical Workload Questionnaire was used to evaluate physical workload, the Extended Nordic Musculoskeletal System Questionnaire was used to evaluate the characteristics of painful areas, and the Beck Depression Scale was used to evaluate the psychological status of the surgeons.

Results: Thirty-four (91.9%) of the surgeons reported that they experienced musculoskeletal disorders at least once in their careers due to their professional responsibilities. The most common causes of pain were poor posture, incorrect positioning, and standing too much. The neck, upper back, and waist were the most affected areas, and only 1 (2.7%) surgeon had received ergonomics training.

Conclusions: Musculoskeletal disorders caused by ergonomic difficulties are common in the surgical field. It is critical to developing evidence-based ergonomic training recommendations that hospitals and residency training programs should follow to protect surgeons from preventable injuries that have the potential to significantly harm their careers.

Keywords: Ergonomics, ergonomics in surgery, work-related disorders, pain, musculoskeletal disorders

In recent years, the mental load associated with doctors' work and its impact on their health have garnered significant attention and have been the subject of extensive research [1]. In contrast, the physical demands of the job, particularly for surgeons, have not been the subject of extensive research or attention. Various symptoms, including discomfort, damage, or persistent pain in the muscles, tendons, ligaments,

nerves, joints, and bones, caused, or exacerbated by occupational risk factors, are defined as work-related musculoskeletal disorders (WRMD) [2]. In developed countries, it is well known that WRMD contributes significantly to the cost of work-related diseases [3]. It also represents an increasing problem of job instability, decline in activity, switching to another job, and becoming a cause of disability [4]. According to a re-

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cent study, WRMD is responsible for 28% of health workers' missing days without working, and health professionals are exposed to up to three times more risks than the general population, depending on the type of activity carried out, the workload and the position taken during work [5, 6]. Ergonomics involves designing the work environment to suit the worker, rather than forcing the person to adapt to the work setting [7]. Ergonomists view surgeons' environments and working conditions as equal to, or even worse than, some industrial workers [8]. Surveys reveal that 23100% of surgeons in various sub-disciplines suffer from musculoskeletal system diseases (MSD) due to insufficient ergonomic procedures in their work environments [8, 9]. It is a fact that, irrespective of expertise, various types of operations exist. Surgical tasks performed by surgeons necessitate mental acuity, concentration, hand-eye coordination, and precise movement. Additionally, these tasks require maintaining a constant posture for extended periods, often involving prolonged static effort [8, 10-11]. Surgery is a dynamic environment characterized by sudden changes, requiring surgeons to adopt ergonomically limited postural positions to optimize visibility and access to the surgical area. Inadequate ergonomic training and improper ergonomic practices during surgery can result in physical discomfort and suffering, alongside psychological problems, less concentration, and decreased surgical speed and endurance [12, 13]. Moreover, outside of their professional duties, surgeons indicate that work-related musculoskeletal problems (MSD) disrupt sleep, hinder social engagements, and adversely impact quality of life, resulting in premature retirement [14, 15].

This study aims to identify surgeons' work-related musculoskeletal disorders (WRMD), assess the physical burden, determine the location, frequency, and characteristics of the condition, evaluate their influence on daily life, and emphasize the need of ergonomics training by examining surgeons' perspectives and attitudes towards ergonomics.

METHODS

This prospective, cross-sectional study was conducted at Bursa Medical Park Hospital from August 14, 2023, to September 14, 2023, with the approval of the ethics

committee, numbered 2023/181, acquired from the Clinical Research Ethics Committee of Istinye University in Istanbul. All procedures were conducted in compliance with the principles of the Helsinki Declaration established by the World Medical Association. Surgeons with a minimum of one year of experience, who accessed the operating room on a weekly basis, maintained an average workweek of 40 hours, and voluntarily participated in the study were included, irrespective of gender and age. Those with less than one year of work experience, those with short working hours, those with systemic or malignant diseases, those who had an operation on the musculoskeletal system, and those who used analgesics regularly in the last month were excluded from the study. Thirty-seven surgeons who met the inclusion criteria were included in the study voluntarily and signed an informed consent form. Questionnaire forms were employed to collect data, which were developed from previously published literature on postural ergonomics in the surgical field. The first part of the survey included socio-demographic characteristics (gender, age, height, weight, surgical expertise, size of the surgery gloves, regular exercise or not), chronic musculoskeletal disease, musculoskeletal system surgeries, presence or absence of ergonomics training, perioperative pain status, sleepiness, predicted causes of pain, age of maximum perceived surgery performance, desire for early retirement, visual analogue scale (VAS) value in the region where the pain is most severe, whether the pain has an impact on daily life or not, whether or not it has been treated, whether there is a need for ergonomic education in the surgeons and whether the time is devoted to training in ergonomics.

In the second part of the forms, we used the Physical Workload Questionnaire (PWQ) to assess physical workload. The questionnaire was developed by Hollman *et al.* [16] and its Turkish validity and reliability study was conducted by Kahraman *et al.* [17]. The PWQ is a self-administered questionnaire designed to evaluate physical workload, and to our knowledge, it is the sole instrument utilized for this purpose in Turkey. It can be utilized in the physical evaluation of augmented workload resulting from body position and intense labour, as well as to mitigate high-risk occupational duties. Weightlifting is questioned when the torso is upright and tilted forward to 60 degrees. Light weights (<10 kg), medium weights (10-20 kg), and

heavy weights (>20 kg) are evaluated in each set of three items. All items are answered on a five-item Likert-type scale ranging from never to very often. To get a raw score, the responses to each item are added. The final scores are calculated by multiplying the raw score by 100 and dividing it by the subscale's highest possible score. A final score ranging from 0 (no workload) to 100 (highest workload) is obtained for each subscale

The Extended Nordic Musculoskeletal Questionnaire (NMQ-E) was used in the third part of the forms. The NMQ-E is a widely used questionnaire designed to assess MDG and its effects on individuals in the workplace. It was used for the first time by Kuorinka *et al.* [18]. The questionnaire consists of different sections covering various body areas and related symptoms. For each part of the body, which is divided into nine parts (neck, shoulder, back, elbow, hand/wrist, waist, hip/thigh, knee, foot/ankle), the age at which the pain occurs, consulting a doctor, using medication, hospitalization, illness. Whether it causes consequences such as taking leave from the workplace or disruption in daily life is evaluated under subheadings. NMQ-E poses binary choice inquiries (yes or no) regarding pain, soreness, or discomfort in nine anatomical locations over the past 12 months, the preceding four weeks, and the day of therapy [19].

In section 4, the Beck Depression Scale (BDS) questionnaire was employed to assess the psychological condition of the surgeons. BDS was created by Beck *et al.* [20]. The scale assesses the risk and vulnerability of adults to develop depression and evaluates the severity of depressive symptoms. The scale does not diagnose depression in an individual but quantifies the severity of their depression through numerical data. The Turkish validation adaptation of the scale employed in this study was conducted by Hisli [21]. The scale comprises 21 items, each representing a depressive symptom. Each item on the scale is evaluated on a range from 0 to 3 points. The maximum score was established at 63. An elevated score correlates with an increase in the individual's depression level. Depression intensity is classified as follows: 0-9 = Minimal, 10-16 = Mild, 17-29 = Moderate, and 30-63 = Severe.

Statistical Analysis

The data were analysed using the IBM SPSSR

Statistics (Version 20.0). The normality of the data distribution was checked by the Kolmogorov-Smirnov/Shapiro-Wilks tests and histograms. The results for characteristics of participants were presented as percentages for categorical variables and mean $\pm$ standard deviation for continuous variables because they were distributed normally. Variations of VAS, PWQ, DLA, and Beck values between different age, gender, height, weight, experience, and exercise status groups were analysed with One Way Anova – Tukey post hoc and independent student t-test when appropriate. Associations between WRMD and occupational groups were evaluated using the One-way Anova (Tukey post hoc). The level of significance was set at $P < 0.05$.

RESULTS

Demographic characteristics are shown in Table 1. Perioperative pain, numbness, and other characteristics of surgeons are presented in Table 2. Thirty-four out of 37 surgeons (91.9%) reported that they had experienced MSD, especially pain, at least once in their ca-

Table 1. Demographic data of the participants

	Data
Gender, n (%)	
Male	31 (83.8)
Female	6 (16.2)
Age (years)	49.21 $\pm$ 7.02
Number of years worked as a surgeon, n (%)	
<10	2 (5.40)
11-20	12 (32.43)
>20	23 (62.16)
BMI (kg/m²)	26.02 $\pm$ 3.20
Height (cm), n (%)	
<160	0
160-170	7 (18.9)
171>	30 (81.27)
Regular exercise, n (%)	
doing	8 (21.62)
not doing	29 (78.37)

Data are shown as mean $\pm$ standard deviation or n (%). BMI= Body Mass Index

Table 2. Other characteristics of the participants

	Data
Number of MSDs diagnosed	7 (18.91)
Number of surgeons with ergonomic training	1 (2.70)
Perioperative Pain	
No	3 (8.1)
Yes	34 (91.9)
Perioperative Numbness Status	
No	28 (75.67)
Yes	9 (24.32)
Early Retirement Request	
Yes	7 (18.91)
No	30 (81.08)
Previous Musculoskeletal Operation	
Yes	3 (8.1)
No	34 (91.89)
Effects of pain on activities of daily living	
Yes	25 (67.56)
No	12 (32.43)
The need for ergonomic improvement in the operating room	
Yes	30 (81.08)
No	7 (18.91)
Those who want to learn about ergonomic surgery	30 (81.08)
Mean VAS value$\pm$sd)	5.4 $\pm$ 2.02
Mean PWQ value (mean$\pm$sd)	14.89 $\pm$ 5.87
Mean Beck Scale value (mean$\pm$sd)	8 $\pm$ 4.41

Data are shown as mean $\pm$ standard deviation or n (%). BMI=Body Mass Index, MSD=Musculoskeletal Disorders, VAS=Visual Analog Scale

reers due to their professional responsibilities. VAS values were above 5 in 20 surgeons (54%), and pain was found to affect daily life in 25 (67.56%). Only 1 surgeon (2.7%) had received ergonomic training, and 30 surgeons (81.08%) stated that ergonomic improvements were needed in the operating room and that they would spend time on ergonomic training. The mean PWQ was 14.89. The mean Beck depression scale was

Table 3. Risk factors of musculoskeletal symptoms among study participants

	n (%)
Bad position	
Can be fixed	25 (67.56)
Cannot be fixed	9 (24.32)
Standing for a long time	21 (56.75)
Surgery time	21 (56.75)
Bad posture	25 (67.56)
Stand still	20 (54.05)
Stress	13 (35.13)
Lean forward too much	18 (48.64)
Insufficient equipment	5 (13.51)
Table height	12 (32.43)
Type of surgery	17 (45.94)
Temperature of the operating room environment	13 (35.13)
Used materials	6 (16.21)
Monitor position	4 (10.81)

8, and symptoms were minimal. Thirteen surgeons had mild depressive symptoms, and 1 surgeon had a moderate depression scale. The most common causes of pain were poor posture and poor positioning (Table 3). The distribution of surgeons and pain areas is shown in Table 4. The neck, upper back and waist were the most affected areas and were the most common reasons for visiting a doctor and using medication. It was determined that the VAS value increased as the surgeon's height increased. A significant difference was found in VAS values in those over and under 170 cm. The Beck depression scale value was significantly higher in surgeons under 45 years of age (Table 5).

DISCUSSION

In our study, we determined that the surgeons had WRMDs, most probably due to increased physical workloads, and lack of ergonomic knowledge and training. They mostly experience discomfort in the neck, upper back, low back, and these disorders adversely affect their daily living activities. In order to mitigate the risk of MSD, Kroemer suggests refraining

Table 4. The distribution of surgeons and pain areas

n (%)	Neck	Shoulder pain	Back Pain	Elbow pain	Wrist-hand pain	Lower Back pain	Hip pain	Ankle-Foot pain	Knee pain
Obstetrics and gynecologic surgery (n=5)	4 (10.8)	4 (10.8)	4 (10.8)	1 (2.7)	1 (2.7)	2 (5.40)	1 (2.7)	1 (2.7)	0
General and pediatric surgery (n=6)	5 (13.5)	3 (8.1)	4 (10.8)	1 (2.7)	1 (2.7)	3 (8.1)	3 (8.1)	1 (2.7)	1 (2.7)
Orthopedics surgery (n=6)	6 (16.2)	1 (2.7)	6 (16.2)	1 (2.7)	1 (2.7)	4 (10.8)	1 (2.7)	0	1 (2.7)
Otolaryngologist (n=3)	2 (5.40)	0	2 (5.40)	1 (2.7)	0	1 (2.7)	1 (2.7)	0	0
Urologic surgery (n=3)	3 (8.1)	0	3 (8.1)	0	0	2 (5.40)	1 (2.7)	1 (2.7)	0
Eye surgery (n=4)	4 (10.8)	2 (5.40)	4 (10.8)	0	1 (2.7)	2 (5.40)	0	0	0
Cardiovascular and thoracic surgery (n=5)	3 (8.1)	0	3 (8.1)	0	0	1 (2.7)	1 (2.7)	0	0
Neurosurgery (n=4)	4 (10.8)	1 (2.7)	4 (10.8)	0	0	3 (8.1)	4 (10.8)	0	0
Total (n=37)	31 (83.7)	11 (29.7)	30 (81.08)	4 (10.8)	4 (10.8)	18 (48.6)	12 (32.43)	3 (8.1)	2 (5.40)
P value*	0.44	0.30	0.42	0.81	0.96	0.81	0.04*	0.68	0.63

*One way Anova (Tukey Post hoc)

from engaging in seven specific activities. (1) repetitions, defined as cycle less than 30 seconds or 1 basic activity element present for more than 50% of the total cycle time, (2) prolonged or repetitive exertion where the person uses more than 30% of their strength, (3) body parts held in extreme positions, (4) prolonged static posture, (5) activities with vibrating instruments, (6) exposure to cold or hot, and (7) combinations of the above conditions [22]. Many of these activities and their various combinations are common for surgeons during surgeries.

WRMDs are commonly observed among surgeons, with prevalence rates varying between 23% and 100% according to several studies [23-27]. The existing body of literature exhibits considerable heterogeneity in the observed outcomes, primarily because of the underreporting of illnesses and the logistical limitations inherent in investigations on surgical ergonomics. In our study, this rate was determined as 91.9%. Many studies have investigated surgeons from various specialties regarding MSD. In all studies, including ours, the neck and upper back were the most frequently affected areas; Excessive forward bending of the head and back, poor posture, and incorrect body position are thought to be the most common problems causing WRMD [8, 28-30]. While numerous surgeons pursue medical intervention for musculoskeletal disorders and adjust their practices in response to discomfort, they lack sufficient training. In a study of 244 surgeons, 88% reported MSD, 29% received treatment, and 9% changed their practice due to pain. Only 1% reported to their institution that they were experiencing pain. and only 16% had formal training in ergonomics [31]. In our study, there were no surgeons who changed their practice due to pain or reported their pain to their institution, and only 2% had received ergonomics training. Although 91% had WRMD, only 19% had diagnosed MSD. This situation may be associated with surgeons' lack of ergonomic awareness and training, their intense work, or their attempt to cope with pain on their own. In addition, it is believed that such practice does not exist in surgical culture. In another study, it was observed that all participants who were members of the European Association of Endoscopic Surgery believed that ergonomics were important in the operating room, but only 11% were aware of published ergonomics guidelines [32]. In our study, it was determined that 98% of surgeons did not have

Table 5. Variation of VAS, PWQ, DLA and Beck values according to gender, age, height, weight, experience and exercise status

		VAS	PWQ	DLA	BECK
Gender	Female (n=6)	4.5±2.8	17.7±7.5	4 (67)	8.5±3.6
	Male (n=31)	5.4±1.9	14.4± 5.6	21 (68)	7.9±4.7
P value		0.33	0.21	0.65	0.77
Age (years)	<45 years (n=12)	5.8±1.7	14.9±6.6	10 (83)	10.1±4.9
	≥45 years (n=25)	5.0± 2.2	14.8± 5.7	15 (60)	7.0± 3.9
P value		0.27	0.98	0.15	0.048
Height (cm)	<170 (n=7)	4.0±3.2	14.0±4.9	4 (57)	7.7± 3.5
	≥170 (n=30)	5.6±1.7	15.1± 6.2	21 (70)	8.1±4.7
P value		0.07	0.68	0.41	0.85
BMI (kg/m²)	<30 (n=30)	5.4±2.0	15.3±6.0	22 (73)	8.1±4.5
	≥30 (n=7)	4.3±2.9	11.8±5.2	3 (43)	7.3±5.2
P value		0.45	0.16	0.14	0.27
Surgical experience (years)	<10 (n=2)	6.0	12.2 ±1.6	2 (100)	11.0±7.1
	10-20 (n=12)	5.8 ±2	14.3±6.6	10 (83)	8.66±5.6
	>20 (n=23)	5±2.3	15.5±6.0	13 (57)	7.4 ±4.0
P value*		0.73	0.69	0.17	0.44
Regular daily exercise	Yes	5.9 ±2.0	13.8± 3.5	7 (19)	9.8 ±6.0
	No	5.1±2.2	15.2±6.5	18 (49)	7.5±4.0
P value		0.36	0.58	0.18	0.2

Data are shown as mean±standard deviation or n (%). BMI=Body Mass Index, VAS=Visual Analog Scale, PWQ=Physical Workload Questionnaire, DLA= Daily Living Activities.

knowledge about ergonomics guidelines, 81% said that improvements were needed in operating room ergonomics, and that they wanted to receive ergonomics training. It was concluded that 92% of surgeons with MSD needed and wanted help in this regard. In a study of 561 spine surgeons, 7.1% had undergone surgery for lumbar disc disease and 4.6% for cervical disc disease; 31.9% of them had to take leave from work due to MSD [33,34]. Similarly, in our study, it was found that 8.1% of the surgeons were operated for cervical or lumbar intervertebral disc disease. A neutral body posture is a comfortable position that can be maintained for long periods of time, supporting the natural curvature of the spine, and giving the body a biomechanical advantage in performing work. Improper working postures can put muscles, tendons, and ligaments at risk. Abnormal loads and stress can damage bones, joints, and cartilage. Consistent with the liter-

ature in our study, the most common causes of WRMD were identified as poor posture, poor position, standing for long periods of time, and long surgery time. Although 67% of surgeons thought these problems could be corrected, they did not take any action [35-37]. Various studies have identified several factors that contribute to postural discomfort in surgeons [22,30]. In our study, although all surgeons stated that they adjusted the table height according to their height and surgical procedure during the operation, 32% still blamed the table height for their MSDs. This result may indicate that the surgeon does not tend to raise the table even if the operating table is low, the frequency of table adjustment is associated with poor posture and discomfort during the operation, and the operating tables are adjusted primarily when postural comfort is significantly affected. These findings highlight the lack of ergonomic practice, such as adjusting

the table or patient rather than the person themselves and may reflect limited ergonomic training for surgeons. While adjusting a suitable operating table height while standing certainly promotes better operating posture, the table can be adjusted for only one person at a time, or it can be adjusted to a common suitable height for more than one person assisting the procedure.

Non-ergonomic working style in surgeons may cause an increase in pain intensity and physical workload, negative effects on daily life activities, and an increase in the stress component. In our study, it was evaluated whether surgeons' age, gender, height, BMI, surgical experience, and regular exercise affected VAS, PWQ, DLA, and Beck scales. A significant relationship was detected only in age and Beck depression anxiety scores and the score was higher in young people. Lack of experience in young surgeons may result in poorer job skills and inability to practice. This may be associated with an increase in the stress component and therefore in Beck depression scores. There was a near-significant relationship between height and VAS values, and VAS values increased as height increased. Being tall was thought to cause neck and torso to bend forward, causing neck and back pain. Additionally, when surgeons were divided according to surgical subspecialties and evaluated according to their painful areas, hip pain was seen more frequently only in neurosurgeons. It was thought that it would be appropriate to re-evaluate this difference by increasing the number of cases. There was no significant difference between other subbranches and painful areas.

Each surgical modality carries its own set of ergonomic dangers. Surgeons accept these risks and disclose pain and discomfort from surgery to their institutions infrequently, ignoring them. Despite the existence of ergonomics guidelines, few surgeons are aware of them, and almost none have received training in ergonomics. Because the focus of surgical procedures is on the patient, little attention is paid to proper posture or spinal stability at the same time. Given the prevalence of WRMD among surgeons, it is essential to investigate the effect of ergonomics on surgeons' health. The lack of implementation of this subject matter has the potential to negatively impact the surgeon's capacity to perform, leading to reduced levels of professional fulfilment, increased weariness, and a heightened inclination toward early retirement. One of the

key findings is that the provision of ergonomics education can significantly enhance individuals' awareness and effectively mitigate pain-related behaviours and symptoms. It is widely recognized that ergonomic issues can arise either during the period of the assistantship or prior to it, and if left unaddressed, they may persist. Hence, the development of an optimal ergonomics curriculum becomes imperative, with a focus on promoting and reinforcing sound ergonomic practices within the realm of early medical education. Future research should focus on the development of objective methods and recommendations for surgical ergonomics as well as establishing a connection between ergonomic assessments in surgeons and the occurrence of pain and tissue-level damage.

Limitations

The main limitations of this study are its cross-sectional design, the reliance on retrospective recall of symptoms, the lack of distinction between open and closed surgeries in the evaluation, and the small sample size. Further large-scale, long-term, prospective studies are needed to gain a better understanding of the cause-and-effect relationships.

CONCLUSION

WRMDs stemming from ergonomic issues are prevalent within the surgical profession, leading to both physical and psychological consequences. These negative effects contribute to musculoskeletal pain, depression, decreased overall quality of life, and increased productivity losses in the workforce. It is imperative to establish evidence-based ergonomic training guidelines required by hospitals and residency training programs to protect surgeons from preventable injuries that have the potential to significantly impact or end their careers.

Ethical statement

Ethics committee approval (number: 2023/181) was obtained from the from the Clinical Research Ethics Committee of Istinye University in Istanbul.

Authors' Contribution

Study Conception: SK, ED, EK, TK, HU; Study Design: SK, ED, EK, TK, HU; Supervision: SK, ED,

EK, TK, HU; Funding: ED; Materials: SK; Data Collection and/or Processing: SK; Statistical Analysis and/or Data Interpretation: ED; Literature Review: EK; Manuscript Preparation: SK and Critical Review: ED.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Evaluation of admissions and inappropriate referrals to pediatric gastroenterology, hepatology and nutrition outpatient clinics

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ABSTRACT

Objectives: The aim of this study was to examine the diagnostic profiles of patients admitted to pediatric gastroenterology, hepatology, and nutrition outpatient clinics within the scope of the state service obligation and to determine the reasons for inappropriate referrals.

Methods: A total of 10,235 patients admitted to the pediatric gastroenterology, hepatology and nutrition outpatient clinics of Mardin Training and Research Hospital between 2022 and 2023 were retrospectively analyzed. Data were analyzed using SPSS 26.0 software according to demographic and clinical variables such as age, gender, reasons for admission and diagnoses.

Results: Of the patients examined, 49.1% were girls and 50.9% were boys, and the most common reason for presentation was inadequate weight gain with a rate of 46%. However, malnutrition or another nutritional disorder was not detected in 28% of the patients referred with a diagnosis of inadequate weight gain. Malnutrition was diagnosed in a total of 1,710 cases, of which 8.2% were mild malnutrition, 5.3% were moderate malnutrition, and 4.2% were severe malnutrition. No pathological findings were found in 40.8% of the applicants. It was also found that most of the complaints of constipation and diarrhea, which are common reasons for admission, can be effectively treated in primary and secondary health care services.

Conclusions: The results of the study show that a significant proportion of referrals to pediatric gastroenterology outpatient clinics are unnecessary and that referrals can be reduced by evaluating these patients in primary and secondary care, thereby increasing the efficiency of health care services.

Keywords: Pediatric gastroenterology, inappropriate referral, inadequate weight gain, constipation, diarrhea

Effective delivery of health services in Turkey is of great importance in terms of correct patient management and prevention of unnecessary referrals, especially in outpatient services provided under the public service obligation. The quality of outpatient services is directly related to the accurate diagnosis and treatment of patients. However,

the absence of pathological findings in a significant number of patients presenting to pediatric gastroenterology, hepatology and nutrition outpatient clinics, in particular, leads to unnecessary congestion in these clinics and prolongs the examination times of patients who really need treatment.

The general pediatric gastroenterology evaluation

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includes a comprehensive assessment of the child's gastrointestinal health, growth parameters, and nutritional status. The goal of this evaluation is to identify any gastrointestinal disorders and related problems that affect growth, digestion, and overall health. This process includes a medical history, physical examination, laboratory and imaging studies, and nutritional assessment [1].

Nutritional assessment is of great importance in the field of pediatric gastroenterology as one of the fundamental elements of a child's overall health. Since childhood is a period of rapid physical and mental development, ensuring a balanced and adequate diet has a significant long-term impact on both physical development and cognitive abilities [2]. A proper nutritional assessment not only identifies the cause of the presenting symptoms, but also helps prevent future complications by improving the child's overall health [3].

This retrospective study aims to identify the diagnoses that lead to inappropriate referrals by reviewing the diagnoses of patients admitted to pediatric gastroenterology outpatient clinics as part of mandatory service.

METHODS

This retrospective study included data of patients admitted to the Pediatric Gastroenterology, Hepatology and Nutrition Outpatient Clinic of Mardin Training and Research Hospital between 2022 and 2023. A total of 10235 patients were analyzed and their demographic characteristics, reasons for admission and outcomes were evaluated in detail. Cases were classified according to sex, age, reasons for admission and diagnoses, and inappropriate referral rates and pathological conditions detected in the outpatient clinic were also analyzed.

Ethical approval was obtained from Mardin Artuklu University Non-Interventional Clinical Research Ethics Committee for this study (Date:10.09.2024, Decision no: 2024/9-6).

Statistical analysis

Statistical analysis of study data was performed using the SPSS software package, version 21. Descriptive statistics include numbers (n) and percentages (%).

RESULTS

The distribution of complaints and diagnoses of patients admitted to Paediatric Gastroenterology, Hepatology and Nutrition Outpatient Clinics is shown in Table 1. Five thousand twenty (49.9%) of the patients were female and 5215 (51.1%) were male.

The most common complaint among patients presenting to the outpatient clinic was inadequate weight gain, which was noted in 4719 cases (46%). No evidence of malnutrition was found in 2896 patients (28%) who presented to the outpatient clinic with a complaint of inadequate weight gain, and these patients were referred to appropriate pediatric specialists for evaluation. Malnutrition was identified in 1710 cases. Mild malnutrition was detected in 844 (8.2%), moderate malnutrition in 542 (5.3%) and severe malnutrition in 436 (4.2%) of these cases. Enteral nutrition support was initiated in patients with malnutrition; percutaneous endoscopic gastrostomy [PEG] was recommended in 7 patients with severe malnutrition and cerebral palsy. All these patients were included in the regular follow-up program.

A total of 1885 patients (18.4%) who presented to the outpatient clinic with complaints of abdominal pain were evaluated; constipation was diagnosed in 1561 (15.3%) of these patients, and no pathological condition was diagnosed in 324 (3.1%) of these patients.

Dietary recommendations and medication were given to 1325 patients who presented to the outpatient clinic with dyspeptic complaints. During the follow-up period, 564 patients (5.5%) underwent endoscopy. Acute gastroenteritis was diagnosed in 956 patients (9.3%) who presented to the outpatient clinic with diarrhea as another reason for presentation. Further investigations were performed in 341 (3.3%) of these cases, and endoscopy and colonoscopy were performed in 128 (1.2%) patients.

Other causes of presentation included elevated transaminases, proctocolitis, gallstones and pancreatitis. These cases were considered as diseases that should be followed up specifically in the gastroenterology subspecialty.

One of the remarkable findings of the study was that 40.8% (4176) of the patients admitted did not have any pathologic findings. This shows that the rate of inappropriate referral is quite high.

Table 1. Distribution of complaints and diagnoses of patients admitted to the Paediatric Gastroenterology, Hepatology and Nutrition Outpatient clinics

Variables		n (%)
Gender	Male	5215 (50.9)
	Female	5020 (49.1)
Total cases	Pathological findings detected	5527(54)
	No pathological findings	4708(46)
Inadequate weight gain	No insufficient weight gain	2835 (28)
	Mild malnutrition	844 (8.2)
	Moderate malnutrition	542 (5.3)
	Severe malnutrition	436 (4.2)
Abdominal pain	No pathological findings	324 (3.1)
	Constipation	1561 (15.3)
Dyspeptic complaints	Dietary recommendations and medication	761 (7.4)
	Endoscopy performed	564 (5.5)
Diarrhea	Acute gastroenteritis	956 (9.3)
	Chronic diarrhea	341 (3.3)
	Endoscopy and colonoscopy performed	128.2)

DISCUSSION

This study provides important insights for improving the efficiency of outpatient services by examining the diagnoses and inappropriate referral rates of patients admitted to pediatric gastroenterology, hepatology, and nutrition outpatient clinics. The results show that a large proportion of referrals from primary and secondary care are unnecessary. This increases the workload of outpatient clinics and prolongs the waiting time for patients who really need care. Most referrals are not for organic pathologies, but for reasons such as poor eating habits or defecation disorders. Therefore, it is important to prevent inappropriate referrals for efficient use of the health system.

The most common pathological condition detected was inadequate weight gain, and malnutrition was detected in 46% of cases. Malnutrition remains a global problem. Worldwide, 7.3% of children under 5 years of age have a weight-for-height z-score of less than -2, indicating acute malnutrition. The rate of acute malnutrition is highest in South Asia, at 15.2% [4]. Children with mild malnutrition often go unrecognized, and the degree of malnutrition may progress if

the necessary precautions are not taken. In this group, with a Z-score between -1 and -2, the risk of death is twice that of healthy children. Especially if it occurs in the first two years of life, it can cause various health problems, such as permanent growth and developmental retardation [5]. In another aspect of the study, 28% of the patients referred for inadequate weight gain were not found to be malnourished. It is believed that in these cases, the correct anthropometric measurements were not taken. It is extremely important to take anthropometric measurements at every examination and to interpret these measurements accurately. Before chronic malnutrition develops, these children should be referred to the appropriate services and followed up regularly [6].

Constipation is one of the most common problems in childhood and in our study constipation was found in 15.3% of cases. In the pediatric population, constipation is a common health problem affecting 0.7% to 29.6% of children worldwide [7]. The results of our study show that many patients presenting with constipation complaints are not questioned about their detailed dietary habits and are therefore exposed to unnecessary treatments. Correcting dietary habits that

lead to constipation will improve patients' quality of life in the long term and reduce unnecessary medication use [8].

The majority of patients who presented to the outpatient clinic with dyspeptic complaints experienced remission with dietary recommendations and medical treatment. Endoscopic examination was performed in 5.5% of patients whose symptoms persisted and who developed additional complications during follow-up. The literature reports that only one third of dyspeptic patients have an underlying organic pathology [9].

Of the cases diagnosed with acute gastroenteritis, 9.3% presented to the outpatient clinic without being evaluated by a pediatrician or without waiting for the end of treatment. Further evaluation was considered necessary in only 3.3% of these cases. Only 1.2% of diarrhea cases were considered chronic diarrhea. Acute diarrhea is one of the most common presentations in pediatric outpatient clinics. However, referral of diarrhea cases of less than four weeks' duration without detailed evaluation increases the workload of outpatient clinics and leads to unnecessary investigations. In these cases, the duration, severity, and general condition of the patient should be carefully evaluated and follow-up should be performed with simple interventions and supportive care, as appropriate [10-12]. Another striking finding of our study was that no pathological findings were found in 40.8% of the outpatient visits. This suggests that unnecessary referral of most of these patients could be avoided if a more comprehensive evaluation was performed in secondary care [13, 14].

Limitations

The limitations of our study are that it was conducted in a single center and retrospectively.

CONCLUSION

Reducing unnecessary referrals not only eases the burden on outpatient clinics, but also improves the efficiency of healthcare services and reduces costs. Assessing patients more comprehensively in primary and secondary care and planning referrals only when necessary is a critical step in improving the efficiency of healthcare services. In addition, the implementation of an effective triage system will support rapid patient

access to treatment by ensuring the correct use of resources. Our study highlights that preventing inappropriate referrals plays a fundamental role in improving the efficiency of the healthcare system.

Ethical Statement

Ethical approval was obtained from Mardin Artuklu University Non-Interventional Clinical Research Ethics Committee for this study (Date:10.09.2024, Decision no: 2024/9-6). All procedures were performed according to the Declaration of Helsinki.

Authors' Contribution

Study Conception: GÇ; Study Design: GÇ, ÖÖ; Supervision: GÇ, ÖÖ; Funding: N/A; Materials: GÇ, ÖÖ; Data Collection and/or Processing: GÇ, ÖÖ; Statistical Analysis and/or Data Interpretation: GÇ, ÖÖ; Literature Review: GÇ; Manuscript Preparation: GÇ, ÖÖ and Critical Review: GÇ, ÖÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Prognostic factors and the impact of adjuvant chemotherapy on recurrence and survival in stage I non-small cell lung cancer: A real-world study

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ABSTRACT

Objectives: Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related mortality. Despite curative surgery, recurrence is common in Stage I NSCLC, highlighting the need for improved prognostic classification. This study aims to evaluate the key pathological factors affecting recurrence and survival and to investigate the potential benefit of adjuvant chemotherapy (ACT) in patients with Stage I NSCLC.

Methods: A retrospective analysis was conducted on patients with Stage I NSCLC who underwent curative surgery between 2010 and 2024. Demographic and disease-related prognostic factors were assessed. The impact of these factors, along with adjuvant chemotherapy (ACT), on overall survival (OS) and disease-free survival (DFS) was analyzed.

Results: A total of 95 patients were included in the study, with a median follow-up period of 47 months. Recurrence occurred in 35.8% of patients, and 16.8% died. The five-year OS and DFS rates were calculated as 76.4% and 67.9%, respectively. Spread through air spaces (STAS) was identified as an independent prognostic factor associated with an increased risk of recurrence. While OS was shorter in patients with LVI positivity, it was not determined to be an independent prognostic factor. Visceral pleural invasion (VPI) did not demonstrate a significant prognostic impact on survival or recurrence. The effect of ACT on OS and DFS was evaluated, but no survival advantage was observed.

Conclusions: Certain pathological factors influence survival and recurrence in Stage I NSCLC. While STAS was identified as an independent prognostic factor, ACT did not provide a significant benefit for OS or DFS. These findings emphasize the importance of individualized treatment approaches and close oncological follow-up after surgery. Future studies should incorporate novel and effective biomarkers, such as circulating tumor DNA, to optimize adjuvant therapy decisions.

Keywords: Non-small cell lung cancer, spread through air spaces, recurrence, survival, prognostic factors, lymphovascular invasion, adjuvant chemotherapy

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Lung cancer is the leading cause of cancer-related deaths in both men and women, posing a significant global health burden [1]. Non-small cell lung cancer (NSCLC), which accounts for approximately 85% of all lung cancer cases, is the most common subtype [1]. In patients with early-stage NSCLC, surgical treatment remains the most effective curative approach [2]. However, even after curative surgery, the risk of recurrence persists in 20-30% of patients, negatively impacting long-term survival rates [3]. The five-year survival rate for stage IB patients remains at 73%, while this rate reaches 85% in stage IA patients [3, 4]. In this context, identifying the factors influencing postoperative recurrence and survival is crucial for accurately determining which patients require adjuvant therapy. This is essential to prevent undertreatment or overtreatment, ensuring optimal management of stage I NSCLC patients.

Among the factors influencing postoperative survival, tumor size, lymphovascular invasion (LVI), visceral pleural invasion (VPI), histological subtype, and surgical margin positivity (SMP) have long been recognized. In recent years, however, spread through air spaces (STAS) has emerged as an increasingly investigated prognostic factor [5-9]. Despite numerous studies, a clear consensus has yet to be reached regarding which parameters indicate a higher recurrence risk in stage I disease, and no definitive agreement has been established on the use of adjuvant therapy. Adjuvant platinum-based chemotherapy is generally recommended for stage I NSCLC patients with tumors ≥ 4 cm. However, conflicting findings exist in the literature regarding the effectiveness of adjuvant chemotherapy (ACT) in patients with tumors smaller than 4 cm or those exhibiting high-risk features such as VPI or LVI [10, 11]. Current guidelines do not recommend adjuvant chemotherapy for stage IA patients; however, they suggest chemotherapy for certain groups of patients with stage IB disease. Specifically, adjuvant chemotherapy is recommended for patients with tumors larger than 4 cm, those showing lymphovascular invasion or pleural invasion, those with poorly differentiated tumor histology, and those with a PET scan SUV value greater than 10 [12].

This study aims to retrospectively evaluate the factors affecting recurrence and survival in NSCLC patients who underwent surgical treatment and continued

oncological follow-up at a single center between 2010 and 2024. By addressing existing gaps in the literature, this study seeks to contribute to the development of improved treatment strategies for this patient population.

METHODS

Study Design and Patients

This study is a single-center cohort study that retrospectively evaluates the factors affecting prognosis in patients with stage I non-small cell lung cancer (NSCLC) who underwent surgery between 2010 and 2024. Local ethics committee approval was obtained for this study (approval number 2025/010.99/12/35), and it was conducted under the principles of the Declaration of Helsinki.

Patients included in the study were those diagnosed pathologically with stage I NSCLC who underwent lobectomy, segmentectomy, or wedge resection and at least six months of oncological follow-up after surgery. Patients with tumors containing small cell components, those who underwent inadequate lymph node dissection, those who received neoadjuvant therapy, and those with synchronous/metachronous cancer were excluded from the study. Staging was performed according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system, and histological subtypes were classified according to the World Health Organization (WHO) classification [13, 14].

Clinical Data Collection

The demographic characteristics of the patients (age, gender), tumor size, histological subtype, and pathological prognostic factors STAS, LVI, VPI, SMP, and main bronchus involvement (MBI) were retrospectively obtained from patient records.

Patients who received adjuvant chemotherapy were compared with those who did not in terms of survival and recurrence. Postoperatively, patients were followed up with computed tomography every 3 to 6 months during the first two years and then annually for at least four years. Patients who were lost to follow-up during the specified follow-up period were excluded from the analyses.

Table 1. Distribution of sociodemographic and clinical variables

Variables	Data
Age (years)	61.61±8.98 / 61.0 (37-82)
≤65 / >65	61 (64.2) / 34 (35.8)
Gender	
Female / Male	26 (27.4) / 69 (72.6)
ECOG score	
0 / 1 / 2	54 (56.8) / 38 (40.0) / 3 (3.2)
Comorbidity	
Absent / Present	44 (46.3) / 51 (53.7)
Tumor location	
Right lung / Left lung	60 (63.2) / 35 (36.8)
Right lung superior / inferior lobe	34 (35.8) / 24 (25.3)
Left lung superior / inferior lobe	17 (17.9) / 20 (21.1)
Upper lobe / lower lobe	50 (56.2) / 39 (43.8)
Surgical type	
Wedge resection / lobectomy and others	16 (16.8) / 79 (83.2)
Adjuvant chemotherapy	
No / Yes	68 (71.6) / 27 (28.4)
Received adjuvant cisplatin	
Not Received / Received	6 (22.2) / 21 (77.8)
Tumor type	
Non squamous / Squamous	65 (68.4) / 30 (31.6)
MBI	
Absent / Present	91 (95.8) / 4 (4.2)
LVI	
Absent / Present	74 (77.9) / 21 (22.1)
PNI	
Absent / Present	83 (87.4) / 12 (12.6)
STAS	
Absent / Present	68 (71.6) / 27 (28.4)
Bronchial involvement	
Absent / Present	89 (93.7) / 6 (6.3)
Surgical margin	
Negative / Positive	89 (93.7) / 6 (6.3)
VPI	
Absent / Present	73 (76.8) / 22 (23.2)
Tumor stage	
T1 / T2	69 (72.6) / 26 (27.4)
TNM stage	
Stage 1A1 / 1A2 / 1A3 / 1B	13 (13.7) / 26 (27.4) / 18 (18.9) / 38 (40.0)
Recurrence	
Absent / Present	61 (64.2) / 34 (35.8)
Mortality	
Alive / Deceased	79 (83.2) / 16 (16.8)
Follow-up duration (months)	46.23±22.01 / 47.0 (8-86.0)

Data are shown as mean±standard deviation or median (minimum-maximum) or n (%) where appropriate. ECOG=Eastern Cooperative Oncology Group, MBI=Main Bronchus Involvement, LVI=Lymphovascular Invasion, PNI=Perineural Invasion, STAS=Spread Through Air Spaces, VPI=Visceral Pleural Invasion, TNM=Tumor Nod Metastasis

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as n and % for categorical variables and as Mean $\pm$ SD and Median (min-max) for continuous variables. The Kaplan-Meier method was used to compare survival and DFS durations between clinical groups. Finally, the results of multivariate Cox regression analysis were provided to assess the impact of various clinical variables on mortality and recurrence risk. A P-value < 0.05 was considered statistically significant.

RESULTS

The median age of the patients included in the study was 61 years (range: 37-82 years), with a male-to-female ratio of 2.8 (69/26). Wedge resection was performed in 16 patients (16.8%), while the remaining patients underwent anatomical resection (lobectomy, pneumonectomy, etc.). The most common tumor location was the right upper lobe (n=34, 35.8%). Histologically, 30 patients (31.6%) had squamous cell carcinoma, while 65 patients (68.4%) had non-squamous histology. A total of 27 patients (28.4%) received ACT, of whom 21 (77.8%) were treated with a cis-

Table 2. Overall survival (OS) comparisons

Variables	2 years (%)	5 years (%)	Median (95% CI)	P value
General	93.6	80.4	- (-)	
Age				
≤65	93.3	81.9	- (-)	0.976
>65	94.1	76.8	- (-)	
Gender				
Female	96.2	96.2	- (-)	0.051
Male	92.6	74.2	- (-)	
ECOG score				
0	94.2	84.6	- (-)	0.718
1	94.7	75.8	- (-)	
2	66.7	66.7	- (-)	
Comorbidity				
Absent	90.8	70.7	- (-)	0.109
Present	96.1	87.8	- (-)	
Tumor location				
Right lung superior lobe	97.1	88.8	- (-)	0.796
Right lung inferior lobe	95.8	69.7	- (-)	
Left lung superior lobe	81.9	73.7	- (-)	
Left lung inferior lobe	95.0	80.9	- (-)	
Right lung	95.0	81.5	- (-)	0.945
Left lung	91.0	78.5	- (-)	
Upper lobe	93.8	85.5	- (-)	0.519
Lower lobe	94.9	70.9	- (-)	
Surgical type				
Wedge resection	100.0	85.7	- (-)	0.267
Lobectomy and others	92.3	79.3	- (-)	
Adjuvant chemotherapy				
Absent	95.5	80.0	- (-)	0.927
Present	88.9	82.1	- (-)	

Table 2 continued. Overall survival (OS) comparisons

Variables	2 years (%)	5 years (%)	Median (95% CI)	P value
Adjuvant cisplatin				
Absent	83.3	83.3	- (-)	0.850
Present	90.5	81.4	- (-)	
Tumor type				
Non squamous	93.7	80.4	- (-)	0.731
Squamous	93.3	80.2	- (-)	
MBI				
Absent	94.4	80.6	- (-)	0.526
Present	75.0	75.0	- (-)	
LVI				
Absent	94.4	84.8	- (-)	0.030
Present	90.5	68.4	79.00 (51.21-106.78)	
PNI				
Absent	93.8	81.6	- (-)	0.665
Present	91.7	73.3	- (-)	
STAS				
Absent	94.0	84.3	- (-)	0.053
Present	92.6	71.3	79.00 (60.20-97.79)	
Bronchial involvement				
Absent	94.3	81.2	- (-)	0.442
Present	83.3	66.7	- (-)	
Surgical margin				
Negative	95.4	83.4	- (-)	0.002
Positive	66.7	33.3	48.00 (0.00-106.38)	
VPI				
Absent	93.0	76.6	- (-)	0.329
Present	95.5	95.5	- (-)	
Tumor stage				
T1	94.1	77.4	- (-)	0.703
T2	92.3	87.2	- (-)	
TNM stage				
Stage 1A1	91.7	73.3	- (-)	0.343
Stage 1A2	96.2	84.6	- (-)	
Stage 1A3	94.4	65.4	79.00 (-)	
Stage 1B	92.1	87.9	- (-)	

ECOG=Eastern Cooperative Oncology Group, MBI=Main Bronchus Involvement, LVI=Lymphovascular Invasion, PNI=Perineural Invasion, STAS=Spread Through Air Spaces, VPI=Visceral Pleural Invasion, TNM=Tumor Node Metastasis
Kaplan-Meier, Log-rank test, P<0.05 statistically significant

platin-containing regimen. The median follow-up period was 47 months (range: 8-86 months). During this period, recurrence was observed in 34 patients (35.8%), and 16 patients (16.8%) died. The patholog-

ical characteristics of the patients and treatment approaches are summarized in Table 1.

The median overall survival (OS) and disease-free survival (DFS) were not reached. The two-year and

five-year OS rates were calculated as 93.6% and 80.4%, respectively, while the two-year and five-year DFS rates were 77.4% and 56%, respectively. Comparisons of OS and DFS according to different variables are presented in Tables 2 and 3, respectively.

For patients with negative LVI, the median OS was not reached, whereas for those with positive LVI, the median OS was 79 months, showing a statistically significant difference ($P=0.03$) (Fig. 1). Similarly, in patients with negative surgical margins, the median OS was not reached, while in those with positive margins, the median OS was 48 months, with a statistically significant difference ($P=0.002$). There was no statistically significant difference in OS between patients with and without VPI ($P=0.329$) (Fig. 1). Univariate analysis identified variables significantly associated with OS, which were subsequently included in a multivariate Cox regression model. According to

this analysis, SMP were found to increase the risk of death by 4.83 times (HR: 4.83, 95% CI: 1.33-17.51, $P=0.016$).

In univariate analysis, MBI ($P=0.011$), STAS ($P=0.008$), and SMP ($P=0.009$) were found to be statistically significant for DFS (Table 3). The median DFS was not reached in patients without STAS, whereas in those with STAS, the median DFS was 42 months, showing a statistically significant difference ($P=0.008$) (Fig. 2). Similarly, the median DFS was not reached in patients with negative surgical margins, while it was 33 months in those with positive margins, with a statistically significant difference ($P=0.009$). Variables found to be significant for DFS in univariate analysis were included in the multivariate Cox regression model. According to the model results, MBI increased the risk of recurrence by 4.46 times (HR: 4.46, 95% CI: 1.26-15.69, $P=0.020$), the presence of STAS

Table 3. Disease-free survival (DFS) comparisons

Variables	2 years (%)	5 years (%)	Median (95% CI)	P value
General	77.4	56.0	- (-)	
Age				
≤65	77.7	61.4	- (-)	0.470
>65	76.5	45.9	53.00 (-)	
Gender				
Female	88.1	68.8	- (-)	0.081
Male	73.4	50.9	- (-)	
ECOG score				
0	78.7	53.2	- (-)	0.407
1	76.2	61.1	- (-)	
2	66.7	-	30.00 (0.0-65.20)	
Comorbidity				
Absent	74.5	53.6	- (-)	0.667
Present	79.7	58.0	- (-)	
Tumor location				
Right lung superior lobe	76.2	55.2	- (-)	0.891
Right lung inferior lobe	78.6	45.0	48.00 (-)	
Left lung superior lobe	81.6	64.9	- (-)	
Left lung inferior lobe	74.7	59.4	- (-)	
Right lung	76.2	49.7	53.00 (-)	0.291
Left lung	79.5	66.6	- (-)	
Upper lobe	79.7	59.7	- (-)	0.588
Lower lobe	76.2	53.9	- (-)	

Table 3 contunied. Disease-free survival (DFS) comparisons

Variables	2 years (%)	5 years (%)	Median (95% CI)	P value
Surgical type				
Wedge resection	81.3	67.7	- (-)	0.465
Lobectomy and others	76.5	53.7	- (-)	
Adjuvant chemotherapy				
Absent	82.2	56.7	- (-)	0.089
Present	64.6	47.9	34.00 (-)	
Adjuvant cisplatin				
Absent	50.0	33.3	12.00 (0.00-39.60)	0.251
Present	68.2	51.9	- (-)	
Tumor type				
Non squamous	81.0	63.7	- (-)	0.064
Squamous	70.0	42.6	48.00 (25.53-70.46)	
MBI				
Absent	79.7	57.1	- (-)	0.011
Present	25.0	25.0	5.00 (-)	
LVI				
Absent	83.3	59.4	- (-)	0.064
Present	57.1	44.4	48.00 (3.45-92.54)	
PNI				
Absent	76.4	56.8	- (-)	0.970
Present	83.3	54.0	- (-)	
STAS				
Absent	83.2	65.0	- (-)	0.008
Present	62.7	33.6	42.00 (22.79-61.20)	
Bronchial involvement				
Absent	79.3	57.5	- (-)	0.091
Present	50.0	33.3	20.00 (0.00-52.40)	
Surgical margin				
Negative	78.3	59.1	- (-)	0.009
Positive	66.7	-	33.00 (0.00-74.91)	
VPI				
Absent	76.4	58.1	- (-)	0.860
Present	80.2	43.8	53.00 (27.63-78.36)	
Tumor stage				
T1	82.2	61.2	- (-)	0.111
T2	64.8	41.6	52.00 (22.51-81.48)	
TNM stage				
Stage 1A1	61.5	52.7	- (-)	0.331
Stage 1A2	92.3	70.3	- (-)	
Stage 1A3	82.6	47.2	50.00 (-)	
Stage 1B	70.1	48.4	53.00 (-)	

ECOG=Eastern Cooperative Oncology Group, MBI=Main Bronchus Involvement, LVI=Lymphovascular Invasion, PNI=Perineural Invasion, STAS=Spread Through Air Spaces, VPI=Visceral Pleural Invasion, TNM=Tumor Nod Metastasis
Kaplan-Meier, Log-rank test, P<0.05 statistically significant

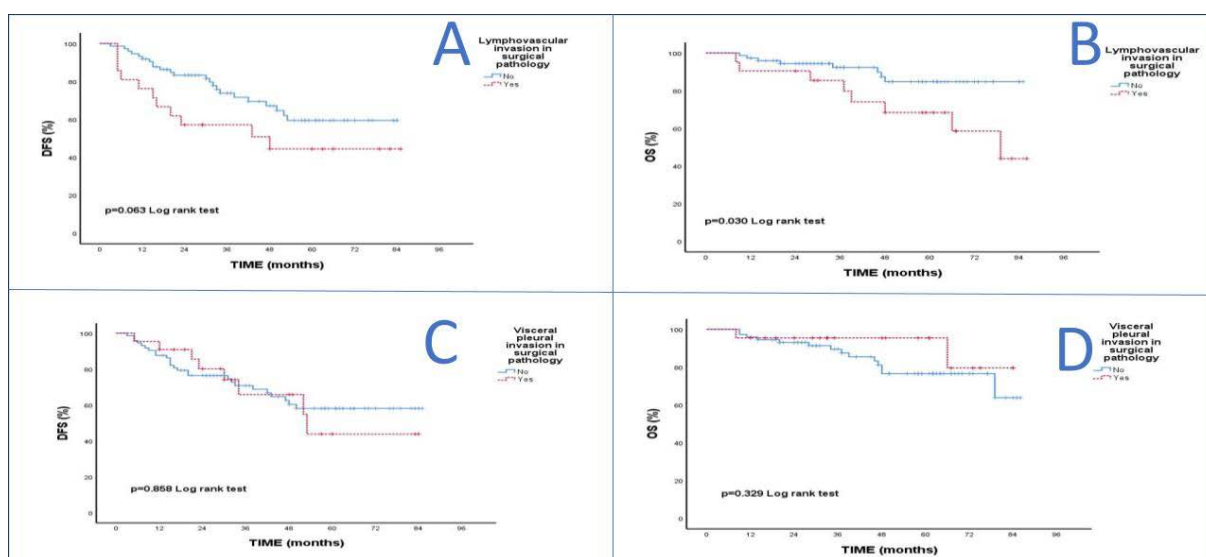


Fig. 1. Kaplan-Meier estimates for disease-free (A) and overall (B) survival, by lymphovascular invasion. Disease-free (C) and overall (D) survival, by visceral pleural invasion.

increased the recurrence risk by 2.79 times (HR: 2.79, 95% CI: 1.39-5.60, $P=0.004$), and SMP increased the recurrence risk by 4.35 times (HR: 4.35, 95% CI: 1.43-13.24, $P=0.019$).

In both patients who received and did not receive ACT, the median OS was not reached. The two-year OS rate was 95.5% in patients who did not receive ACT and 88.9% in those who did (Fig. 3). The five-

year OS rate was 80% in patients without ACT and 82% in those with ACT, with no statistically significant difference ($P=0.927$). Regarding DFS, the median DFS was 34 months in patients who received ACT, whereas it was not reached in those who did not receive it. The two-year DFS rate was 82.2% in patients without ACT and 64.6% in those with ACT. The five-year DFS rate was 56.7% in patients without ACT and

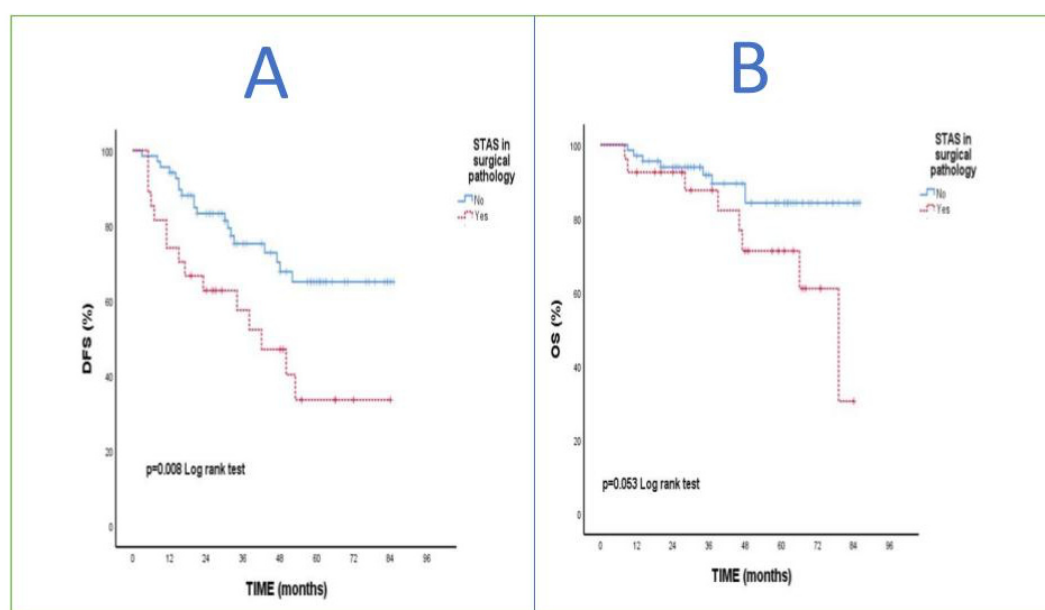


Fig. 2. Kaplan-Meier estimates for disease-free (A) and overall (B) survival, by STAS.

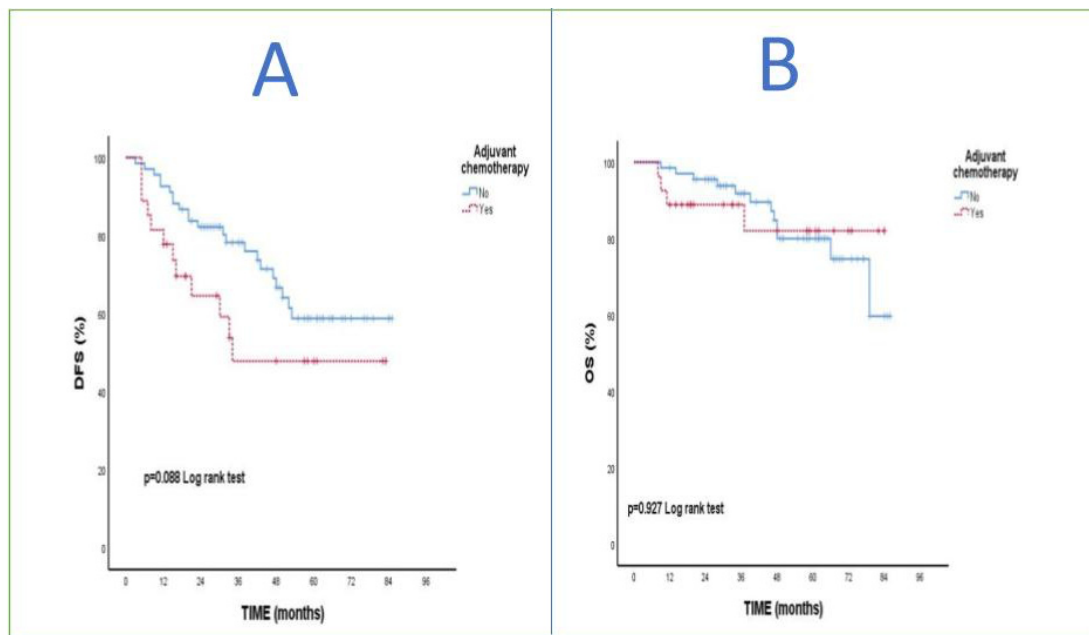


Fig. 3. Kaplan-Meier estimates for disease-free (A) and overall (B) survival, by adjuvant chemotherapy.

47.9% in those with ACT, with no statistically significant difference ($P=0.089$) (Fig. 3).

To assess the impact of adjuvant chemotherapy in high-risk patients a subgroup analysis was conducted. Among patients over 65 years old who did not receive adjuvant chemotherapy had a significantly longer DFS ($P<0.05$). However, in subgroup analyses based on other high-risk factors, no statistically significant difference was found in OS or DFS between patients who received adjuvant chemotherapy and those who did not (Fig. 4).

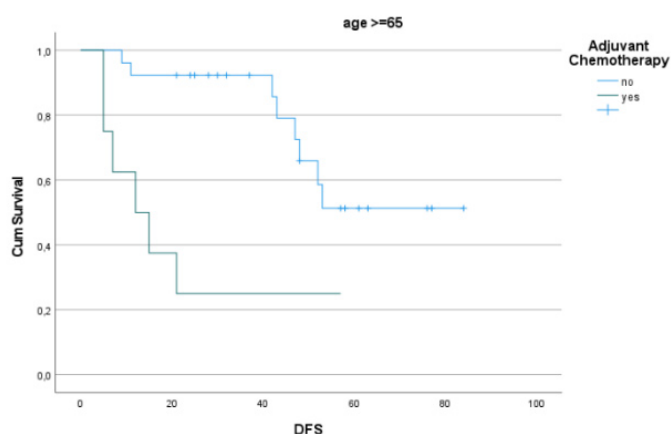


Fig. 4. Effects of adjuvant chemotherapy on disease-free survival in patients over 65 years old.

DISCUSSION

The identification of poor prognostic factors in stage I NSCLC patients is of great importance for predicting the course of the disease after surgery and optimizing adjuvant treatment strategies. However, no standardized consensus has been reached in the literature, and different variables are highlighted in various studies. In our study, while SCP, MBI, and STAS were found to be significant determinants of survival and recurrence, factors such as age, gender, histological subtype, ACT, LVI, and VPI - considered prognostically important in the literature - were not identified. It is well known that prognostic factors in stage I NSCLC are not consistently determined across studies and may vary between different patient populations. Our findings reflect this heterogeneity, emphasizing the need for standardization of prognostic markers in stage I disease and a more individualized, patient-centered approach.

STAS, which defines tumor spread through air spaces, is a histopathological feature increasingly recognized for its prognostic significance and is associated with poor prognosis in early-stage NSCLC [15]. While various studies have shown that anatomical resection may not be necessary for every stage I NSCLC

patient, it has been reported that wider surgical resections, such as lobectomy, provide better survival outcomes, particularly in STAS-positive patients [16]. Our study detected STAS positivity in 2 of the 16 patients who underwent wedge resection, and both experienced recurrences. In contrast, among the 14 STAS-negative patients, recurrence was observed in only 2 cases. Although further analysis could not be performed due to the small sample size, this finding supports the notion that wedge resection may be an inadequate surgical option for STAS-positive patients and that lobectomy may be a more appropriate approach [16, 17].

VPI is a crucial pathological finding indicating tumor extension to the pleural surface and, in the current TNM staging system, leads to an upgrade to T2 classification regardless of tumor size. This underscores the prognostic significance of VPI; however, some studies suggest that in smaller tumors, LVI may be a stronger prognostic factor than VPI [7]. In our study, LVI was found to be significant in univariate survival analysis, but its borderline significance in multivariate analysis suggests that this may be due to the small cohort size. The lack of a significant effect of VPI on survival or recurrence aligns with the literature suggesting that LVI may be biologically more aggressive than VPI in smaller tumors. Given that most of our patient population had tumors ≤ 3 cm, this could explain why VPI did not appear to have a significant impact [7, 18]. However, large-scale studies are needed to make a definitive conclusion on this matter.

Studies on prognostic factors in stage I NSCLC indicate that while some factors have well-established prognostic significance, others show variability. SMP and MBI have been identified in numerous studies as poor prognostic factors for survival and recurrence [16, 19, 20], and our study confirmed them as independent prognostic indicators. Conversely, factors such as age, male gender, and histological subtype have shown inconsistent prognostic value in the literature, and our study did not find a significant association between these variables and survival or recurrence [3, 21, 22]. This discrepancy may be due to differences in patient populations, treatment approaches, or the limited sample size. To improve prognostic accuracy in stage I NSCLC, larger-scale studies and the use of biomarkers are necessary.

The efficacy of ACT in stage I NSCLC remains

controversial, and proper identification of high-risk patients is essential. The LACE meta-analysis demonstrated that adjuvant chemotherapy provides a survival benefit for tumors larger than 4 cm but does not significantly contribute to smaller tumors [10]. Various studies have reported that adjuvant therapy improves survival in tumors >3 cm or those with positive VPI [23-25]. In our study, no significant survival difference was observed between patients who received ACT and those who did not, which may be attributed to the limited sample size and treatment selection heterogeneity.

In addition to conventional prognostic factors, recent research has investigated the prognostic and predictive value of biomarkers such as circulating tumor DNA (ctDNA). The literature suggests that preoperative ctDNA presence is associated with a high risk of recurrence in early-stage NSCLC patients and that these patients may derive greater benefit from adjuvant chemotherapy [26]. When considered alongside high-risk factors such as STAS and SMP, ctDNA is believed to be a valuable tool for guiding adjuvant therapy decisions. Although ctDNA was not assessed in our study, incorporating ctDNA into future research alongside standard prognostic factors may contribute to a more accurate determination of the need for adjuvant therapy in stage I NSCLC.

Our study confirms that STAS, LVI, SMP, and MBI are poor prognostic factors in stage I NSCLC, whereas VPI, age, gender, and histological subtype were not found to be significant. In subgroup analyses of adjuvant chemotherapy, it was concluded that adjuvant chemotherapy showed detrimental impact on DFS in patients aged over 65 and was ineffective in patients with other risk factors. However, these findings may be due to the small sample size and patient heterogeneity. The impact of adjuvant chemotherapy on survival remains unclear, necessitating better identification of high-risk patients. In the future, integrating biomarkers such as ctDNA with pathological factors like STAS and LVI may improve patient selection. Larger-scale studies are needed to establish personalized treatment approaches for stage I NSCLC.

Limitations

This study has some limitations. Its single-center retrospective design may limit generalizability, and the small sample size in certain subgroups may reduce statistical power, making it difficult to draw definitive

conclusions about the impact of adjuvant chemotherapy. Additionally, the absence of molecular biomarker analyses, such as ctDNA, restricts the ability to fully stratify high-risk patients. Another important limitation is the long study period, during which changes in staging systems and evolving chemotherapy indications may have influenced treatment decisions. This variability could have introduced heterogeneity into the study population, affecting the consistency of the results. However, a strength of this study is the inclusion of relatively novel prognostic factors, such as STAS. Future multicenter prospective studies incorporating molecular profiling may help refine risk stratification and optimize treatment strategies.

CONCLUSION

In this retrospective study, we identified key prognostic factors influencing recurrence and survival in stage I NSCLC patients who underwent surgical treatment. Our findings demonstrate that STAS, LVI, SMP, and MBI are significant predictors of poor outcomes, whereas VPI, age, sex, and histological subtype did not show a statistically significant impact on survival or recurrence. The role of ACT in stage I NSCLC remains inconclusive, as our analysis did not confirm a definitive survival benefit. However, our findings emphasize the importance of risk stratification to avoid both overtreatment and undertreatment in this patient population. Given the heterogeneity of prognostic factors, individualized treatment approaches remain crucial in optimizing outcomes. Emerging biomarkers such as ctDNA may offer additional insights into recurrence risk and could refine patient selection for adjuvant therapy. Future large-scale prospective studies incorporating molecular profiling and pathological markers such as STAS and LVI are needed to establish more precise prognostic models and personalized treatment strategies for stage I NSCLC. Our study contributes to the growing body of literature advocating for a standardized risk assessment model to guide treatment decisions in stage I NSCLC. By integrating both histopathological and molecular prognostic factors, we can improve risk-adapted therapy and enhance long-term survival in surgically treated NSCLC patients.

Ethical Statement

This study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethics Committee (Decision no: 2025/010.99/12/35 and date:24.01.2025) and was conducted in accordance with the principles of the Declaration of Helsinki.

Authors' Contribution

Study Conception: AD; Study Design: AD, SY, HNE; Supervision: GA, ZYY; Funding: AD, Nİ; Materials: AD, Nİ; Data Collection and/or Processing: AD, ZYY, ET; Statistical Analysis and/or Data Interpretation: AD, GA, ET; Literature Review: AD, HNE; Manuscript Preparation: AD, HNE; and Critical Review: SY, HNE, SAE.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Evaluation of APRI and FIB-4 indices in early and late-onset preeclampsia

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ABSTRACT

Objectives: This study aimed to evaluate the relationships between maternal and neonatal outcomes and the Fibrosis-4 Index (FIB-4) and Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) in healthy pregnancies, late-onset preeclampsia (LOP), and early-onset preeclampsia (EOP).

Methods: A retrospective study was conducted on 239 pregnant women diagnosed with EOP (n=62), LOP (n=56), and healthy pregnancies (n=121) at Etlik City Hospital. Maternal and neonatal outcomes, as well as APRI, and FIB-4 scores were compared. Statistical analyses included ANOVA, chi-square tests, and ROC curve analysis.

Results: EOP was associated with lower gestational age at birth, lower fetal birth weight, and higher NICU admission rates compared to LOP and control groups. APRI scores were significantly elevated in LOP compared to controls (P=0.012). FIB-4 scores were significantly higher in LOP than controls (P=0.005). ROC analysis showed modest predictive power for APRI (AUC=0.614) and FIB-4 (AUC=0.617) in distinguishing LOP from controls. The best cut-off values for APRI and FIB-4 were 0.2347 and 0.65, respectively.

Conclusions: Elevated APRI and FIB-4 scores in LOP suggest their potential roles as complementary markers in preeclampsia management. However, their moderate predictive performance indicates the need for further studies.

Keywords: Preeclampsia, APRI (Aspartate Aminotransferase-to-Platelet Ratio Index), FIB-4 (Fibrosis-4 Index)

Globally, preeclampsia remains one of the main causes of morbidity and mortality among mothers and newborns [1]. After 20 weeks of pregnancy, it is defined by newly developed hypertension and proteinuria, or in the absence of proteinuria, by the presence of disorders such as thrombocytopenia, poor liver function, or fetal growth limitation. Preeclampsia is broadly classified into early-onset preeclampsia (EOP), often presenting before 34 weeks

of gestation, and late-onset preeclampsia (LOP), which manifests later. Early-onset preeclampsia is frequently associated with placental dysfunction, leading to severe maternal and neonatal complications [2].

In recent years, studies on biomarkers aimed at predicting preeclampsia have appeared in the literature [3]. Among these, the Aspartate Aminotransferase-Platelet Ratio Index (APRI) emerged as a non-invasive marker that was initially developed to assess liver fi-

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brosis [4]. Elevated APRI scores have been shown to correlate with liver function impairment in various pregnancy-related conditions, including HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) and intrahepatic cholestasis of pregnancy. FIB-4, like APRI, is a non-invasive biomarker used to evaluate liver fibrosis. The pathophysiology of preeclampsia is believed to be associated with systemic inflammation and endothelial dysfunction. [5]. However, specific studies directly examining the use of FIB-4 in preeclampsia or other pregnancy-related conditions are limited.

Several studies have investigated the utility of APRI in predicting adverse maternal and neonatal outcomes. For instance, Tolunay *et al.* [6] demonstrated that elevated first-trimester APRI scores could predict the development of HELLP syndrome, with high sensitivity and specificity. Similarly, APRI has been explored as a potential predictor of superimposed preeclampsia in pregnancies complicated by chronic hypertension [7]. These results emphasize the potential role of APRI in identifying high-risk pregnancies early, facilitating timely interventions.

The present study aims to evaluate and compare APRI and FIB-4 scores among EOP, LOP and healthy pregnancies, with a focus on their associations with maternal and neonatal outcomes.

METHODS

This retrospective study was carried out at Etlik City Hospital Perinatology Clinic between January 2022 and November 2024. Women diagnosed with preeclampsia (early and late onset) and healthy pregnancies comprised the study group. Ethical approval was obtained prior to the initiation of the study. Ethical principles were followed throughout the study and all necessary precautions were taken to ensure patient privacy and data confidentiality in accordance with institutional regulations.

Clinical and laboratory data of the mothers and newborns were retrieved from the hospital's medical record system. EOP and LOP were defined according to ISSHP criteria [8]. The pregnancies included in the study consisted of three groups: EOP, LOP and healthy pregnancies. Women aged 18-45 who were diagnosed with preeclampsia or have a healthy pregnancy, whose

pregnancy follow-up and birth took place in our clinic were included in study. Exclusion criteria included pregnancies with systemic diseases, pregnancies with follow-up or delivery in another center, and pregnancies with fetal anomalies.

Data collection was performed retrospectively and included maternal blood pressure measurements, medications used, and laboratory parameters. The study collected maternal demographic data, preeclampsia-related information, ultrasound measurements, medications, maternal outcomes, complications associated with preeclampsia (e.g., HELLP syndrome, eclampsia, and severe hypertension), delivery methods and indications, birth weight, gestational age, and neonatal intensive care unit (NICU) requirements. The following formula was used to calculate the APRI: $(AST / \text{Upper Limit of Normal AST}) \times 100 / \text{Platelet count}$, where AST levels were measured in U/L, the upper limit of normal AST was defined based on laboratory reference ranges, and platelet counts were recorded in $\times 10^9/L$. The formula for calculating the FIB-4 index was: $(\text{Age} \times AST) / (\text{Platelet count} \times \sqrt{ALT})$.

Statistical Analysis

For the statistical analysis in this study, the Statistical Package for the Social Sciences (SPSS) software version 23.0 was used. Based on the results, appropriate parametric or non-parametric tests were applied after evaluating the normality of continuous variables. Non-parametric tests, such as the Mann-Whitney U test, were used for skewed data, whereas one-way ANOVA and Tukey post-hoc tests were applied for group comparisons of normally distributed variables. The chi-square test was also used to assess categorical variables. The diagnostic performance of the APRI and FIB-4 scores was evaluated using receiver operating characteristic (ROC) curve analysis. Sensitivity, specificity, and the area under the curve (AUC) were calculated using ROC analysis. The cut-off point was determined as the value that optimized the balance between sensitivity and specificity, ensuring both measures were maximized as much as possible.

RESULTS

The analysis of maternal age across the three groups did not reveal a statistically significant overall differ-

Table 1. Maternal demographic characteristics and laboratory findings

	Early preclampsia (n=62)		Late preclampsia (n=56)		P value	Post-Hoc comprasions P value		
	Early preclampsia (n=62)	Late preclampsia (n=56)	Control (n=121)	Control (n=121)		Early-late preclampsia	Early preclampsia- Control	Late preclampsia - Control
Maternal age (years)	30.19±5.84	30.46±6.58	28.48±5.27	28.48±5.27	0.057	0.965	0.139	0.085
BMI (kg/m ²)	33.85±6.68	33.91±6.34	29.05±4.30	29.05±4.30	0.001	NA	0.001	0.001
Gravidity	2±2	2±2	2±2	2±2	0.465			
Parity	0±2	1±2	1±2	1±2	0.415			
Living children	0±2	1±2	1±1	1±1	0.457			
Gestational age at diagnosis (weeks)	30.06±2.26	35.58±1.05			0.001			
Hemoglobin (g/dL)	12.0±1.40	11.69±1.44	11.5±1.32	11.5±1.32	0.139			
WBC (×10 ⁹ /L)	12.0±3.65	10.60±3.06	10.58±3.32	10.58±3.32	0.011	0.044	0.012	NA
Platelet (×10 ⁹ /L)	247.89±69.46	224.59±60.77	246.70±68.11	246.70±68.11	0.089			
AST (U/L)	18.5±10	18.0±9	16.0±6	16.0±6	0.020	NA	0.050	NA
ALT (U/L)	11.00±9	11.00±7	10.00 (4)	10.00 (4)	0.011	NA	0.011	NA
24-hour proteinuria (mg/24h)	634±2454	530±563			0.348			
APRI	0.22±0.17	0.25±0.12	0.20±0.10	0.20±0.10	0.014	NA	NA	0.012
FIB-4	0.66±0.42	0.73±0.53	0.59±0.36	0.59±0.36	0.020	NA	NA	0.005

Data are shown as mean±standard deviation or median (IQR). BMI=body mass index, WBC=white blood cell, AST=aspartate aminotransferase, ALT=alanine aminotransferase, APRI=AST to platelet ratio index, FIB-4=fibrosis-4 score.

Table 2. Comparasion of neonatal outcomes among EOP, LOP and control groups

	Early preclampsia (n=62)		Late preclampsia (n=56)		P value	Post-Hoc comprasions P value		
	Early preclampsia (n=62)	Late preclampsia (n=56)	Control (n=121)	Control (n=121)		Early-late preclampsia	Early preclampsia- Control	Late preclampsia - Control
Gestational age at birth (weeks)	34.31 ± 2.94	36.75 ± 1.11	38.55 ± 1.69	38.55 ± 1.69	0.001	0.001	0.001	0.001
Fetal birth weight (g)	2073±833	2696±583	3137±476	3137±476	0.001	0.001	0.001	0.001
Apgar 1 minute	8±3	9±1	9±1	9±1	0.001	0.001	0.001	NA
Apgar 5 minute	10±1	9±2	10±0	10±0	0.001	0.011	0.001	NA
C/S, n (%)	50 (80)	42 (75)	72 (60)	72 (60)	0.0071	NA	0.0042	0.0458
NICU, n (%)	36 (58.1)	14 (25)	13 (10.7)	13 (10.7)	0.001	0.044	0.012	NA

Data are shown as mean± standard deviation, median (IQR) or n (%) where appropriate. EOP=early-onset preclampsia, LOP= late-onset preclampsia, C/S=cesarean section, NICU=neonatal intensive care unit

ence ($P=0.057$). Maternal BMI was significantly higher in both preeclampsia groups compared to the control group ($P=0.001$). Gestational age at diagnosis was significantly earlier in the EOP group than in the LOP group ($P=0.001$). White blood cell counts (WBC) were significantly elevated in the EOP group compared to both the LOP and control groups ($P=0.011$). AST and ALT levels were higher in the EOP group compared to the control group ($P=0.020$ and $P=0.011$, respectively). Notably, the APRI score was significantly higher in the LOP group compared to the control group ($P=0.014$). The FIB-4 index showed significant differences among the groups ($P=0.020$), with post-hoc analysis revealing that the LOP group had significantly higher FIB-4 values compared to the control group ($P=0.005$) (Table 1).

Neonatal outcomes showed significant differences across the EOP, LOP, and control groups. Gestational age at birth was significantly lower in the EOP group compared to both the LOP and control groups ($P=0.001$). Similarly, fetal birth weight was lowest in the EOP group and highest in the control group ($P=0.001$). The 1-minute Apgar scores were significantly lower in the EOP group compared to the other groups ($P=0.001$), while the 5-minute Apgar scores were also significantly reduced in the LOP group compared to the control group ($P=0.011$). The rate of cesarean delivery was highest in the EOP group (80%),

followed by the LOP (75%) and control groups (60%; $P=0.0071$). NICU admission rates were significantly higher in the EOP group (58.1%) compared to the LOP (25%) and control groups (10.7%; $P=0.001$) (Table 2).

According to the ROC analysis results, APRI and FIB-4 demonstrated a statistically significant distinction between late-onset preeclampsia and control groups (APRI AUC: 0.614, $P=0.010$; FIB-4 AUC: 0.617, $P=0.008$). The cutoff point for APRI was determined to be 0.2347, with a sensitivity of 61% and a specificity of 60%. For FIB-4, the optimal cutoff point was 0.65, with a sensitivity of 57% and a specificity of 56% (Fig. 1).

Chi-square analysis was performed between the control group and the preeclampsia group based on the cutoff points determined for APRI and FIB-4. The proportion of individuals below the 0.23 cutoff point for APRI was 57.6% in the control group and 42.4% in the preeclampsia group, while the proportion of individuals above the cutoff point was 43.0% in the control group and 57.0% in the preeclampsia group ($P=0.024$). The rate of individuals below the 0.65 cutoff point for FIB-4 was 56.8% in the control group and 43.2% in the preeclampsia group, whereas the rate of individuals above the cutoff point was 43.9% in the control group and 56.1% in the preeclampsia group ($P=0.046$) (Table 3, Fig. 2).

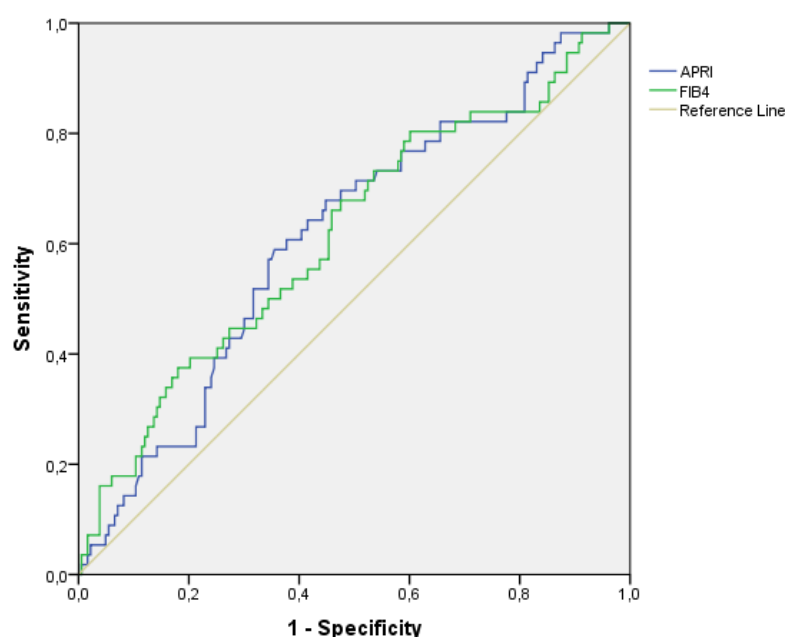


Fig. 1. ROC Curve for diagnostic performance evaluation.

Table 3. Distribution of APRI and FIB-4 according to cutoff values

Category	Group	Control)	Preeclampsia	Total
APRI (<0.23)	<0.23	72 (57.6%)	53 (42.4%)	125 (52.3%)
APRI (≥0.23)	≥0.23	49 (43.0%)	65 (57.0%)	114 (47.7%)
FIB-4 (<0.65)	<0.65	71 (56.8%)	54 (43.2%)	125 (52.3%)
FIB-4 (≥0.65)	≥0.65	50 (43.9%)	64 (56.1%)	114 (47.7%)

Data are shown as n (%). APRI= aspartate aminotransferase to platelet ratio index, FIB-4=fibrosis-4 score

Note: Counts and percentages for control and preeclampsia groups are presented based on the cutoff values for APRI (0.23) and FIB-4 (0.65).

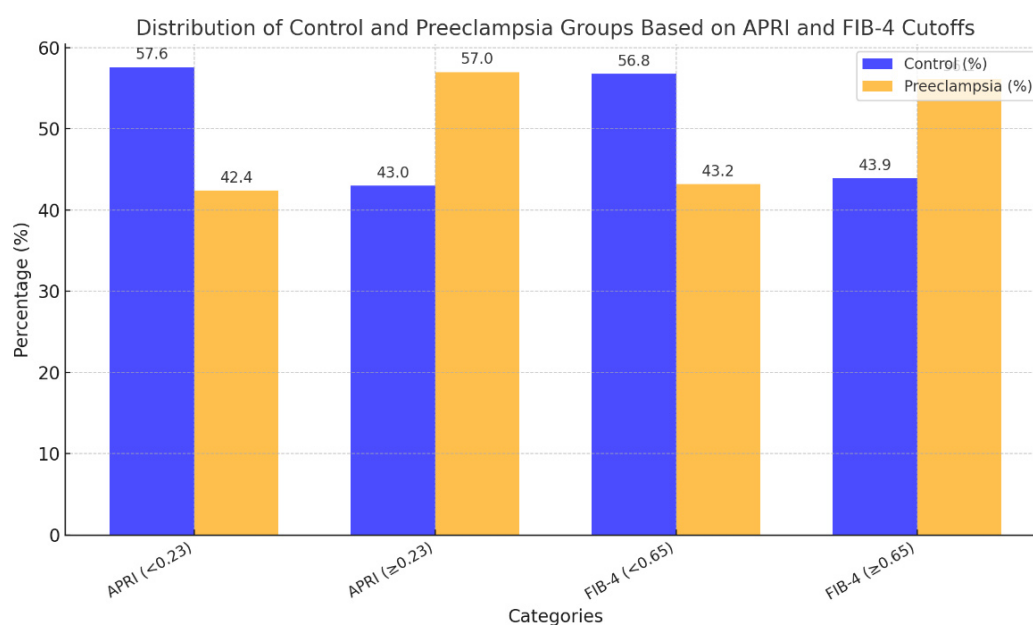
DISCUSSION

Our study identified significant differences in clinical and neonatal outcomes among the EOP, LOP, and control groups. EOP was associated with lower gestational age at birth, lower fetal birth weight, and higher NICU admission rates compared to the LOP and control groups. The APRI score in the LOP group was noticeably higher than that in the control group, while elevated white blood cell counts (WBC) were observed in the EOP group. These findings highlight distinct clinical profiles across the groups and emphasize the importance of these parameters in preeclampsia. Neonatal outcomes showed marked differences among the early-onset, late-onset preeclampsia, and control groups, with the most adverse outcomes observed in

the early-onset preeclampsia group, particularly in parameters such as gestational age, birth weight, Apgar scores, and NICU admissions.

Preeclampsia is a pregnancy-specific condition that complicates approximately 5% of all pregnancies [9]. Despite its relatively low prevalence, it holds significant importance among pregnancy complications due to its severe adverse maternal and fetal outcomes [10]. Preeclampsia and its complications account for 10-15% of maternal death. Perinatal morbidity and mortality rates are also markedly higher, especially in preeclampsia that begins before the 34th week [11]. These serious outcomes highlight the need for studies aimed at predicting and managing preeclampsia.

In this study, no statistically significant difference in maternal age was observed among the groups

**Fig. 2.** Distribution of control and preeclampsia groups according to APRI (0.23) and FIB-4 (0.65) cutoff values.

($P=0.057$). This finding aligns with existing literature, which identifies advanced maternal age as a risk factor associated with vascular and metabolic changes that predispose individuals to hypertensive disorders in pregnancy [12]. Nulliparity is also recognized as a potential risk factor for preeclampsia [12]. However, in our study, no significant difference was observed between the groups for gravida and parity ($P=0.465$ and $P=0.415$, respectively). BMI was significantly higher in both preeclampsia cohorts compared to the control group ($P=0.001$). High BMI is a known contributing factor to metabolic dysregulation, systemic inflammation, and endothelial dysfunction [13]. The similar BMI observed between the EOP and LOP groups suggests that obesity may contribute to the development of both subtypes, although the severity and onset may vary depending on other factors.

In our study, the WBC level in the EOP group (12.0 ± 3.65) was significantly higher than that in the LOP group (10.60 ± 3.06 ; $P=0.044$) and the control group (10.58 ± 3.32 ; $P=0.012$), but no significant difference was observed between the LOP and control groups. These findings highlight the role of the inflammatory response in preeclampsia. The literature describes preeclampsia as a systemic inflammatory condition, with leukocytosis considered an indicator of inflammation. Redman and Sargent [14] emphasized the relationship between preeclampsia, maternal immune system activation, and inflammatory processes. The AST and ALT levels in the early preeclampsia cohort were significantly higher compared to the control group ($P=0.050$ and $P=0.011$, respectively), but no significant difference was observed in the LOP group. These increases in AST and ALT levels can be considered indicators of liver dysfunction and HELLP syndrome in preeclampsia [15]. Bartal and Sibai [16] stated that preeclampsia may impair liver function, but these changes are generally limited in the early period. İpek *et al.* [17] investigated the efficacy of the APRI score assessed in the first trimester for predicting superimposed preeclampsia. In this retrospective case-control study, APRI scores at two different time points, designated as APRI1 and APRI2, were evaluated. The most appropriate cutoff value for APRI1 in predicting superimposed preeclampsia was determined to be 0.036, with a sensitivity of 65.2% and a specificity of 83.7%. The most appropriate cut-

off value for APRI2 was determined to be 0.057; at this threshold, sensitivity was reported as 67.4% and specificity as 52.0%. These findings suggest that APRI scores measured in the first trimester may serve as a potential marker for predicting the development of superimposed preeclampsia [17]. Although the APRI score is primarily used as a biomarker for assessing liver fibrosis, its elevation in preeclampsia patients has been linked to liver dysfunction and inflammation. In our study, APRI scores showed no significant difference between the early and late preeclampsia groups; however, they were significantly elevated in the late preeclampsia group compared to the control group ($P=0.012$). In the literature, Itakura *et al.* [18] highlighted that the APRI score serves as a non-invasive indicator of liver fibrosis in chronic liver disorders.

Our ROC analysis indicated that APRI and FIB-4 scores provided significant discrimination between late-onset preeclampsia and control groups. These findings suggest that both scores may be useful in evaluating cases of late-onset preeclampsia. However, the use of APRI and FIB-4 in the context of preeclampsia is limited in the literature. For instance, Yen *et al.* reported that APRI offers moderate sensitivity and specificity in diagnosing hepatic fibrosis, suggesting that the score may reflect inflammatory processes [18]. Similarly, there are some studies linking FIB-4 to extrahepatic conditions such as metabolic syndrome and hypertension [19]. Considering the systemic inflammation, endothelial dysfunction, and microvascular damage characteristic of the pathophysiology of preeclampsia, these two scores may provide meaningful discrimination. Nevertheless, given that the AUC values in our ROC analysis (0.614 for APRI and 0.617 for FIB-4) are in the low-to-medium range, these scores alone are insufficient as predictors and should be evaluated alongside other clinical and biochemical parameters.

The similarity in APRI and FIB-4 scores between the EOP and LOP groups suggests that these biomarkers might be more closely linked to liver function and levels of systemic inflammation rather than the timing of preeclampsia onset. However, further research with a larger patient population is necessary to clarify this distinction. Notably, our results show that the APRI and FIB-4 scores in the LOP group (0.25 ± 0.12 and 0.73 ± 0.53 , respectively) were higher than those in

both the EOP (0.22 ± 0.17 and 0.66 ± 0.42 , respectively) and control groups (0.20 ± 0.10 and 0.59 ± 0.36 , respectively), which aligns with the increased systemic inflammation and potential liver fibrosis associated with LOP [20]. Despite these findings, the difference between the LOP and EOP groups did not achieve statistical significance, likely due to the small sample size. In contrast, the difference between the LOP and control groups was statistically significant for both APRI ($P=0.012$) and FIB-4 ($P=0.005$). On the other hand, the absence of a difference between the EOP and control groups may be attributed to EOP typically reflecting a scenario limited to local placental dysfunction. The localized effects in EOP may not have led to a significant alteration in APRI and FIB-4, which assess systemic inflammation and liver function. These results underscore the necessity for larger studies to more effectively evaluate the role of APRI and FIB-4 in differentiating between preeclampsia subtypes.

Although APRI and FIB-4 are not sufficient as independent predictors of preeclampsia, they may be useful in risk stratification and management as complementary tools alongside existing clinical and biochemical markers. These scores can play a supportive role, particularly in the early diagnosis and follow-up of preeclampsia. However, larger-scale prospective studies are necessary to fully confirm the diagnostic and prognostic value of APRI and FIB-4 in the context of preeclampsia. Such studies are crucial to clarifying the role of these scores in clinical practice.

CONCLUSION

APRI and FIB-4 may be useful as supplementary tools in risk stratification and preeclampsia management, especially in late-onset cases, even though they are insufficient as stand-alone predictors. To verify their therapeutic usefulness and investigate how they might be integrated with current diagnostic frameworks, larger-scale, prospective investigations are needed.

Ethical Statement

This study was approved by the Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee (Decision no: AEŞH-BADEK-2024-1143, and date: 11.12.2024). Ethical principles were followed throughout the study and all necessary precautions

were taken to ensure patient privacy and data confidentiality in accordance with institutional regulations.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contribution

Study Conception: NVT; Study Design: NVT, GK; Supervision: ATÇ; Funding: GK, ZŞ; Materials: GA, SÇ; Data Collection and/or Processing: GA; Statistical Analysis and/or Data Interpretation: NVT; Literature Review: BTÇ; Manuscript Preparation: NVT; and Critical Review: NVT, ATÇ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Corticosteroids and rising tide in femoral head avascular necrosis following COVID-19: A critical analysis

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ABSTRACT

Objectives: During the COVID-19 pandemic, increased corticosteroid use to treat severe cases has been linked to a rise in femoral head avascular necrosis (FHAVN) cases post-recovery. This study evaluated FHAVN patients referred to an outpatient clinic after COVID-19, focusing on the severity of FHAVN related to corticosteroid use, and aimed to connect the drug dosage, and disease grade.

Methods: The study was prospectively designed. Patients diagnosed with FHAVN who received corticosteroids for COVID-19 were included. Data collected included demographic information, medical history, corticosteroid dosage, and magnetic resonance imaging results for radiological grading.

Results: A total of 48 patients were evaluated, with a mean age of 46.13 years. A significant majority (81.3%) of the respondents had bilateral FHAVN. The patients received a mean prednisolone equivalent dose of 1295.16±857.98 mg over approximately 18 days. This study found a significant positive correlation between the severity of FHAVN and the dosage and total corticosteroid treatment time.

Conclusions: The findings indicate that the severity of FHAVN is correlated with corticosteroid use. Although corticosteroids have shown benefits in severe COVID-19 cases, their prolonged and high-dose administration poses risks, including the development of FHAVN.

Keywords: Avascular necrosis, corticosteroids, COVID-19

Femoral head avascular necrosis (FHAVN) is an aseptic osteonecrosis resulting in osteocyte death due to impaired blood supply to the proximal femur. FHAVN can occur due to ischemia in a traumatic or non-traumatic background. The most

common etiological factors are corticosteroid therapy, fractures, hip joint dislocation, and alcohol abuse. It typically affects physically active individuals between 20 and 40 years old. Symptoms of this condition usually include hip pain, limited range of motion, and

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limping [1]. Non-traumatic osteonecrosis of the femoral head is one of the leading causes of disability in young individuals and results in significant healthcare expenditure [2].

Corticosteroids are widely used to treat rheumatic, autoimmune, and allergic diseases. Mechanisms such as impaired microcirculation in the femoral head, imbalance between osteogenic and adipogenic differentiation, fat embolism, coagulation disorders, and intramedullary pressure change have been proposed for the pathophysiology of FHAVN caused by corticosteroids. Among the various mechanisms of steroid-induced FHAVN, the vascular hypothesis is the most compelling and influential. Bone endothelial cells, which include bone microvascular endothelial cells and endothelial progenitor cells, play a crucial role in maintaining vascular homeostasis. Therefore, these bone endothelial cells are key regulators in both the occurrence and progression of steroid-induced FHAVN. Dysfunction of bone endothelial cells can lead to impaired angiogenesis, abnormal apoptosis, thrombosis, and fat embolism, all of which are considered to contribute to the pathogenesis of steroid-induced FHAVN [3].

During the COVID-19 pandemic, corticosteroids were extensively used to slow down the pulmonary inflammatory cascade and prevent cytokine storms in severely ill patients. However, a significant proportion of patients who survived steroid treatment developed avascular necrosis with rapid and aggressive destruction of the femoral heads [4-6]. The long-term consequences of COVID-19, including unfavorable non-pulmonary complications following recovery, have created a physical, psychological, and financial burden on patients, relatives, and healthcare systems [7-9].

This study aimed to assess FHAVN patients referred to our outpatient clinic after the COVID-19 pandemic. The principal objective of this study was to understand the severity of FHAVN caused by corticosteroid use in patients with COVID-19 and to establish a connection between the drug dosage, total corticosteroid treatment time, and disease stage. Our secondary objective was to conduct a comprehensive review of the existing literature and evaluate the scientific and rational basis for the dosage and duration of corticosteroids used to treat severe cases of

COVID-19. In addition, we sought to provide recommendations to minimize the risk of FHAVN in similar scenarios in the future.

METHODS

The study was initiated after approval from the Kayseri City Hospital Clinical Research Ethics Committee (Decision no: 738 and date: 08.11.2022). The sample size was determined to be 45, with a power of 80% (beta) and a type I error rate of 0.05 (alpha). This calculation was performed using the G*Power software (version 3.1.9.7, 2020) developed by the University of Düsseldorf, Germany, for Windows 10 with references from similar studies in the literature. Patients referred to our outpatient hyperbaric medicine clinic between November 2022 and November 2023 who were clinically and radiologically diagnosed with FHAVN and received corticosteroid treatment due to COVID-19 were prospectively included in the study. COVID-19 diagnosis was made objectively by scanning past patient information through the hospital automation system and seeing PCR test positivity. Also, the patient's corticosteroid treatment was determined objectively by scanning the patient's past hospitalization information through the hospital automation system (time to start corticosteroid treatment, corticosteroid dose, and duration of corticosteroid treatment). Before their involvement in the study, all patients were provided with a comprehensive document delineating the study objectives and procedures. Patients were invited to raise any queries about the document's contents, and their signatures were obtained to indicate their willingness to participate in the study.

The following data were included in the study: age, gender, height, weight, body mass index, smoking habit, history of COVID-19 infection, and use of corticosteroids. The time interval between the onset of FHAVN symptoms and the diagnosis of COVID-19 was documented. The duration and dosage of corticosteroid therapy received by patients with COVID-19 infection treated with corticosteroids were also recorded. The doses of dexamethasone and methylprednisolone administered to patients were converted to prednisolone equivalent doses according to the formulas we present below for comparison with other

steroids. In this calculation, prednisolone and prednisone are typically considered equivalent, and 5 mg of each equals. Other conversions include: 4 mg of methylprednisolone, 0.75 mg of dexamethasone, and 20 mg of hydrocortisone, all equivalent to 5 mg of prednisolone [10].

To ensure standardization, radiological FHAVN diagnosis was made by a single radiologist experienced in this field and immediately after magnetic resonance imaging of the patients according to the Ficat grading system [11]. In patients with bilateral FHAVN, the side with the higher grade was considered the patient's grade.

Patients who did not undergo MRI, whose corticosteroid doses could not be quantified, who received corticosteroid treatment for both COVID-19 and other reasons, and who had a confirmed diagnosis of COVID-19 infection but did not receive corticosteroids as a result of that infection were excluded from the study.

Statistical Analysis

The data collected from the study were analyzed using the SPSS 24.00 software. Descriptive statistics were calculated, such as mean, median, percentage, and number of observations. The Kolmogorov-Smirnov test assessed whether the data followed a normal distribution. For normally distributed measurements, an independent groups t-test was applied for data sets comprising two groups. One-way ANOVA and Kruskal Wallis tests were used to compare more than two groups. Post hoc analysis of significance between Ficat grade groups was performed with one-way ANOVA and post hoc Tukey's test according to the homogeneity test result. After the Kruskal Wallis test, Bonferroni correction and Mann Whitney U test were used. A p-value of less than 0.05 at a 95% confidence interval was considered significant for statistical significance. In post hoc analysis, significance was accepted as significant at values below 0.017 for Ficat grade subgroups with Bonferroni correction, and adjusted P values were used in other post hoc evaluations. The Chi-square (X²) test was used to compare categorical variables. Pearson's and Spearman's correlation analysis examined the relationship between patient data and grades. The statistical tests used in creating the tables are stated as footnotes under all tables.

RESULTS

A total of 48 patients were included in the study. Of the patients, the mean age was 46.13 ± 13.33 years and FHAVN was found bilaterally in 81.3% (Table 1). Patients were treated with prednisolone at a dose equivalent to 1295.16 ± 857.98 mg for 17.85 ± 11.88 days.

The correlation between patient data and Ficat grade was analyzed, and a significant positive correlation was found between prednisolone dose and Ficat grade ($r=0.379$, $P=0.008$), and a significant positive correlation was found between total corticosteroid treatment time and Ficat grade ($r=0.306$, $P=0.035$). The Ficat grade increased with increasing prednisolone dose and total corticosteroid treatment time (Tables 2 and 3, Fig. 1).

A high positive correlation between prednisolone dose and total corticosteroid treatment time was also identified with the Pearson correlation test, $r = 0.678$ and $P < 0.001$ (Fig. 2). It is determined that the pred-

Table 1. Demographic characteristics and diagnostic profiles of patients

Variables	Data
Age (years)	46.13±13.33
Height (cm)	170.50±9.29
Weight (kg)	84.77±14.21
Prednisolone dose (mg)	1295.16±857.98
Gender, female	17 (35.4)
Smoking habit, yes	8 (16.7)
Location, bilateral	39 (81.3)
BMI (kg/m ²)	
< 24.9	9 (18.8)
25-29.9	20 (41.7)
>30	19 (39.9)
Ficat grade	
Grade 2	21 (43.8)
Grade 3	19 (39.6)
Grade 4	8 (16.7)
Total corticosteroid treatment time (days)	17.85 ± 11.88

Data are shown as mean±standard deviation or median (minimum-maximum) where appropriate. BMI=body mass index

Table 2. Correlation between the severity of the grade and patient data.

Patient data	Grade gegree	
	r	P value
Age	0.177	0.229**
BMI	0.134	0.364**
Height	-0.173	0.240**
Weight	0.033	0.826**
Gender	0.174	0.237*
Smoking habit	0.230	0.116*
Prednisolone dose	0.379	0.008*
Total corticosteroid treatment time	0.338	0.019**

BMI_body mass index, r=correlation coefficient.

*Spearmen's rho test, **Pearson correlation test

nisolone dose increases as the total corticosteroid treatment time increases.

The mean time between the start of corticosteroid treatment and FHAVN diagnosis was 10.88±6.29 months. No correlation was found between the time between corticosteroid treatment - FHAVN diagnosis and Ficat grade with an $r = 0.080$ and $P=0.589$ (Pearson correlation test).

DISCUSSION

The present study identified a correlation between the severity of FHAVN and increased corticosteroid dose and total corticosteroid treatment time. Corticosteroids are frequently administered to patients with severe

COVID-19 during the ongoing pandemic. However, at the onset of the pandemic, several studies raised concerns about the use of corticosteroids in this context [12, 13]. A systematic literature review has indicated that the administration of corticosteroids does not result in a reduction in mortality rates or a decrease in hospitalization durations among patients diagnosed with Severe Acute Respiratory Syndrome (SARS) or Middle East Respiratory Syndrome (MERS) [14]. Studies in this review highlight the importance of corticosteroid dosage and total corticosteroid treatment time. The World Health Organization (WHO) initially issued a recommendation against the routine utilization of corticosteroids for the management of viral pneumonia. This advice was grounded in the understanding that the use of corticosteroids carries with it

Table 3. Relationship between treatment parameters and Ficat grade

Variable	Ficat grade 2	Ficat grade 3	Ficat grade 4	P value
Prednisolone dose (mg) ^a	1013.30 (50.00-2.500.00)	1.352.00 (266.70-4.076.7)0	1.939.46 (793.30-2913.30)	0.030*
Total corticosteroid treatment time (days) ^b	14.86 ± 7.70	17.16 ± 14.48	27.38 ± 10.38	0.034**
Time between FHAVN diagnosis and corticosteroid treatment (months)	10.67 ± 7.41	10.42 ± 5.84	12.50 ± 4.11	0.729**

Data are shown as mean±standard deviation or median (minimum-maximum) where appropriate.

*Kruskal Wallis Test, ** One-Way ANOVA test,

^aMann Whitney U test, In the subgroup analysis, a difference was identified between Grade 2 and Grade 4 with $P=0.010$ in favor of group 4.

^bTukey's test, In the subgroup analysis a difference was identified between Grade 2 and Grade 4 with $P=0.028$ in favor of group 4.

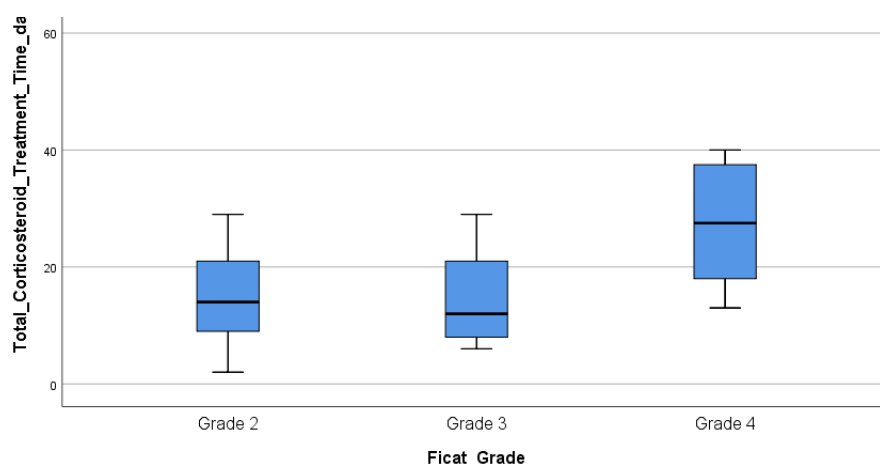


Fig. 1. Histogram showing the relationship between total corticosteroid treatment time (day) and Ficat grade.

a series of potential risks, including the possibility of delayed viral clearance and an elevated mortality risk [15]. Furthermore, the presence of viral RNA was observed to be persistent in patients receiving corticosteroids, indicating a potential delay in recovery.

The publication of the results of the RECOVERY study has precipitated a major shift in the approach to the treatment and study of patients with COVID-19 [16]. Following this development, the WHO recommended administering systemic corticosteroids to patients with severe or critical COVID-19, rather than not administering them [17].

Despite concerns about the use of corticosteroids,

some studies suggest that low-dose corticosteroids may lower mortality in patients with severe COVID-19, particularly among those on mechanical ventilation [18]. Moreover, the early administration of corticosteroids in severe cases has been associated with better clinical outcomes [19]. However, administration of high-dose corticosteroids has been associated with an elevated risk of bacteremia [20].

It was highlighted that long-term, high-dose corticosteroid use during the pandemic contributed to the development of FHAVN, underscoring the importance of caution when administering corticosteroids to patients with confirmed or suspected COVID-19 infec-

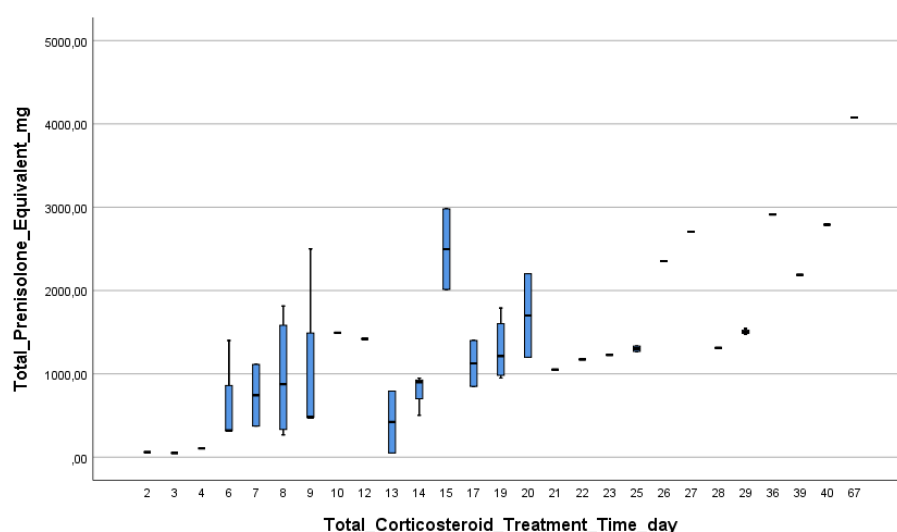


Fig. 2. Histogram of total prednisolone equivalents versus total corticosteroid treatment time (day).

tion. Based on experience following the SARS outbreak in 2003, an incidence of FHAVN from 23% to 28.8% was reported in patients receiving corticosteroids [21]. In a systematic review, individuals who developed FHAVN after COVID-19 used corticosteroids for an average of 24.8 ± 11 days, with a mean prednisolone equivalent dose of 1238.5 ± 492.8 mg. In detail the systematic review analyses 14 studies of which only six mention the steroid dose. Of these six, three report a higher, and the other three report a lower than the steroid dose in our study. Similarly, the total corticosteroid treatment time is presented in nine reports. Seven of them report a longer time than our study [22]. In our study, patients used an average prednisolone equivalent dose of 1295.16 ± 857.98 mg for 17.85 ± 11.88 days. The dosage and the total corticosteroid treatment time vary between studies, and our results do not contradict these findings.

Non-COVID-19 and corticosteroid-induced AVN tend to occur in multiple sites, as shown in studies of SLE patients receiving long-term glucocorticoid therapy. The reported proportion of patients with AVN involving more than two joint sites ranges from 70% to 90% in several case series. Furthermore, the hip was the most common site of involvement, with bilateral hip involvement occurring in 72% of patients [23]. The present study reports an 81.3% bilateral FHAVN rate, which may suggest that the development of FHAVN is not solely dependent on corticosteroids, but may also be influenced by other factors in the context of COVID-19 infection. The potential mechanisms contributing to the development of FHAVN in COVID-19 infection include the release of cytokines that inhibit bone cell growth, ACE2 deficiency contributing to bone loss, and a hypercoagulable state caused by systemic inflammation, microthrombus formation, and other factors [24, 25].

It is feasible to avoid the recurrence of this catastrophic outcome in similar circumstances in the future, contingent on a more profound understanding of the disease. It is hypothesized that genetic factors play a significant role in the development of avascular necrosis in patients diagnosed with COVID-19. The utilization of biomarkers may help identify high-risk individuals [26]. In some studies, it is claimed that “the administration of nutritional supplements [27]” or “bisphosphonates, anticoagulants, vasodilators, and traditional Chinese medicine may be considered in

combination with extracorporeal shock wave therapy (ESWT), hyperbaric oxygen (HBO), and other physical therapies [21]” could help in reducing the risk of developing FHAVN. Further research in these areas will undoubtedly provide valuable insights.

CONCLUSION

Our study demonstrated that the severity of FHAVN is correlated with the dosage of corticosteroid therapy and total corticosteroid treatment time. Studies examining corticosteroid-associated FHAVN in COVID-19 have identified a high rate of prolonged and high-dose corticosteroid use. In light of this evidence, it seems reasonable to conclude that high-dose and long-term corticosteroid administration may be a riskier approach for treating severe COVID-19-like conditions in terms of the potential risk of FHAVN. Although challenging, implementing personalized treatment strategies and comprehensive evaluation may prove an effective means of preventing a similar post-pandemic FHAVN pandemic in the future.

Ethical Statement

This study was approved by the Kayseri City Hospital Clinical Research Ethics Committee (Decision no: 738 and date: 08.11.2022).

Authors' Contribution

Study Conception: LD, MA, MÖ, MŞT, SK; Study Design: LD, MK, MÖ, MŞT; Supervision: LD, MA, TYU, SK; Funding: LD, TYU, MK, SK; Materials: LD, TYU, MK, SK; Data Collection and/or Processing: LD, MA, TYU, SK; Statistical Analysis and/or Data Interpretation: LD, MÖ, MŞT; Literature Review: LD, MK, MŞT; Manuscript Preparation: LD, MA, MÖ; and Critical Review: LD, MA, TYU, MÖ, MŞT, SK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Comorbidity results of an obesity center

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ABSTRACT

Objectives: Obesity is linked to numerous severe health conditions, including type 2 diabetes mellitus, heart disease, hypertension, and stroke. This study aimed to compare metabolic parameters and anthropometric measurements between male and female patients with obesity to identify gender-based differences in obesity-related health markers.

Methods: This prospective study enrolled 393 obese patients (52 male, 341 female) from an outpatient clinic. After an overnight fast (8-10 hours), blood samples were collected to assess a range of parameters: complete blood count, fasting blood glucose, insulin, Hemoglobin A1c (HbA1c), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Thyroid-stimulating hormone (TSH), total cholesterol, triglycerides, Low-density lipoprotein (LDL), High-density lipoprotein (HDL), 25-hydroxy vitamin D3 (25OHD3), ferritin, iron, and vitamin B12. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and Body Mass Index (BMI) were calculated, while soft lean mass (SLM) and percent body fat (PBF) were also analyzed.

Results: Males with obesity had significantly higher levels of insulin, HOMA-IR, 25OHD3, ferritin, iron, hemoglobin, hematocrit, urea, and ALT compared to females ($P<0.05$ for all). Conversely, males had lower HDL and platelet levels ($P<0.05$). The prevalence of thyroid disease was significantly higher in females ($P=0.027$).

Conclusions: Thyroid disease prevalence was significantly higher in females compared to males. Additionally, metabolic parameters such as insulin, HOMA-IR, and urea were elevated in females, while HDL and platelet levels were lower in males.

Keywords: Obesity, insulin resistance, metabolic parameters, diabetes mellitus, body mass index

The obesity pandemic is expanding globally at an accelerating rate, affecting not only adults but also children and adolescents, irrespective of socioeconomic status. It is recognized as a significant health issue that strains healthcare systems and increases costs at every level [1]. According to a World Health Organization (WHO) report, it is estimated that 1 billion people worldwide will suffer from

obesity by 2030, with one out of every five women and one out of every seven men [2]. The World Obesity Federation (WOF) forecasts that by 2035, 1.9 billion people will be obese, equating to one in four individuals [3]. Childhood obesity is expected to increase by 100%, and the global economic burden of obesity will reach 4.32 trillion dollars in the next decade [4].

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This issue is also significant in our country, where 24.8% of women are obese, and 30.4% are classified as pre-obese. The obesity rate in men is 17.3%, with 39.7% in the pre-obese category [5]. Socioeconomic status, age, and gender are key factors contributing to the rise of obesity and related diseases.

In insulin resistance, the pancreas continues to produce and secrete insulin, but target cells fail to respond adequately to blood insulin concentrations [6]. This resistance primarily affects the liver, muscles, and adipose tissue, and is a common complication of obesity, forming a major criterion for metabolic syndrome [7]. Despite many studies aiming to clarify the mechanisms of insulin resistance, its exact etiology remains unclear. However, low-grade chronic inflammation in adipose tissue is believed to be a primary cause in the early stages of insulin resistance development [6-7]. Elevated C-reactive protein (CRP) levels are used clinically to detect inflammation, and deactivating the genetic structures affecting insulin function has been shown to reduce inflammation and improve glucose metabolism. Inflammation in adipose tissue decreases as circulating insulin levels drop. Insulin resistance is present in 90% of patients with Type 2 Diabetes Mellitus (T2DM), and the risk of cardiovascular disease is doubled in these patients [8].

Obesity is associated with numerous severe diseases, including T2DM, heart disease, hypertension, and stroke. A weight gain of 6-8 kg doubles the risk of developing T2DM compared to individuals who do not gain weight. Additionally, obesity is linked to several types of cancer (breast, endometrial, prostate, colon, and gallbladder), hypoxia, sleep apnea, hernias, and arthritis. Obesity-related disorders include insulin resistance (T2DM), lipoprotein metabolism disorders, cardiovascular issues (low high-density lipoprotein [HDL], hypertriglyceridemia, increased low-density lipoprotein [LDL], fibrinolytic anomalies, atherothromboscclerosis), hypertension (metabolic syndrome), and gastrointestinal disorders (reflux esophagitis, hiatal hernia, gallstones, hepatosteatosi, and steatohepatitis) [9].

The most effective long-term strategy for managing T2DM is weight loss. However, certain medications and physiological factors in the hypothalamus cause patients to regain weight, reducing feelings of satiety and increasing hunger. Early treatment of insulin resistance and reducing Body Mass Index (BMI)

to near-normal levels can help prevent the progression of diabetes [10].

This study aims to provide a descriptive comparison of metabolic parameters and anthropometric measurements, such as BMI, Soft Lean Mass (SLM), and Percent Body Fat (PBF), with respect to gender.

METHODS

This prospective study enrolled 393 patients (52 male, 341 female) diagnosed with obesity at our institution's outpatient clinic. All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (both institutional and national) and in line with the Helsinki Declaration of 1975, as revised in 2008. Ethical approval was obtained from our institution's ethics committee (protocol number 2021/514/208/11), and informed consent was secured from all participants.

Baseline demographic information, including age, gender, and treatment regimens, was obtained from hospital records. After an 8-10 hour fasting period, blood samples were collected to assess complete blood count, fasting blood glucose, insulin, Hemoglobin A1c (HbA1c), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Thyroid-stimulating hormone (TSH), total cholesterol, triglycerides, LDL, HDL, 25-hydroxy vitamin D3 (25OHD3), ferritin, iron, and vitamin B12. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated using the formula: $\text{fasting blood glucose (mg/dL)} \times \text{insulin } (\mu\text{IU/mL}) / 405$. BMI was calculated (kg/m^2), and additional anthropometric measurements, such as SLM and PBF, were assessed using the Tanita MC-580 body composition analyzer (TANITA, MC-580, Japan).

Patients with a BMI $> 30 \text{ kg/m}^2$ were included in the study, while individuals under 18 or over 80 years of age, pregnant women, and those who had undergone gastrointestinal obesity surgery were excluded.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 26.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard

deviation for continuous data were given as descriptive values. The distribution of the data was checked using the Kolmogorov-Smirnov test. Parameters with normal distribution were presented as mean and standard deviation, while those with non-parametric distribution were expressed as median and interquartile range. Categorical parameters were reported as count and percentage. $AP < 0.05$ was accepted as significant. For comparisons between groups, the “Independent Sample T-test” was used for two groups, and the “Pearson Chi-Square Test” was used to compare categorical variables. The results were considered statistically significant when the P-value was less than 0.05.

RESULTS

A total of 393 patients (52 male, 341 female) were enrolled in this prospective study. The general characteristics of the patients are shown in Table 1. The gender distribution was 86.8% female and 13.2% male. Male patients had significantly lower PBF levels, but significantly higher SLM and waist/hip ratios compared to females ($P < 0.001$, $P = 0.004$ and $P < 0.001$, respectively). The distribution of diseases we detected together with obesity in patients are shown in Table 2. The prevalence of thyroid diseases was significantly higher in females than in males ($P = 0.027$). There was

Table 1. Baseline demographics of the study population

		Gender			P value*
		Total (n=393)	Male (n=52)	Female (n=341)	
Age (years)		46.8±12.2 (17-86)	48.3±12.8 (18-69)	46.6±12.1 (17-86)	0.356 [#]
Education	0 (illiterate)	28 (7.1)	1 (1.9)	27 (7.9)	<0.001
	1 (primary)	240 (61.1)	22 (42.3)	218 (63.9)	
	2 (high school)	76 (19.3)	17 (32.7)	59 (17.3)	
	3 (university)	49 (12.5)	12 (23.1)	37 (10.9)	
Job	No	297 (75.6)	23 (44.2)	274 (80.4)	<0.001
	Yes	96 (24.4)	29 (55.8)	67 (19.6)	
Exercise	0 (no walk)	273 (69.5)	42 (80.8)	231 (67.7)	0.163
	1 (2day/w walk)	51 (13.0)	4 (7.7)	47 (13.8)	
	2 (5day/w walk)	69 (17.6)	6 (11.5)	63 (18.5)	
Weight (kg)		101.4 (91-113.8)	114.8 (103-130.3)	99.8 (89.8-111.7)	<0.001 [£]
Height (cm)		160 (155-165)	172 (167.3-177)	159 (155-163.5)	<0.001 [£]
BMI (kg/m²)		39.1 (35.2-43.7)	39 (35.2-43.5)	39.2 (35-43.9)	0.560 [£]
BMI	Obese	215 (54.7)	29 (55.8)	186 (54.5)	0.875
	Morbid obese	153 (38.9)	19 (36.5)	134 (39.3)	
	Super obese	25 (6.4)	4 (7.7)	21 (6.2)	
PBF		40.9 (36.3-44)	35.3 (32.6-39)	41.5 (37.6-44.5)	<0.001
SLM		50.2 (42.9-57.6)	61.5 (35.1-73.9)	50 (43-56)	0.004
Waist/Hip		0.96 (0.92-1)	1.01 (0.97-1.06)	0.95 (0.91-0.99)	<0.001
Cigarette		132 (33.6)	22 (42.3)	110 (32.3)	0.153

Data are shown as mean±standard deviation (minimum-maximum) or median (IQR) or n (%) where appropriate. BMI=Body mass index, PBF=Percentage of body fat, SLM=Smooth lean mass

[#]Student t Test *Chi Square Test

also a significant difference in the nutritional habits between the gender groups ($P<0.001$). The frequency of comorbidities according to gender is shown in Fig. 1.

Insulin, HOMA, 25OHD3, ferritin, iron, hemoglobin, hematocrit, urea, and ALT levels were significantly higher in males, while HDL and platelet levels were lower compared to females ($P=0.003$, $P=0.007$, $P=0.022$, $P<0.001$, $P=0.007$, $P<0.001$, $P<0.001$,

$P=0.042$, $P=0.004$, $P<0.001$ and $P=0.004$, respectively). Additionally, insulin, HOMA-IR, ferritin, creatinine, ALT, and hemoglobin levels were higher in males, while iron and hematocrit levels were normal, with higher rates of high HDL and low HDL in males than in females ($P=0.021$, $P=0.029$, $P=0.023$, $P<0.001$, $P=0.001$, $P=0.007$, $P<0.001$, $P=0.012$ and $P=0.016$, respectively). Laboratory results are shown in Table 3.

Table 2. Distribution of diseases in study group

Diseases, n (%)	Total (n=393)	Male (n=52)	Female (n=341)	P value*
Diabetes mellitus	127 (36.1)	14 (31.8)	113 (36.7)	0.529
Pre-diabetes mellitus	94 (23.9)	11 (21.2)	83 (24.3)	0.616
Hypertension	137 (34.9)	22 (42.3)	115 (33.7)	0.226
Thyroid disease	102 (26.0)	7 (13.5)	95 (27.9)	0.027
Anemia	26 (6.6)	1 (1.9)	25 (7.3)	0.228
Cardiovascular disease	36 (9.2)	6 (11.5)	30 (8.8)	0.604
Asthma	50 (12.7)	9 (17.3)	41 (12.0)	0.287
Hyperlipidemia	29 (7.4)	2 (3.8)	27 (7.9)	0.401
Depression	29 (7.4)	1 (1.9)	28 (8.2)	0.152
Polycystic over syndrome	15 (3.8)	0 (0.0)	15 (4.4)	0.237
Cancer	7 (1.8)	1 (1.9)	6 (1.8)	1.000
Rheumatic disease	18 (4.6)	1 (1.9)	17 (5.0)	0.488
Epilepsy	3 (0.8)	0 (0.0)	3 (0.9)	1.000
Sleep apnea syndrome	16 (4.1)	4 (7.7)	12 (3.5)	0.246
Osteoporosis	10 (2.5)	1 (1.9)	9 (2.6)	1.000
Venous insufficiency	3 (0.8)	0 (0.0)	3 (0.9)	1.000
Gastroesophageal reflux	2 (0.5)	0 (0.0)	2 (0.6)	1.000
Renal diseases	10 (2.5)	0 (0.0)	10 (2.9)	0.371
Gout	2 (0.5)	0 (0.0)	2 (0.6)	1.000
Glocom	1 (0.3)	0 (0.0)	1 (0.3)	1.000
Amputated leg	5 (1.3)	0 (0.0)	5 (1.5)	1.000
Gallbladder diseases	3 (0.8)	0 (0.0)	3 (0.9)	1.000
Cirrhosis	1 (0.3)	0 (0.0)	1 (0.3)	1.000
Psychiatric disease (bipolar)	1 (0.3)	0 (0.0)	1 (0.3)	1.000
Herniated disc	7 (1.8)	1 (1.9)	6 (1.8)	1.000
COVID-19	393 (100)	52(100)	341 (100)	-
Obesity history	110 (28.2)	17 (32.7)	93 (27.5)	0.440
Family history	270 (68.7)	33 (63.5)	237 (69.5)	0.382

Data are shown as n (%).

Student t Test Ki Square Test

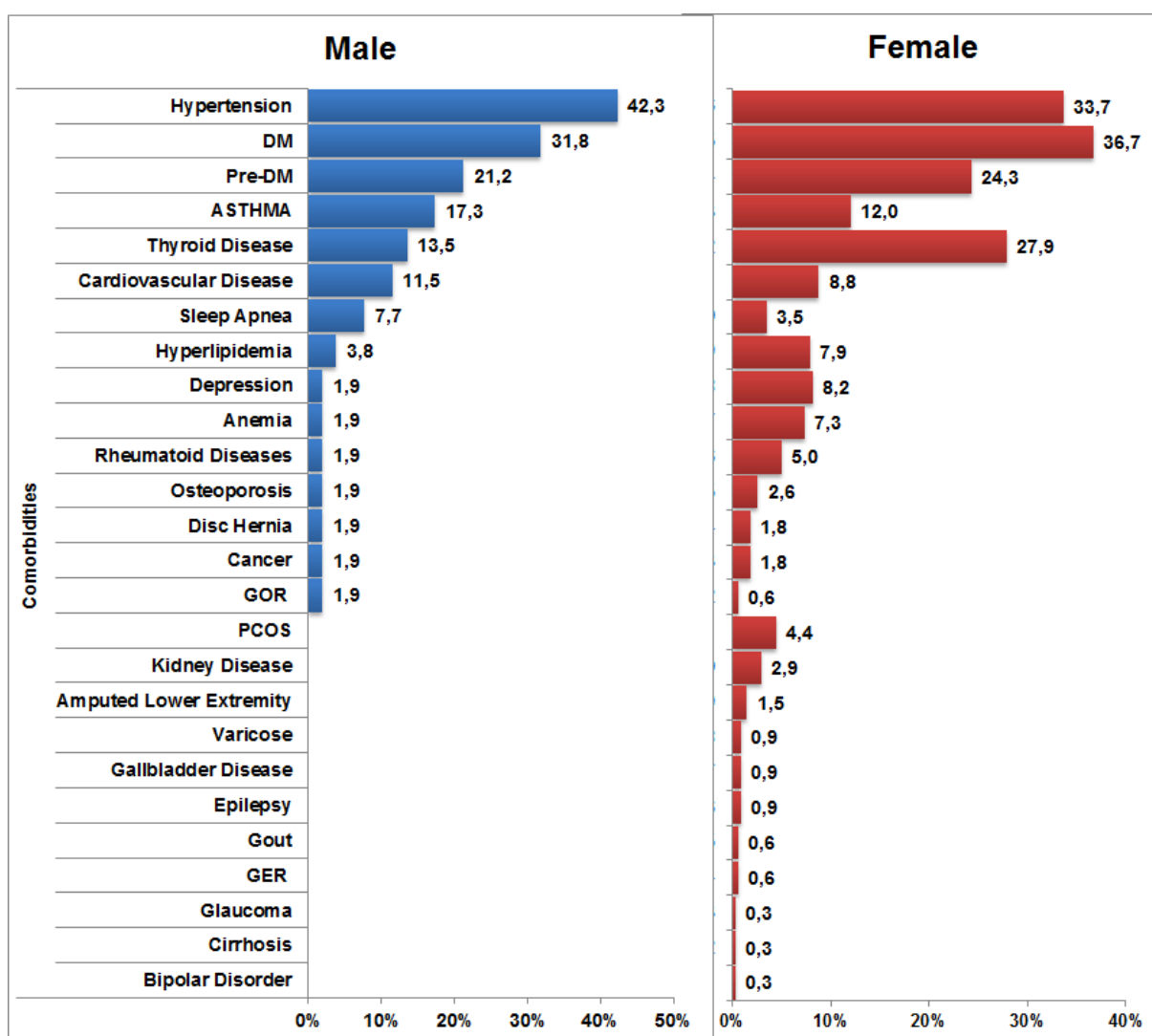


Fig. 1. Tabulated list of diseases according to frequency.

DISCUSSION

The World Health Organization (WHO) European Regional Obesity Report (2022) highlighted that Turkey has the highest rate of overweight and obesity among all European countries. The obesity rate in Turkey stands at 32.1%, compared to the European average of 23.3%. Furthermore, the rate of obesity in Turkish women is 39.2%, higher than the European average of 24.5%, and the rate in men is 24.4%, higher than the European male average of 21.8% [2]. In line with these statistics, our study demonstrated a gender distribution of 86.8% female and 13.2% male, consistent with the higher prevalence of obesity in women as reported in the literature.

Obesity has evolved into a complex issue influenced by biological, genetic, and environmental factors. Recent studies suggest that obesity is not merely the result of personal lifestyle choices, but a biological condition that stems from dysfunction within fatty tissue. The dysregulation of adipose tissue contributes to chronic low-grade inflammation, a primary mechanism in the development of insulin resistance (IR). Obesity, through inflammatory cytokines and metabolic disruptions, leads to insulin resistance, which is strongly associated with a variety of comorbidities such as diabetes, hypertension, heart disease, stroke, and certain cancers [5]. Early identification of insulin resistance and achieving a normal BMI can help prevent the onset of diabetes [11].

Table 3. The metabolic parameters and laboratory tests of the study population

	Gender			P value [‡]
	Total (n=393)	Male (n=52)	Female (n=341)	
Glucose (mg/dL)	113.1±44.5	111.1±36.6	113.4±45.6	0.760
HbA1C (%)	6.29±1.36	6.27±1.18	6.29±1.39	0.640
Insulin (μU/mL)	20.0±20.2	29.7±44.2	18.6±13.1	0.003
HOMA-IR	5.61±6.06	8.01±12.23	5.26±4.43	0.007
25-OHD3 (ng/mL)	17.8±11.6	20.1±10.3	17.4±11.8	0.022
TSH (μU/mL)	2.55±2.76	2.57±2.76	2.54±2.76	0.447
Total cholesterol (mg/dL)	199.8±40.7	194.3±34.9	200.7±41.5	0.312 [#]
LDL (mg/dL)	124.1±42.2	123.4±49.6	124.2±41.0	0.522
HDL (mg/dL)	50.1±11.1	45.0±9.9	50.9±11.1	<0.001
Triglyceride (mg/dL)	153.0±81.1	170.2±91.8	150.3±79.1	0.166
Vitamin B12 (pg/dL)	308.1±252.6	365.3±559.1	299.3±160.6	0.740
Ferritin (ng/dL)	60.1±89.8	116.0±102.4	51.4±84.6	<0.001
Iron (μg/dL)	67.8±33.6	81.5±36.4	65.7±32.7	0.007
Urea (mg/dL)	28.0±11.6	29.8±4.1	27.7±12.3	0.042
Creatinine (mg/dL)	1.55±7.91	0.74±0.27	1.67±8.47	0.071
ALT (U/L)	22.8±13.8	36.9±23.5	20.7±10.4	0.004
AST (U/L)	22.0±13.2	24.7±8.7	21.6±13.7	0.091
Hemoglobin (g/dL)	13.3±4.9	14.2±1.7	13.2±5.3	<0.001
Hematocrit (%)	42.2±24.7	43.0±4.5	42.1±26.5	<0.001
Platelets (×10 ⁹ /L)	287.2±74.2	258.6±75.7	291.7±73.1	0.004[#]

Data are shown as mean±standard deviation. HbA1c=Hemoglobin A1c, HOMA-IR= Homeostatic Model Assessment for Insulin Resistance, 25-OHD3=25-hydroxy vitamin D3, TSH=Thyroid-stimulating hormone, LDL=Low-density lipoprotein, HDL=High-density lipoprotein, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase

[#]Student t Testi [‡]Mann Whitney U testi

Adipose tissue, particularly visceral fat, plays a key role in the clinical manifestation of obesity-related diseases. Visceral fat is more closely linked to insulin resistance, cardiovascular risk, and metabolic disorders than subcutaneous fat. In our study, males had significantly lower PBF and higher SLM and waist/hip ratios compared to females. This finding supports the idea that male and female adipose tissue distributions differ, with males generally having more visceral fat, which is more detrimental to metabolic health. Visceral fat cells, especially macrophages and immune cells, secrete inflammatory cytokines and adipokines, which in turn modulate immune responses and contribute to obesity-related diseases [12].

The persistent inflammation associated with hypertrophic adipose tissue leads to impaired insulin sensitivity, increased circulating free fatty acids, and dysfunctional fat storage in organs such as the liver and pancreas. This condition, characterized by elevated CRP and other inflammatory markers, further exacerbates metabolic dysfunction. [13, 14].

Our findings showed that insulin, HOMA, ferritin, iron, hemoglobin, hematocrit, and ALT levels were significantly higher in males, while HDL and platelet levels were lower than in females. Additionally, male patients exhibited higher rates of insulin resistance (HOMA-IR) and ferritin, creatinine, ALT, and hemoglobin. These findings suggest that male obesity is as-

sociated with more severe metabolic disturbances compared to female obesity. The blunted leptin response and the hyperleptinemia observed in obesity further complicate the regulation of energy balance, increasing the difficulty in managing obesity and its comorbidities [15].

Long-term management of T2DM heavily relies on weight loss, yet the weight-increasing effect of some medications and the physiological pressure exerted by the hypothalamus makes it challenging to maintain weight loss over time. This leads to a cycle of hunger and satiety that undermines the effectiveness of weight management strategies [16]. The risk of developing T2DM increases with each kilogram of weight gain, and the presence of insulin resistance in 90% of T2DM patients doubles the risk of cardiovascular disease [17].

The Framingham Study has shown that obesity leads to a shorter life expectancy, with obese women and men living 5.8 and 7.1 years less, respectively, than their non-obese counterparts [18]. Furthermore, obesity significantly increases the risk of hypertension and ischemic heart disease. The Framingham and Nurses Health Studies also showed that obesity increases the risk of both fatal and nonfatal myocardial infarction [18-20]. This reinforces the critical need for early intervention in managing obesity to prevent cardiovascular diseases and improve long-term health outcomes.

A meta-analysis by Guh *et al.* [21] also highlighted that the relative risks for conditions like T2DM and coronary artery disease (CAD) are higher in obese patients compared to those who are overweight. While some studies, such as those by Faeh *et al.* [23] and Chu *et al.* [24], report lower cut points for obesity-related comorbidities in different populations, the overall association between obesity and comorbidities is well-established across various ethnic groups.

The relationship between obesity and hypertension is influenced by sex, as demonstrated by a large cohort study evaluating the incidence of hypertension in Japanese adults with obesity. The study found that female patients had a greater risk of developing hypertension compared to males with similar BMI values. This supports the notion that women may be more vulnerable to certain obesity-related comorbidities, such as hypertension, than men. This finding is consistent with our study, where females exhibited a

higher prevalence of thyroid diseases and other obesity-related complications, reinforcing the need for gender-specific interventions in the management of obesity and its associated health risks [25].

National Health and Nutrition Examination Survey (NHANES I, II, III) studies also support this data, with findings suggesting that the risk of developing Type 2 diabetes is significantly higher in individuals with high BMI. Specifically, the age-adjusted relative risk of developing diabetes was reported to be 100 times higher in women with a BMI >35 kg/m² compared to women with a BMI <22.4 kg/m² over 14 years. Similarly, the relative risk was 50.7 times higher in men with a BMI ≥ 35 kg/m² compared to those with a BMI <23 kg/m². Furthermore, the Framingham Heart Study found that the risk of heart failure was doubled in obese individuals, emphasizing the serious long-term consequences of obesity on cardiovascular health [19, 20].

In our study, we observed a significantly higher rate of thyroid disease in females compared to males, consistent with previous literature indicating that obesity is associated with various endocrine disorders. Additionally, the metabolic consequences of obesity, including its effect on cardiovascular risk, highlight the need for early intervention to prevent the onset of complications such as diabetes, hypertension, and cardiovascular disease [26]. In Turkey, obesity-related diseases, particularly ischemic heart disease and diabetes, contribute to a substantial burden on healthcare, with 57,143 deaths annually attributed to obesity-related conditions [27].

CONCLUSION

This study reveals significant gender differences in obesity-related health risks, with women showing higher thyroid disease prevalence and men experiencing more severe metabolic disturbances. Obesity is strongly linked to increased risks of Type 2 diabetes, cardiovascular disease, and hypertension. Given Turkey's high obesity rates, particularly among women, urgent action is needed to address these health threats and prevent long-term complications.

Ethical Statement

This study was approved by the Kartal Dr. Lütfi

Kırdar City Hospital Clinical Research Ethics Committee (Decision no: 2021/514/208/11 and date: 25.08.2021). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Informed consent was obtained from all participants.

Authors' Contribution

Study Conception: MT, SA; Study Design: MT; Supervision: MT, ŞK; Funding: MT; Materials: MT; Data Collection and/or Processing: MT, ŞK; Statistical Analysis and/or Data Interpretation: ÖÇM; Literature Review: ÖÇM; Manuscript Preparation: MT; and Critical Review: ÖÇM.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Radiation dose comparison of transradial and transfemoral access in transarterial radioembolization and chemoembolization

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ABSTRACT

Objectives: To compare radiation doses associated with transradial access (TRA) and transfemoral access (TFA) in transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) procedures for hepatic cancers.

Methods: This retrospective, single-center study analyzed 119 patients who underwent TACE or TARE between October 2016 and October 2024. Radiation dose parameters were compared between TRA and TFA groups, including fluoroscopy time, fluoroscopy and fluoroscopy-digital radiography combined dose-area product (DAP), and total air kerma (AK). Statistical analyses were performed using the Mann-Whitney U test and Chi-squared test.

Results: TRA was associated with significantly higher radiation exposure compared to TFA, including increased fluoroscopy time (median: 15.2 vs. 8.9 minutes, $P<0.001$), fluoroscopy DAP (median: 84.4 vs. 45.2 Gy·cm², $P<0.001$), fluoroscopy-digital radiography combined DAP (median: 246 vs. 156.5 Gy·cm², $P=0.003$), and AK (median: 959 vs. 612.9 mGy, $P=0.001$). No significant differences were observed in patient demographics, tumor localization, or treatment approach between the groups.

Conclusions: TRA is associated with higher radiation exposure compared to TFA in TACE and TARE procedures. While TRA offers procedural benefits, further research is needed to optimize techniques and reduce radiation risks, particularly in interventional radiology.

Keywords: Transarterial radioembolization, transarterial chemoembolization, transfemoral access, transradial access, radiation dose

Transarterial chemoembolization (TACE) is a widely accepted treatment for unresectable hepatic cancers, traditionally performed through transfemoral access (TFA) [1]. Recently, transradial access (TRA) has gained attention for its potential advantages, including reduced bleeding risk,

shorter recovery times, and improved patient comfort [2]. However, TRA also presents challenges, such as radial artery occlusion (RAO) and concerns regarding radiation exposure, which may complicate its application in interventional radiology [3].

Following the established role of TACE in the

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treatment of hepatic cancers, transarterial radioembolization (TARE) has emerged as an alternative locoregional therapy, particularly for patients who are not candidates for TACE or those with advanced disease features such as portal vein thrombosis [4]. TARE involves the administration of radioactive microspheres, typically loaded with yttrium-90 (Y-90), directly into the hepatic artery to deliver targeted radiation to the tumor. Unlike TACE, TARE does not rely on arterial embolization, which allows for better tolerability in patients with compromised liver function [5]. Recent advancements in interventional radiology, including the use of TRA, have also been explored in TARE procedures, offering potential benefits such as reduced bleeding risk, shorter recovery times, and improved patient comfort [6].

In the context of TARE and TACE, TRA offers potential benefits over TFA, particularly in reducing access site-related complications. However, the application of TRA in non-coronary procedures remains underexplored, particularly regarding its impact

on radiation exposure during interventions [7].

This study aims to compare the radiation doses associated with TRA and TFA in TARE and TACE procedures, providing insights into their respective advantages and limitations.

METHODS

Study Sample

The review board approved this retrospective study and granted a waiver for informed consent regarding the collection, analysis, and presentation of anonymized medical data. This study adheres to the STROBE guidelines for reporting.

We retrospectively reviewed consecutive patients who underwent TARE or TACE procedures between October 2016 and October 2024. A total of 119 patients underwent TARE or TACE review. From 119 patients all of them were included in the study. The flowchart of the study is given in Fig. 1.

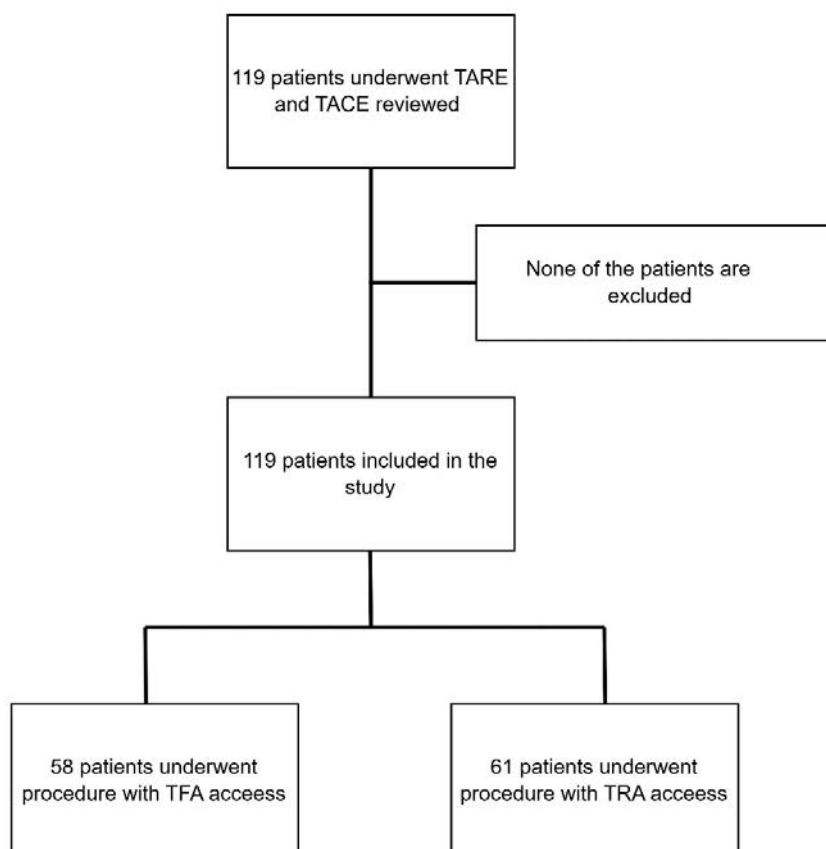


Fig. 1. Flowchart of the study. TARE=transarterial radioembolization, TACE=transarterial chemoembolization, TFA=transradial access, TRA=transfemoral access

Procedure

Prior to the procedure, each patient underwent a 99m Technetium macro aggregated albumin (99mTc-MAA) planning-mapping celiac-mesenteric angiography. If the treatment was planned for both sides of the liver, both sides were assessed separately. TFA or TRA access was assessed with the modified Allen test with a pulse oximeter and radial artery evaluation. Patients with negative Allen test or with radial artery diameter smaller than 2.5 mm, were planned for TFA. Two different vendor cone beam CT scans (Axiom Artis Cath/Angio System, Siemens, Germany; Azurion, Philips, Amsterdam, Netherlands) were performed during angiography for all patients. Tumor localization was done with a 2.4 Fr Progreat microcatheter (Terumo Medical Corporation, Somerset, NJ, USA) in all procedures. Arterial access was reassessed for the treatment session as previously.

For the TARE procedure, treatment dosing was calculated and designed with Simplicit90Y software (Boston Scientific Corp., Marlborough, MA). Y-90 glass microspheres with 20 micrometer diameter (Boston Scientific Corp., Marlborough, MA, USA) were used as the radioembolization agent. After that catheters were removed, and all contaminated materials were disposed of in accordance with institutional radiation safety guidelines. Following the administration of the radiation dose, patients underwent a CT scan to assess the distribution and coverage of the microsphere dose.

For the TACE treatment, a Beacon Tip 5 Fr multipurpose angiographic catheter (Cook Medical, Bloomington, IN, USA) was used. A solution of 2.5 mg of verapamil, 200 mcg of Nitroglycerin, 2 mL of 2% lidocaine, and 2000 IU of heparin was administered for vasospasm and clot formation. A 4F×125 cm Ultimate 1 Performa catheter was then advanced into the abdominal aorta over a 0.038-inch×180 cm Glide wire with a 1.5 mm J-tip. Super selective catheterization was achieved by advancing a 2.7-F microcatheter into the hepatic artery supplying the tumors. Embolization was carried out using an emulsion of calibrated microspheres LifePearl (Terumo Medical Corporation, Somerset, NJ, USA) loaded with doxorubicin 50 mg. The doses of the chemotherapeutic agents used for embolization were tailored to the tumor and patient conditions.

All procedures were carried out by a single inter-

ventional radiologist with 20 years of experience in hepatic embolization. Cone beam CT vendor-specific dose reduction software (syngo DynaCT, Siemens, Germany; ClarityIQ, Philips, Amsterdam, Netherlands) and maximum operation room shielding were used. Diagnostic CTs were not included in radiation dosing calculations, and they were taken after standard run-offs. For patients opting for sedation, procedures were performed under standard institutional protocols. Only liver fluoroscopy dose-area product values were extracted for comparison.

Radial Access

For all TRA procedures, the left arm of the patient was positioned alongside the body, and under ultrasound guidance radial artery was accessed. 3000 IU of heparin was administered. A 5 F angiographic Optitorque catheter (Terumo Medical Corporation, Somerset, NJ, USA) was used. Upon completion, a compression device (Terumo Interventional Systems) with an 18 mL air capacity was placed on the wrist, with the balloon positioned over the access site, and inflated as the vascular sheath was withdrawn. The band remained inflated for 30 minutes, after which 2 mL of air was released every 5 minutes. The wristband was removed 60 minutes after initial placement, and the access site was covered with a sterile dressing. Post-procedure, bed rest was not necessary; patients were allowed to sit up and use the bathroom, and they were discharged within two hours.

Femoral Access

For all TFA, the right or left femoral artery was accessed using ultrasound guidance and the Seldinger technique. 3000 IU of heparin was administered. Upon completion of the TFA procedures, manual compression was applied to the femoral artery entry site to achieve hemostasis. Once bleeding was controlled, a sterile compression hemostasis bandage was applied, and a sandbag was placed over the site for six hours. After this period, the patient was assessed and encouraged to ambulate, with plans for discharge.

Statistical Analysis

All analyses were performed using the R statistical software (Austria, R Core Team, version 4.1.0). A confidence level of 0.95 was considered statistically significant. Data normality was evaluated using the

Table 1. Characteristics of the patient group and treatment

Categories		Transfemoral Access (n=58)	Transradial Access (n=61)	P value
Sex, n (%)	Female	23 (39.6%)	25 (41%)	1
	Male	35 (60.4%)	36 (59%)	
Age (year)		60 (17.25)	60 (11)	0.53
Procedure type, n (%)	TARE	53 (91.4%)	144 (89.5%)	0.01
	TACE	5 (8.6%)	17 (10.5%)	
Cone beam CT vendor, n (%)	Siemens	38 (65.5%)	33 (54.1%)	0.27
	Philips	20 (34.5%)	28 (45.9%)	
Tumor localization, n (%)	Lobar	47 (81.1%)	49 (80.3%)	1
	Segmental	11 (18.9%)	12 (19.7%)	
Treatment approach, n (%)	Focal	6 (10.3%)	11 (18%)	0.34
	Multifocal	52 (89.7%)	50 (82%)	
Coiling, n (%)		5 (8.6%)	6 (9.8%)	0.93

Data are shown as median (IQR) or n (%). CT=computed tomography

Kolmogorov-Smirnov test, along with skewness and kurtosis values. Variables that did not meet normality assumptions were described using the median and interquartile range (IQR). Categorical and ordinal variables were reported as absolute frequencies.

Differences between age, median fluoroscopy time, median fluoroscopy dose-area product value, median fluoroscopy and digital radiography combined dose-area product value, total air kerma in access site groups were analyzed with Mann-Whitney U Test. Differences between group distribution differences of sex, TARE and TACE, coiling status, tumor localization and treatment approach were analyzed with Chi-Squared test.

RESULTS

From included 119 patients with a mean age of 61.1 ± 10.8 years, 48 (40.3%) of them were females and 71 (59.7%) of them were males. Demographic and treatment characteristics of the TRA and TFA patients are given in Table 1. Three cases continued with femoral access, started with radial in planning-mapping celiac-mesenteric angiography phase due to thrombosis formation in radial artery. No further complications were seen in any patients. No statistically

significant difference of sex distribution and age was found between the TRA and TFA groups ($P=1$ and $P=0.53$, respectively) (Fig. 2). There was a statistically significant difference in procedure type distribution between TRA and TFA groups ($P=0.01$). There were

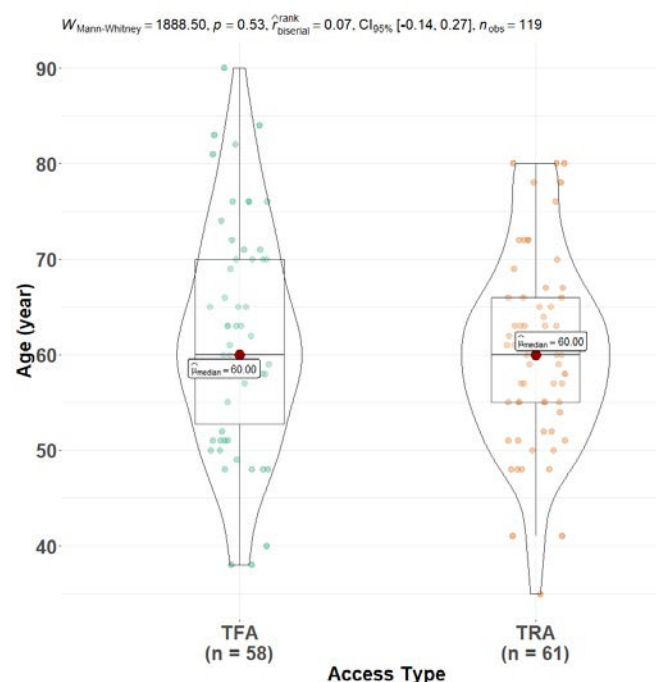
**Fig. 2. Distribution of age between access routes.**

Table 2. Characteristics of radiation dose parameters between access routes

Categories	Transfemoral Access (n=58)	Transradial Access (n=61)	P value
Median fluoroscopy time (minutes)	8.9 (9.5)	15.2 (14.9)	<0.001
Median fluoroscopy dose-area product value (Gy·cm²)	45.2 (45.3)	84.4 (115.9)	<0.001
Median fluoroscopy and digital radiography combined dose-area product value (Gy·cm²)	156.5 (142.1)	247 (227.5)	0.003
Total air kerma (mGy)	612.9 (730.5)	959 (1202)	0.001

Data are shown as median (IQR)

no statistically significant differences in cone beam CT vendor, tumor localization, treatment approach, and coiling status between TRA and TFA groups (P=0.27, P=1, P=0.34, and P=0.93; respectively). Details of radiation dose parameters between access routes were given in Table 2. Median TFA median fluoroscopy time was 8.9 minutes (IQR, 9.5), statistically significantly different than TRA (median:15.2, IQR:14.9, P<0.001). The median of TFA median fluoroscopy dose-area product value (DAP) was 45.2 Gy·cm² (IQR, 45.3), statistically significantly different than TRA (median:84.4 Gy·cm², IQR:115.9, P<0.001). Median of TFA median fluoroscopy and digital radi-

ography combined DAP was 156.5 Gy·cm² (IQR, 142.1), statistically significantly different than TRA (median:247 Gy·cm², IQR:227.5, P=0.003) (Fig. 3). Median of total air kerma (kinetic energy transferred per unit mass) (AK) was 612.9 mGy (IQR, 730.5), statistically significantly different than TRA (median:959 mGy, IQR:1202, P=0.001) (Fig. 4).

DISCUSSION

The study explores the comparative advantages and limitations of TRA and TFA in TACE and TARE pro-

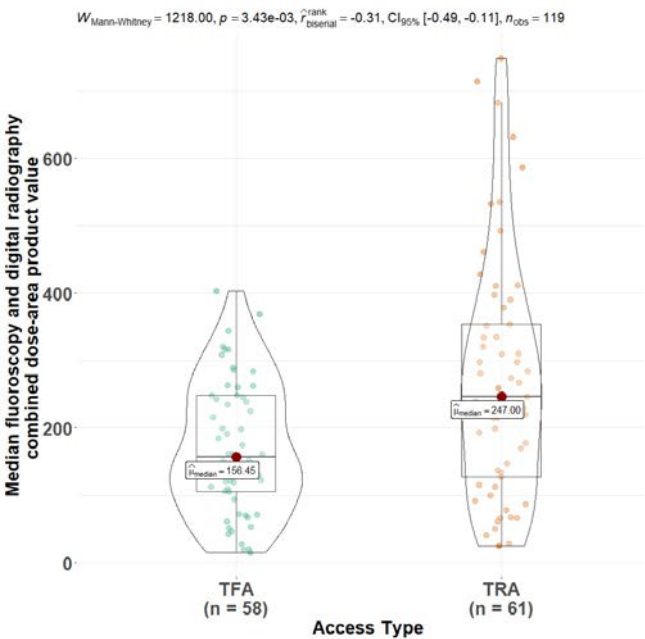


Fig. 3. Distribution of median fluoroscopy and digital radiography combined dose-area product value (Gy·cm²) between access routes.

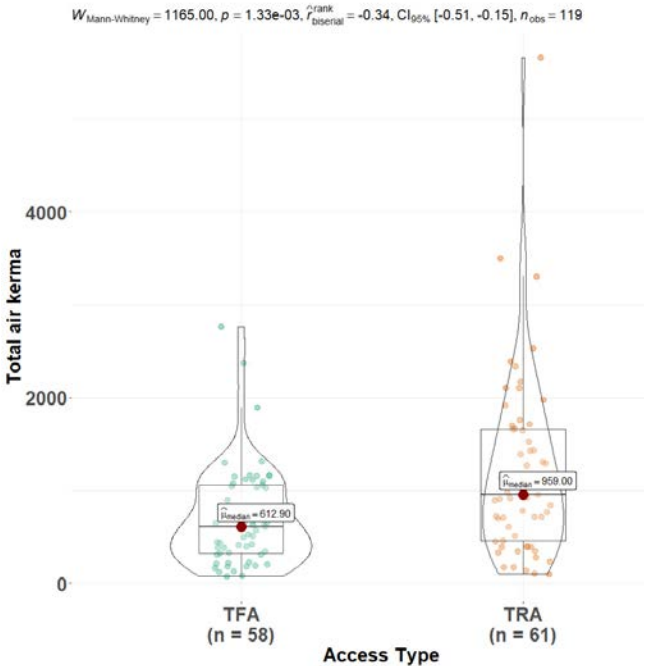


Fig. 4. Distribution of total air kerma (mGy) between access routes.

cedures for hepatic cancers. The retrospective analysis of 119 patients revealed no significant differences in demographic characteristics or tumor localization between TRA and TFA groups. However, TRA was associated with significantly higher fluoroscopy time, DAP, and total AK compared to TFA, indicating increased radiation exposure. Despite these findings, TRA remains a promising alternative to TFA, particularly for reducing access site complications, though its impact on radiation exposure warrants further investigation. This study highlights the need for a balanced approach when selecting access routes, considering both procedural safety and radiation risks.

When comparing TACE and TARE, both treatments exhibit similar effectiveness and toxicity profiles; however, TARE has demonstrated a longer time-to-progression and reduced toxicity, despite no significant differences in overall survival rates [8, 9]. Factors such as tumor multifocality, vascular invasion, and hepatitis C seropositivity have been linked to poorer survival outcomes, regardless of the treatment method employed for hepatocellular carcinoma [9]. Recent studies comparing TRA and TFA in TARE and TACE procedures have yielded mixed results. For instance, Loewenstern *et al.* found no significant differences in patient radiation exposure between TRA and TFA during Y-90 radioembolization [10]. Conversely, Pedersoli *et al.* [11] reported significantly higher operator radiation exposure with TRA compared to TFA, particularly noting higher rates of exposure per fluoroscopy time. Jiang *et al.* [12] found that the radiation doses received by the operator at various body parts were lower in the TRA group, especially when the left radial artery was accessed with the patient in a feet-first position. However, Sciahbasi *et al.* [13] also noted higher radiation doses in the TRA group during hepatic radioembolization.

Regarding patient radiation doses, multiple studies have found no significant differences between TRA and TFA. For example, a propensity score-matched analysis showed no statistical differences in fluoroscopy time, DAP, or cumulative AK between the two access methods [14]. However, some studies reported higher patient radiation doses with TRA, particularly during hepatic radioembolization [13].

Procedural variables also play a crucial role in the comparison of TRA and TFA. While some studies in-

dicate that fluoroscopy time is generally longer for TRA [10, 13], others have found no significant differences [14]. Both access methods demonstrate high technical success rates and similar complication rates, with TRA often preferred by patients for its comfort and reduced postprocedural stay [11, 15, 16].

The observed higher radiation exposure associated with TRA compared to TFA in this study may be attributed to several procedural and anatomical factors inherent to the two access routes. First, the radial artery's smaller diameter and more tortuous course compared to the femoral artery often necessitate increased fluoroscopy time for precise catheter navigation and positioning. This is particularly relevant during complex hepatic interventions such as TACE and TARE, where super-selective catheterization of small hepatic arteries is required. Additionally, the need for repeated adjustments and repositioning of catheters and guidewires during TRA can further contribute to prolonged fluoroscopy use [17]. Second, the ergonomic setup during TRA procedures may also play a role; operators often adjust the C-arm angulation or patient positioning to accommodate the radial approach, which can inadvertently increase scatter radiation and overall dose exposure. Third, the learning curve associated with adopting TRA for non-coronary interventions, such as TACE and TARE, might result in less efficient techniques compared to the well-established TFA. Studies have shown that operator experience significantly influences radiation doses, with less experienced operators tending to require longer fluoroscopy times and more frequent acquisitions [18].

Limitations

This study has several limitations. First, the relatively low number of TACE cases included may limit the generalizability of the findings, particularly when comparing radiation exposure between TRA and TFA in this subgroup. Second, the retrospective, single-center design may introduce selection bias and limit the applicability of the results to broader populations or different clinical settings. Future multicenter, prospective studies with larger sample sizes and multi-operator are needed to validate these findings and provide a more comprehensive understanding of the radiation dose differences between TRA and TFA.

CONCLUSION

In conclusion, this study demonstrates that TRA is associated with significantly higher radiation exposure compared to TFA, as evidenced by increased fluoroscopy time, DAP, and AK. These findings emphasize the need for further research to optimize TRA techniques and minimize radiation risks, ensuring its safe application in interventional radiology.

Ethical Statement

All procedures conducted in studies involving human participants complied with the ethical standards of the institutional and/or national research committee, as well as the 1964 Helsinki Declaration and its subsequent amendments or equivalent ethical guidelines. The local ethics committee approved this retrospective study and waived the requirement for informed consent for the retrospective analysis of anonymized medical data (Decision number: 2024-14/576 and date: 19.09.2024).

Data availability

The data sets produced and/or examined over the course of the present investigation can be obtained from the lead author upon a justified request.

Authors' Contribution

Study Conception: YB, KG; Study Design: YB, KG; Supervision: YB; Funding: N/A; Materials: N/A; Data Collection and/or Processing: YB, MG; Statistical Analysis and/or Data Interpretation: YB, MES; Literature Review: YB; Manuscript Preparation: YB and Critical Review: YB, MES, KG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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Radiology's role in dermatology: A closer look at two years of data

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ABSTRACT

Objectives: Radiological imaging plays a vital role in dermatology, addressing complex diagnostic needs beyond visual examination. The study focuses on the use of radiology services by the dermatology clinic at Bilecik Training and Research Hospital over two years (January 2023-December 2024), focusing on modality preferences, clinical indications, and diagnostic impact.

Methods: Data from 451 imaging referrals were analyzed, covering patient demographics, imaging types, and clinical indications. Modalities included ultrasonography (USG), X-ray, magnetic resonance imaging (MRI), computed tomography (CT), and other specialized techniques. Trends and diagnostic yields were assessed, with subgroup analysis by age and gender.

Results: Ultrasonography was the most frequently used imaging method (65.2%), followed by X-ray (18.6%), with MRI and CT used less often (5.1% and 4.4%, respectively). General medical examinations (29.93%) were the leading indication, achieving the highest diagnostic yield (85%). Pruritus (9.31%) and psoriasis (7.76%) were also notable indications. Most referrals involved middle-aged (41-60 years) and older adults (61+ years).

Conclusions: Ultrasonography and X-ray remain foundational tools in dermatology, providing essential support for diagnosis and management. These findings highlight the need for resource optimization and stronger collaboration between dermatology and radiology. Future research should explore imaging outcomes and emerging technologies to advance dermatological care.

Keywords: Dermatological imaging trends, radiology utilization in dermatology, X-Ray, ultrasound, CT, MRI

Radiology has become an indispensable component of dermatology, providing critical insights beyond what is discernible through visual inspection alone. While many dermatological conditions can be diagnosed based on clinical examination, certain cases require additional imaging to confirm or refine the diagnosis. In such instances, radiological modalities play a pivotal role in bridging the gap between clinical suspicion and definitive assessment. Imaging tech-

niques such as ultrasonography (USG), X-ray, computed tomography (CT), and magnetic resonance imaging (MRI) have significantly enhanced the diagnostic and management capabilities of dermatologists. These technologies facilitate the precise evaluation of subcutaneous lesions, vascular anomalies, inflammatory disorders, and malignancies [1, 2].

Among these modalities, USG is particularly valuable due to its accessibility, non-invasive nature, and

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real-time imaging capabilities. It is especially advantageous in assessing soft tissue pathologies and vascular abnormalities [3, 4]. Additionally, X-ray remains a fundamental tool, particularly in cases involving osseous structures or calcifications, often serving as the initial imaging modality when further investigation is required [5]. In more complex scenarios, such as those involving deep tissue involvement or suspected malignancies, CT and MRI provide superior resolution and detailed anatomical visualization, making them essential for both diagnostic and interventional purposes [6, 7]. Despite the growing integration of radiology into dermatological practice, there remains a limited understanding of its utilization patterns. Key questions persist regarding which imaging modalities are most frequently employed, the primary indications prompting dermatological referrals to radiology, and how these trends have evolved. Addressing these inquiries is essential for optimizing interdisciplinary collaboration, enhancing workflow efficiency, and ensuring that radiology departments are adequately equipped to meet the increasing demands of dermatological care [8, 9].

This study aims to explore the utilization of radiology services by the dermatology clinic at Bilecik Training and Research Hospital over two years (January 2023-December 2024). By focusing on the practical and operational aspects of imaging use in dermatology, this research seeks to provide valuable insights into:

- The most frequently utilized imaging modalities and their corresponding clinical indications.
- The evolution of referral patterns over time and the implications of these trends for dermatological practice.
- Potential strategies for enhancing the efficiency and effectiveness of radiology services in dermatology.

METHODS

Study Design and Population

This retrospective study analyzed the utilization of radiology services by the dermatology clinic at Bilecik Training and Research Hospital over a two-year period (January 2023-December 2024). Ethical approval was

obtained from the hospital's Ethics Committee, and patient confidentiality was strictly maintained.

Inclusion criteria was the following: (a) All patients referred by the dermatology clinic for imaging, irrespective of age. (b) Referrals for any imaging modality, including ultrasonography (USG), X-ray, computed tomography (CT), magnetic resonance imaging (MRI), or specialized techniques.

Exclusion criteria was included incomplete or missing medical records, imaging conducted outside the hospital or unrelated to dermatology referrals, repeat imaging without a new dermatological consultation.

Imaging Modalities

Various imaging techniques were evaluated based on their indications and frequency of use:

- Ultrasonography (USG)*: Preferred for soft tissue lesions and vascular anomalies, particularly with Doppler USG for assessing blood flow.

- X-ray*: Frequently utilized for skeletal abnormalities and calcifications due to its accessibility and cost-effectiveness.

- MRI*: Used for systemic diseases, deep-seated lesions, and connective tissue disorders, offering superior soft tissue contrast.

- CT*: Reserved for complex cases, including deep infections and suspected malignancies, providing high-resolution imaging.

Other techniques included specialized imaging for interventional guidance and targeted assessments.

USG and X-ray were the most frequently utilized modalities, while MRI and CT were reserved for advanced diagnostic needs.

Ethical Considerations

All patient data were anonymized to ensure confidentiality. As a retrospective study, no direct patient involvement was required, eliminating the need for informed consent.

Data Analysis

Collected data were systematically analyzed to identify trends in:

- Patient demographics*: Age, gender, and referral characteristics.

- Imaging utilization*: Frequency and distribution of different imaging modalities.

- Indications for imaging:* Common clinical scenarios necessitating radiological evaluation.
- Operational efficiency:* Turnaround times and workflow optimization.

Statistical Analysis

Descriptive statistics were used to summarize patient demographics, imaging modality distributions, and clinical indications. Mean, median, standard deviation, minimum, and maximum values were calculated for age. Categorical variables, including gender distribution and imaging modality preferences, were presented as frequencies and percentages. Stratification by age and gender was conducted to assess referral patterns across different demographics. The study also evaluated diagnostic yield percentages for various clinical indications.

RESULTS

Demographic Characteristics

A total of 451 patients were referred by the dermatology clinic for radiological imaging between January 2023 and December 2024. The age range spanned from 4 to 96 years, with a mean age of 51.7 years and a median of 50 years. The interquartile distribution indicated that 25% of patients were under 37 years, while another 25% were over 69 years, demonstrating a broad age representation (Table 1).

Gender distribution was nearly equal, with 229 male (50.8%) and 222 female (49.2%) referrals. Stratification by age and gender revealed a peak in female

Table 1. Demographic details of dermatology imaging referrals by age

	Data
Number of patients	451
Mean age	51.7
Standard deviation	21.2
Minimum age	4
25th percentile	37
Median age (50th Percentile)	50
75th percentile	69
Maximum age	96

Table 2. Demographic details of dermatology imaging referrals by gender and age group

	Age groups			
Gender	0-18	19-40	41-60	61+
Male	32	68	57	55
Female	25	72	89	53

referrals within the 41–60 age group, suggesting either a higher prevalence of dermatological conditions requiring imaging or increased healthcare-seeking behavior in this demographic (Table 2).

These findings highlight the dermatology clinic’s capacity to address dermatological conditions across all life stages. The near-equal gender distribution underscores the broad applicability of radiological services in dermatology. The observed referral trends provide valuable insights for optimizing imaging-resource allocation.

Distribution of Imaging Modalities

Ultrasonography (USG) was the most frequently utilized modality, with 294 referrals (152 males, 142 females), reinforcing its central role in dermatological imaging (Table 3). X-ray, the second most used technique (84 referrals), showed a slightly higher utilization among males (45) than females (39), indicating its frequent application in systemic or skeletal assessments. MRI and CT referrals were lower but evenly distributed between genders. Notably, CT referrals were slightly higher in females (11) than males (9), reflecting its selective use in complex cases (Table 4).

Age-group analysis showed that USG was the pre-

Table 3. Frequency and distribution of imaging modalities used in dermatology referrals

Imaging modality	n	%
Ultrasonography	294	65.19
X-Ray	84	18.63
MRI	23	5.10
CT	20	4.43
Other	30	6.65

CT=Computed Tomography, MRI=Magnetic Resonance Imaging

Table 4. Distribution of imaging modalities by gender

Gender	Ultrasonography	X-Ray	MRI	CT	Other
Male	152	45	11	9	12
Female	142	39	12	11	18

CT=Computed Tomography, MRI=Magnetic Resonance Imaging

Table 5. Distribution of imaging modalities by age group

Age Group	Ultrasonography	X-Ray	MRI	CT	Other
0-18	42	8	2	1	4
19-40	103	24	9	6	7
41-60	87	29	7	7	16
61+	62	23	5	6	3

CT=Computed Tomography, MRI=Magnetic Resonance Imaging

dominant imaging modality across all demographics, with the highest usage in the 19-40 age range (103 referrals). X-ray referrals peaked in the 41–60 age group (29 referrals), correlating with a higher prevalence of systemic conditions in middle-aged individuals. CT and MRI were evenly distributed, emphasizing their targeted role in specific diagnostic needs. Specialized imaging categorized as "Other" was most frequently used in the 41-60 age group (16 referrals), suggesting an increased need for advanced diagnostic approaches (Table 5).

- Trends Over Two Years*
- A longitudinal analysis of imaging utilization from January 2023 to December 2024 revealed distinct patterns (Fig. 1).
- Ultrasonography: Maintained consistently high referral rates, with a gradual increase, peaking in mid-2024, reflecting its expanding role in dermatological assessments.
 - X-ray: Showed a steady upward trend, indicating its continued relevance for systemic evaluations.
 - MRI: Displayed a slight increase toward late

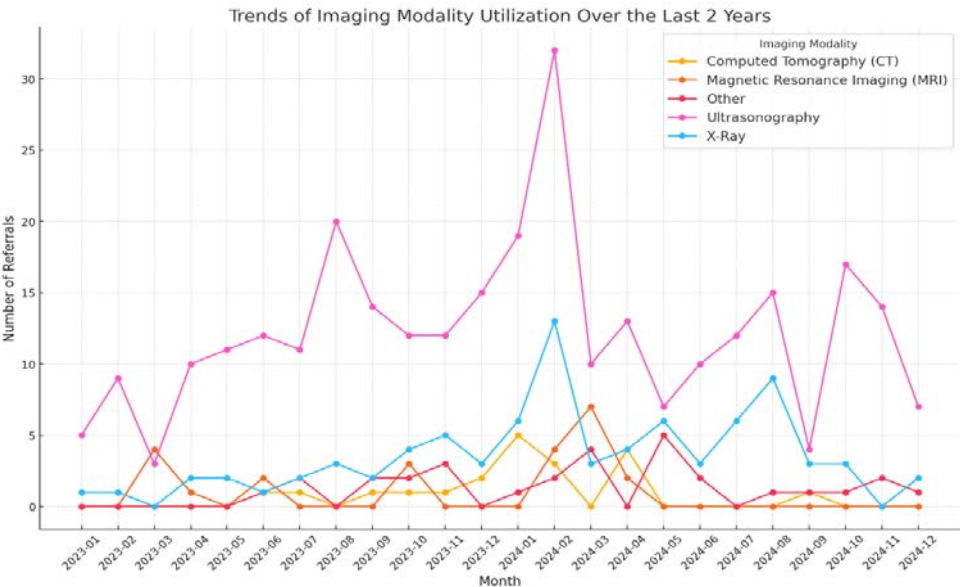


Fig. 1. Trends of imaging modality utilization over the last 2 years

Table 6. Clinical indications for imaging

Clinical indication	Number of referrals	Percentage (%)
General medical examination	135	29.93
Pruritus	42	9.31
Psoriasis	35	7.76
Dermatitis	34	7.54
Other Dermatitis	24	5.32

2024, highlighting its growing role in complex cases.

- CT*: Although the least utilized, its steady usage underscores its necessity for specialized diagnoses.
- Other modalities*: Showed sporadic yet increasing utilization, reflecting their value in unique clinical scenarios.

These trends emphasize dermatology’s increasing reliance on radiology, underscoring the need for strategic resource planning.

Clinical Indications for Imaging

The most common reason for imaging referrals was a general medical examination, underscoring the routine role of radiology in dermatology (Table 6). Gender-based analysis showed a slightly higher prevalence of pruritus and psoriasis in females, while dermatitis referrals were evenly distributed (Table 7). Age-specific trends revealed that the 41-60 age group had the highest number of referrals, likely due to a higher prevalence of systemic and chronic dermatological conditions. The 19-40 age group showed a notable number of referrals for pruritus and psoriasis, while referrals for pediatric patients (0-18 years) were minimal (Table 8).

Diagnostic Yield

Imaging effectiveness was evaluated based on diagnostic yield:

- General medical examinations*: 85% diagnostic yield, reinforcing the role of imaging in routine dermatological assessments.

- Pruritus and psoriasis*: 75-80% yield, reflecting the utility of imaging in detecting deeper tissue involvement.
- Dermatitis*: 65-70% yield, underscoring the role of imaging in differentiating inflammatory conditions.

These findings highlight radiology's nuanced role in dermatological care, supporting both routine and complex diagnostic needs (Fig. 2).

DISCUSSION

The use of radiology in dermatology has become increasingly important as dermatological conditions grow more complex and diverse [7]. This two-year retrospective study sheds light on how radiological services are utilized in dermatological practice at Bilecik Training and Research Hospital (2023-2024). The findings emphasize the essential role of imaging in refining diagnoses, aiding clinical decisions, and improving patient outcomes in dermatological care [8].

Why Radiology Matters in Dermatology

One of the standout findings in this study is the consistent reliance on radiological tools for dermatological evaluations. Ultrasonography (USG), accounting for 65.2% of referrals, emerged as the preferred modality due to its accessibility and ability to assess subcutaneous and vascular conditions effectively [9].

The steady demand for radiological services can be attributed to several factors: (1) Improved imaging

Table 7. Clinical indications for imaging by gender

Gender	General medical examination	Pruritus	Psoriasis	Dermatitis	Other dermatitis
Male	72	19	16	15	10
Female	63	23	19	19	14

Table 8. Clinical indications for Imaging by age group

Age groups	General medical examination	Pruritus	Psoriasis	Dermatitis	Other dermatitis
0-18	12	4	2	1	1
19-40	35	12	8	9	6
41-60	52	18	14	12	10
61+	36	8	11	12	7

technology: Advances like Doppler USG have enhanced the precision and reliability of imaging in dermatology; (2) Complex cases: Imaging has become indispensable for diagnosing conditions involving deep-seated infections, systemic diseases, or malignancies with cutaneous involvement; and (3) Demographic trends: Middle-aged (41-60 years) and older adults (61+ years) were the primary users, reflecting the burden of chronic conditions requiring advanced diagnostic approaches.

These insights underscore the need for better resource allocation in radiology departments. Investments in staffing, equipment, and training are critical to meet the growing demand.

What Imaging Methods are Most Common?

USG dominated referrals, making up more than 65% of imaging requests. Its versatility, cost-effectiveness, and ability to provide real-time imaging for superficial tissues made it an invaluable tool in dermatological practice [9]. Doppler USG, in particu-

lar, proved essential for evaluating vascular anomalies like hemangiomas and venous malformations.

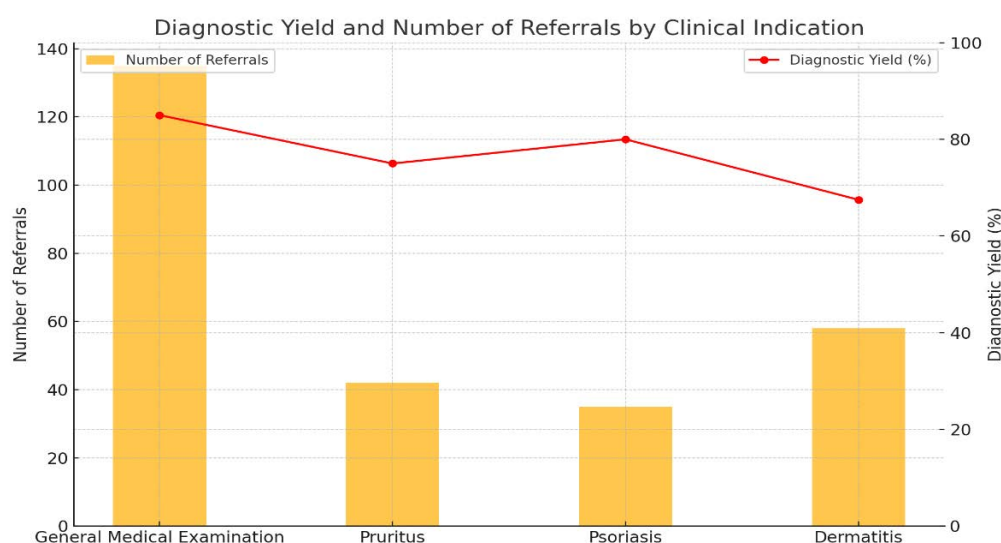
X-rays, the second most used method (18.6%), were primarily applied to systemic or skeletal evaluations, particularly in older adults with calcifications or bone involvement [10].

Advanced imaging modalities such as MRI (5.1%) and CT (4.4%) were reserved for complex or critical cases, including: (a) MRI: Ideal for detailed soft tissue evaluation, systemic conditions, and deep-seated lesions [11]; (b) CT: Essential for assessing deep infections, suspected cancers, and staging malignancies [12]. Each modality had a clearly defined role, ensuring efficient use of radiological resources.

Why Were These Scans Ordered?

The study revealed a range of clinical indications for imaging referrals, with notable diagnostic yields:

- Routine medical evaluations:* The most common reason (29.93%) had an impressive diagnostic yield of 85%, showing its value in general dermatological care.

**Fig. 2. Diagnostic referrals and yields across clinical indications**

•*Pruritus and Psoriasis*: Chronic inflammatory conditions like these had diagnostic yields of 75-80%, highlighting their utility in detecting systemic or sub-clinical issues [13, 14].

•*Dermatitis*: Imaging helped differentiate benign conditions from deeper issues, with yields ranging between 65-70% [15].

These findings highlight the indispensable role of radiology in managing both straightforward and complex cases in dermatology.

Shifts in Imaging Trends

Over the two years, several trends emerged in imaging utilization:

•*Ultrasonography*: Maintained its dominance, with increasing usage reflecting greater awareness of its benefits.

•*X-rays*: Usage grew slightly, particularly among older adults, where systemic evaluations are common.

•*MRI and CT*: Usage remained stable but highly targeted, underscoring their importance in specialized diagnostic approaches.

These patterns reflect the evolving needs of the dermatological practice and highlight the value of interdisciplinary collaboration between dermatology and radiology [16].

How Do These Trends Compare Globally?

The findings align with global trends, particularly in the widespread use of ultrasonography and the selective application of advanced modalities like MRI and CT. Ultrasonography's popularity stems from its non-invasive nature, accessibility, and diagnostic versatility.

However, the study also reveals unique aspects of radiology use in Turkey:

•*Reliance on standard USG*: While consistent with global trends, the heavy reliance on standard ultrasonography emphasizes its practicality and availability in Turkey.

•*Limited MRI and CT use*: These modalities are reserved for complex cases, likely influenced by economic constraints and demographic factors.

•*X-rays as a Staple*: Despite global shifts toward non-ionizing methods, X-rays remain vital in resource-limited settings.

These comparisons highlight areas where targeted investments-such as advanced ultrasonographic tools

and interdisciplinary training further optimize radiology's role in dermatology.

Practical Implications

The study offers actionable insights for improving collaboration between dermatology and radiology:

•*Training dermatologists*: Providing training on the appropriate use of imaging modalities can lead to more precise referrals and better resource use [17].

•*Optimizing resources*: Prioritizing ultrasonography and X-ray investments can ensure departments meet rising demand [18].

•*Fostering collaboration*: Regular meetings between dermatologists and radiologists can refine imaging protocols and improve outcomes [19].

Limitations

Like any study, this research had its limitations: (a) Retrospective design: Relied on existing records, which may limit data depth; (b) Single-center focus: Findings may not apply universally; and (c) Limited outcome data: The study focused on diagnostic yield but not on long-term patient outcomes.

Future research could address these gaps by: (1) Expanding to multiple centers for broader applicability. (2) Using prospective designs to evaluate clinical outcomes. (3) Exploring emerging technologies like high-frequency ultrasonography and AI-driven imaging tools for better precision.

CONCLUSION

Radiology has become indispensable in dermatology, providing critical support for diagnosing and managing increasingly complex conditions. Ultrasonography emerged as the most utilized modality, thanks to its accessibility and diagnostic accuracy, while X-rays, MRI, and CT found targeted applications in specialized diagnostic approaches. The study emphasizes the growing demand for radiological services tailored to specific age and gender groups. This underscores the need for customized strategies to address patient-specific challenges. Looking ahead, fostering interdisciplinary collaboration and integrating emerging technologies like AI into radiology can further enhance dermatological care. These efforts promise to align clinical practices with technological advance-

ments, transforming patient outcomes and setting new standards for healthcare delivery.

Ethical Statement

The study was conducted under the Declaration of Helsinki, and approved by the Institutional Review Board of the Ethics Committee of Non-Interventional Clinical Research of Bilecik Şeyh Edebali University (Decision date: 27.11.2024 and no: 3). Informed consent was obtained from all subjects involved in the study.

Authors' Contribution

Study Conception: BTB; Study Design: BTB; Supervision: BTB; Funding: N/A; Materials: N/A; Data Collection and/or Processing: HGB; Statistical Analysis and/or Data Interpretation: BTB, HGB; Literature Review: BTB, HGB; Manuscript Preparation: BTB and Critical Review: BTB.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Editor's note

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The time interval between the hCG trigger and the oocyte pickup on IVF outcomes in patients with decreased ovarian reserve and poor prognosis

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ABSTRACT

Objectives: This study aimed to evaluate the effect of varying intervals between human chorionic gonadotropin (hCG) administration and oocyte pickup (OPU) at 34, 35, and 36 hours on in vitro fertilization (IVF) outcomes and embryo development in patients with diminished ovarian reserve (DOR).

Methods: This retrospective cohort study utilised the Istanbul Memorial Şişli Hospital, assisted reproductive technology (ART) and Reproductive Genetics Center databases from January 2017 to March 2024. The study included women undergoing ART cycles with DOR, as defined by the Bologna criteria, and follicle-stimulating hormone (FSH) levels exceeding 12 IU/L on day 2 of menstruation. Nine hundred and forty-nine ovarian stimulation cycles were analysed using the gonadotropin-releasing hormone antagonist protocol and triggered by recombinant hCG (r-hCG). The cycles were divided into three groups based on the time interval between r-hCG injection and OPU at 34, 35, and 36 hours. Demographic characteristics, ovarian stimulation parameters, embryological outcomes, and pregnancy results were compared across these groups.

Results: The 36-hour OPU group demonstrated the highest fertilization, best embryological outcomes, including the highest blastocyst formation rate (14.95%) compared to the 34-hour (14.23%) and 35-hour (12.43%) groups ($P=0.025$). The 36-hour group also had the highest proportion of day 5–6 embryo transfers (33.8%, $P=0.001$). However, there were no significant differences in pregnancy outcomes.

Conclusions: In DOR patients, extending the OPU interval to 36 hours with hCG triggering showed higher fertilization rates and better embryo development than 34 and 35 hours. However, it did not affect pregnancy outcomes.

Keywords: Oocyte pickup (OPU), diminished ovarian reserve (DOR), in vitro fertilization (IVF), pregnancy outcomes

The management of in vitro fertilization (IVF) procedures in patients with diminished ovarian reserve (DOR) presents significant challenges for clinicians. These patients often exhibit limited retrievable oocytes, poor oocyte quality, and

suboptimal response to ovarian stimulation. These factors contribute to reduced fertilisation rates, lower pregnancy success rates, and impaired embryo development [1]. Among the critical determinants of successful IVF outcomes in this population are oocyte

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maturation and quality, which depend on precise timing during assisted reproductive technology (ART) cycles [2].

The relationship between physiological ovulation timing and luteinizing hormone (LH) elevation highlights the importance of precise timing in ART cycles. Ovulation, the release of an oocyte from the follicle, usually occurs 34-36 h after the LH surge onset or 10-12 h following the LH peak. This timing is critical to ensure that the oocyte reaches the mature metaphase II (MII) stage, which is essential for successful fertilisation in both natural and assisted reproductive cycles. However, individual variability in LH secretion patterns, follicular responsiveness, and hormonal feedback mechanisms can significantly influence ovulation timing. Physiological studies have demonstrated that ovulation can occur within 24 and 56 h after the LH surge onset, with an average duration of 32 h [3].

In controlled ovarian stimulation (COS) protocols, exogenous human chorionic gonadotropin (hCG) is given to simulate the LH surge and induce a similar physiological cascade. The timing of oocyte pickup (OPU) relative to HCG administration is critical for retrieval of mature oocytes. If OPU is performed too early after the hCG trigger, oocytes may stay in the germinal vesicle (GV) or metaphase I (MI) stages, resulting in reduced fertilization potential [4]. Conversely, if OPU is delayed beyond the optimal window, there is an increased risk of premature ovulation, which can lead to the loss of oocytes into the peritoneal cavity or post-maturation changes that compromise oocyte quality and subsequent embryo development [5].

While studies have explored the impact of trigger to OPU intervals in general IVF populations, limited data are available on this parameter in patients with DOR and poor prognosis. These patients, often characterised by low oocyte yield and suboptimal quality, may be particularly susceptible to slight timing variations. Understanding the complex relationship between the trigger to OPU interval and oocyte development is crucial for creating customised protocols to enhance outcomes for this challenging subgroup.

METHODS

Study Population

This retrospective cohort study utilised the Şişli Memorial Hospital, ART, and Reproductive Genetics Center databases from January 2017 to March 2024. The study included women undergoing ART cycles with diminished ovarian reserve, according to the Bologna criteria, and follicle-stimulating hormone (FSH) levels exceeding 12 IU/L on day 2 of menstruation. Patients with congenital or acquired uterine abnormalities, a history of thin endometrium, or FSH levels above 20 IU/L on day 2 of the menstrual cycle were excluded. In total, 949 ovarian stimulation cycles employing the gonadotropin-releasing hormone (GnRH) antagonist protocol and triggered by recombinant human chorionic gonadotropin (r-hCG) were analysed. In patients whose LH levels begin to rise on the day of triggering or whose estradiol (E2) values drop the day after triggering, the OPU time is scheduled for 34 or 35 hours rather than 36 hours. Cycles were categorized into three groups based on the time interval between r-hCG injection and OPU: group one (34 h), group two (35 h), and group three (36 h). The groups were compared in terms of demographic characteristics, ovarian stimulation cycle parameters, embryological data, and pregnancy outcomes. The ethical approval was obtained from the Institutional Review Board of Istanbul Memorial Şişli Hospital, Istanbul, Türkiye (approval number: 29.04.2024/002).

Ovarian Stimulation Protocol

Ovarian stimulation was started on the second day of menstruation using the antagonist protocol. The initial dose of gonadotropins was adjusted based on body mass index (BMI), number and size of antral follicles, and relevant ultrasound and hormonal findings. Ovarian stimulation was conducted using one of the following medications: human menopausal gonadotropin (hMG) (Menogon®, Ferring, Switzerland), a combination of recombinant follicle-stimulating hormone (rFSH) (Gonal-F®, Merck Serono, Switzerland) with recombinant luteinizing hormone (rLH) (Pergoveris®, Merck Serono, Switzerland), or rFSH alone. The timing of ovulation triggering was determined based on follicle size and serum hormone levels. Ovulation was induced using r-hCG (Ovitrelle®, Merck Serono, Switzerland).

Oocyte Pickup and Intracytoplasmic Sperm Injection (ICSI)

Oocyte Pickup was performed 34-36 h after the trigger under sterile conditions using transvaginal ultrasonography guidance. 16-17G diameter aspiration needle was employed with a negative pressure of approximately 120-130 mmHg. Retrieved oocytes were sent to the embryology laboratory in Earle's Balanced Salt Solution (EBSS) flushing medium (Multicell, Wisent INC, Québec, Canada). Oocytes were observed under 100× magnification using HEPES-buffered medium and transferred to culture medium (LifeGlobal, Cooper Surgical, Brussels, Belgium). Oocytes were typically denuded within three h of aspiration and assessed for maturity. Mature oocytes were subjected to Intracytoplasmic Sperm Injection (ICSI) within 1 h of denudation.

Embryo Grading

Day 3 embryos were graded using Gardner's classification based on blastomere number, symmetry, and fragmentation. Grade 1 embryos were characterised by blastomeres of equal size, fragmentation of less than 10%, and a homogeneous cytoplasm. Grade 2 embryos had slight asymmetry and 10%-20% fragmentation. Grade 3 embryos showed more asymmetry and more than 20% fragmentation. Grade 4 embryos had high fragmentation and marked asymmetry. Blastocysts also using Gardner's classification are categorised as follows: Top quality (TQ): Hatched AA, 6AA, 5AA, 4AA; Good quality (GQ): Hatched AB/BA/BB, 5AB/BA/BB, 4AB/BA/BB, 3AA; Medium quality (MQ): 3AB/BA, 2AA; Poor quality (PQ): others.

Luteal Phase Support

For luteal phase support, vaginal progesterone gel (Crinone 8%, 90 mg; Merck Serono, Switzerland) was administered twice daily from January 2017 to November 2020. After November 2020, the luteal support protocol was modified due to the Crinone gel's commercial unavailability. Patients were then prescribed daily subcutaneous progesterone injections (Progestan Dex 25 mg/mL, Koçak, Türkiye) along with vaginal progesterone tablets (Progestan 100 mg, Koçak, Türkiye) administered three times daily.

Statistical Analysis

The study provided descriptive statistics as means

and standard deviations for quantitative variables and as numbers and percentages for qualitative variables. The normal distribution of quantitative variables was assessed graphically using the Kolmogorov-Smirnov test. The Anova test was used to compare differences between OPU groups. The relationship between qualitative variables and OPU groups was analysed using the Pearson's chi-square test. Statistical analyses and calculations were performed using IBM SPSS Statistics 27.0 (IBM Corp., Released 2020; IBM SPSS Statistics for Windows, Version 27.0; Armonk, NY: IBM Corp.) and MS Excel 2016. Statistical hypotheses were evaluated with a Type I error level of $\alpha=0.05$.

RESULTS

The IVF cycle parameters and demographic data of the OPU groups are shown in Table 1. The anti-Müllerian hormone (AMH) levels and antral follicle counts were lowest in the 35-hour group and highest in the 36-hour group, while LH and FSH levels were lowest in the 36-hour group and highest in the 34-hour group. The daily gonadotropin dose was lowest in the 36-hour group and highest in the 35-hour group, whereas the total gonadotropin dose and COS length were lowest in the 36-hour group and highest in the 34-hour group. The estradiol level on trigger day was lowest in the 34-hour group and highest in the 36-hour group. The PN2 values were lowest in the 34-hour group and highest in the 36-hour group ($P<0.05$). A significant negative relationship was found between OPU timing and embryo transfer (ET) cancellation, OPU cancellation, and ET cancellation groups ($P<0.05$). The study compared embryological outcomes across 34h, 35h, and 36h OPU groups. Day 3 grade 1-2 embryo rates were similar ($P=0.185$), but blastocyst formation rate was highest in the 36-hour group (14.95%), followed by 34-hour (14.23%) and 35-hour (12.43%) ($P=0.025$). The proportion of top-quality and good-quality blastocysts on day 5 was significantly higher in the 34-hour (12.82%) and 36-hour (12.81%) groups than in the 35-hour group (10.55%) ($P=0.029$). A significantly increased rate of day 5–6 embryo transfers was observed in the 36-hour group (33.8%) compared to the 34-hour (14.8%) and 35-hour (18.3%) groups ($P=0.001$). However, single vs. double

Table 1. Comparison of patient demographics and IVF cycle characteristics

	Group 1 34.h OPU (n= 83)	Group 2 35.h OPU (n= 231)	Group 3 36.h OPU (n= 635)	P value
Female age (years)	39.50±5.35	38.16±4.97	39.12±4.06	0.581
Female BMI (kg/m²)	21.03±1.37	24.09±3.81	23.63±3.73	0.058
Duration of infertility (years)	3.75±2.50	4.66 ± 3.70	4.32±3.97	0.218
Number of previous cycles	5.25±3.30	2.95±3.21	5.04±3.74	0.182
AMH (ng/mL)	0.33±0.13	0.36±0.24 ^b	0.38±0.31	<0.001*
LH level on the trigger day (IU/L)	13.46±10.00 ^a	8.54±6.43	5.85±9.42 ^c	<0.001*
Basal antral follicle count	1.50±0.58	1.63±0.76 ^b	2.24±1.41	0.012*
FSH level on the second day of menstruation (IU/L)	19.50±11.93 ^a	15.53±2.04	15.35±2.68	<0.001*
Daily gonadotropin dosage used (IU)	261.67±64.68	274.33±97.65	259.42±83.54 ^c	<0.001*
Totally gonadotropin dosage used (IU)	1856.25±663.44	2211.84±1426.20	2147.60±1270.83 ^c	<0.001*
Duration of controlled ovarian stimulation (days)	7.00±1.83	7.68±2.77	7.93±2.59 ^c	0.003*
Estradiol level on trigger day (pg/mL)	433.75±267.67	572.05±363.09	637.45±484.03 ^c	<0.001*
Number of aspirated oocytes, (COC)	1.00±0.00	1.89±1.45	2.27±1.40	0.080
Number of MII	1.00±0.00	1.58±1.31	2.02±1.25	0.079
Number of PN2	0.50±0.58	1.16±1.12 ^b	1.63±1.05	0.003*
Oocyte maturation rate (%)	83.2±20.53	88.42±21.61	92.37±17.23	0.047*
Fertilization rate (%)	50.00±57.74	78.07±41.59	82.92±29.87	0.038*
OPU cancellation rate (premature ovulation)	13/83 (15.7)	8/231 (3.5)	14/635 (2.2)	<0.001*
ET cancellation rate	44/70 (62.9)	103/223 (46.2)	309/621 (49.8)	0.049*
Causes of ET cancellation, n (%)				
All freeze (other reasons)	9/44 (20.5)	11/103 (10.7)	44/309 (14.2)	
PGT/All freeze	9/44 (20.5)	33/103 (32.0)	146/ 309(47.2)	
No oocyte	8/44 (18.2)	10/103 (9.7)	19/ 309 (6.1)	
No mature oocyte	4/44 (9.1)	6/103 (5.8)	10/ 309 (3.2)	
Fertilization failure	3/44 (6.8)	20/103 (19.4)	38/ 309 (12)	
Embryo developmental arrest	6/44 (13.6)	15/103 (14.6)	34 /309 (11.0)	
Degenerated oocyte	0 (0.0)	0 (0.0)	3/309 (1.0)	
Abnormal fertilization	1/44 (2.3)	2/103 (1.9)	8 /309(2.6)	
PN arrest	4/44 (9.1)	6/103 (5.8)	7/309 (2.3)	

Data are shown as mean±standard deviation or n (%). IVF=In vitro fertilization, OPU=Oocyte pickup, BMI=Body mass index, AMH=Anti-mullerian hormone, LH=Luteinizing hormone, FSH=Follicle stimulating hormone, COC=Cumulus-oocyte complex, MII=Metaphase II, PN=Pronuclear, ET=Embryo transfer, PGT=Preimplantation genetic testing

^aThere was a significant difference from the other groups.

^bThere was a significant difference from Group 3.

^cThere was a significant difference from the other groups.

Table 2. Comparison of embryological development and transfer characteristics in ICSI cycles

Comparison of embryologic developmental characteristics of ICSI cycles				
	Group 1 34.h OPU (n=73)	Group 2 35.h OPU (n=223)	Group 3 36.h OPU (n=621)	P value
D3 grade 1-2 embryo ratio (%)	33.65	37.35	32.87	0.185
Blastocyst ratio (%)	14.23	12.43	14.95	0.025*
D5 TQ-GQ ratio (%)	12.82	10.55	12.81	0.029*
Comparison of the characteristics of embryo transfer cycles				
	Group 1 34.h OPU (n=27)	Group 2 35.h OPU (n=126)	Group 3 36.h OPU (n=352)	P value
Day of embryo transfer, n (%)				0.001*
D3-4	23 (85.2)	103 (81.7)	233 (66.2)	
D5-6	4 (14.8)	23 (18.3)	119 (33.8)	
Number of embryos transferred, n (%)				0.576
Single	22 (81.5)	92 (73.0)	254 (72.2)	
Double	5 (18.5)	34 (27.0)	98 (27.8)	

embryo transfer rates did not differ significantly ($P=0.576$) (Table 2). Pregnancy outcomes showed no significant differences between the groups (Table 3).

DISCUSSION

Our study investigated the impact of OPU timing conducted at 34, 35, and 36 h after hCG trigger on ovarian response parameters, embryologic outcomes, and cycle cancellation rates in patients with poor prognosis. The significant differences observed among the groups suggest that optimising OPU timing can improve outcomes, particularly in patients with a poor prognosis. While female age and body mass index (BMI) did not show significant differences between the groups, significant differences were observed in AMH levels, and the 36-hour OPU group was found to have higher AMH values. This indicates that patients in this group had a relatively better ovarian reserve than those in the earlier OPU groups. Similarly, the basal antral follicle count was significantly higher in the 36-hour group, further supporting enhanced ovarian capacity in this cohort [6, 7]. Additionally, FSH levels were significantly found higher in the 34-

hour OPU group, which is consistent with a DOR and may explain the lower oocyte yield in this subgroup. Oocyte maturation and fertilisation rates were significantly higher in the 36-hour OPU group, suggesting that prolonging the trigger-OPU interval may increase oocyte yield and maturation and thus affect fertilisation. Several studies have supported our findings [8-12]. For instance, Wang *et al.* [8] performed a meta-analysis showing that extending the interval between hCG priming and oocyte retrieval can lead to an increase in the percentage of MII oocytes. Similarly, Garor *et al.* [9] reported higher fertilisation, embryo transfer, and pregnancy rates when oocyte pick-up was performed after 36 hours post-trigger, particularly in GnRH agonist cycles. Furthermore, Shen *et al.* [10] identified an optimal trigger-to-pickup interval of 36.4-37.8 hours in progestin-primed ovarian stimulation cycles, which was correlated with higher rates of mature oocytes, improved implantation rates, and increased live birth rates. Weis *et al.*'s [13] study found that fewer MII oocytes were retrieved when the period between oocyte triggering and OPU was between 33.45 and 34.45 hours. They observed an increase in the MII oocyte rate with a 35-hour delay, which then stabilized up to 38 hours. However,

Table 3. Comparison of pregnancy outcomes per embryo transfer

	Group 1 34.h OPU (n=27)	Group 2 35.h OPU (n=126)	Group 3 36.h OPU (n=352)	P value
Biochemical pregnancy rate, n (%)	6/27 (22.2)	33/126 (26.2)	115/352 (32.7)	0.252
Clinical pregnancy rate, n (%)	6/27 (22.2)	31/126 (24.6)	92/352(26.1)	0.867
Total pregnancy loss rate, n (%)	2/6 (33.3)	15/33 (45.5)	50/115(43.5)	0.859
Live birth rate, n (%)	4/27 (14.8)	15/126 (11.9)	61/352(17.3)	0.338

other studies report contrasting results [14-16]. For instance, Nargund *et al.*'s [14] prospective study found no significant differences in oocyte maturation between OPU procedures performed 33 to 41 hours post-trigger. Bosdou *et al.* [15] showed that in normo-ovulatory women, extending the interval between HCG administration and oocyte collection from 36 to 38 hours did not significantly affect the oocyte collection rate, fertilization rate, or live birth rate. In this study, in contrast to our study, the study group consisted of normovulatory patients [159]. Ranit *et al.* [16] analysed 438 cycles and showed that GnRHa trigger and OPU interval between 32.03 and 39.92 h did not significantly affect oocyte yield and maturation rate. These findings suggest that while optimising timing may benefit certain patient groups, its impact could vary based on specific stimulation protocols and individual patient characteristics. In our study, the 36-hour OPU group had the highest fertilization rate (82.92%), followed by the 35-hour (78.07%) and 34-hour (50.00%) groups. In contrast to our study, a meta-analysis by Wang *et al.* [8] found that a longer interval between hCG triggering and OPU (>36 hours) increased MII oocyte yield but did not significantly improve fertilisation, implantation, or pregnancy rate. Gan *et al.* [3] also found no significant differences in oocyte maturation, fertilisation, or high-quality embryo rates between short (≤ 36 h) and long (>36h) hCG-OPU intervals. There are also studies with results compatible with our study. Choi *et al.* [17] reported higher fertilisation rates at 36th hour, which is compatible with our findings. Garor *et al.* [9] also associated delayed OPU with more embryos and higher fertilisation than early OPU. An important observation in this study was the significantly higher OPU cancellation rate due to early ovulation in the 34 hour OPU

group (15.7%) compared to the 35-hour (3.5%) and 36-hour (2.2%) groups ($P < 0.001$). In the 34-hour OPU group, we aimed to reduce the risk of premature ovulation by scheduling the OPU procedure earlier due to the high LH level on the trigger day. However, early OPU did not reduce the risk of premature ovulation in this group and resulted in fewer mature oocytes and lower fertilisation rates. In line with our study findings, Choi *et al.* [17] reported that early oocyte retrieval during an early LH surge did not effectively reduce cycle cancellation rates and may lead to lower fertilisation rates.

Furthermore, embryo development parameters were superior in the 36-hour OPU group, reinforcing the potential advantage of extended OPU timing. Some studies in the literature support our results [11, 18]. Skvirsky *et al.* [11] showed that extending the time interval between hCG administration and OPU may improve oocyte maturation and embryo quality in women over 36 years of age. The blastocyst formation rate was significantly different among the groups ($P = 0.025$), with the highest rate observed in the 36-hour OPU group. This finding suggests that delaying OPU to 36 h may benefit blastocyst development, possibly due to improved oocyte maturity and cytoplasmic competence. Similarly, the D5 TQ-GQ embryo ratio was significantly different between the groups ($P = 0.029$), with the highest values in the 36-hour group. These findings indicate that a longer interval between the trigger and OPU might improve embryo quality at later stages. In our study, the 34-hour OPU group had higher rates of early ovulation, PN arrest, increased immature oocyte rates, and embryo transfer cancellation due to failure to obtain oocytes. There are many studies supporting our findings [9, 12, 17]. According to our findings, there was no statistically sig-

nificant differences between the groups in terms of biochemical pregnancy rate ($P=0.252$), clinical pregnancy rate ($P=0.867$), total pregnancy loss rate ($P=0.859$), or live birth rate ($P=0.338$). While there was a trend toward higher biochemical and clinical pregnancy rates in the 36-hour OPU group, the lack of statistical significance indicated that OPU timing variations may not significantly impact pregnancy outcomes. In line with our findings, Wang *et al.* [8] reported that the timing of OPU has not significant impact on pregnancy rates. However, other studies have demonstrated improved pregnancy outcomes with later OPU timings [9, 12, 18].

CONCLUSION

Our study highlights the significant impact of OPU timing on ovarian response, embryologic outcomes, and cycle cancellation rates in patients with poor prognosis. The findings suggest prolonging the hCG trigger to OPU interval to 36 hours may enhance oocyte yield, maturation, and embryo development. However, despite these advantages, pregnancy and live birth rates were not statistically significant different among the groups, indicating that while optimising OPU timing may improve laboratory outcomes, its effect on clinical pregnancy remains unclear.

These results align with some studies in the literature, while contradicting others, emphasising the complexity of OPU timing and its dependence on stimulation protocols and individual patient characteristics. Given the variability in outcomes, further prospective, randomised studies are necessary to determine the optimal OPU timing, particularly in patients with DOR and a poor prognosis, to maximise both embryologic and clinical success.

Ethical Statement

The study was approved by Memorial Şişli Hospital Ethics Committee (Decision date and no: 29.04.2024/002).

Authors' Contribution

Study Conception: SK, GÖ, İNB, SÖ; Study Design: GÖ, İNB, SÖ; Supervision: SK, GÖ, İNB, SÖ; Funding: GÖ, İNB, SÖ; Materials: GÖ, İNB, SÖ; Data Collection and/or Processing: GÖ, İNB,

SÖ; Statistical Analysis and/or Data Interpretation: GÖ, İNB, SÖ; Literature Review: GÖ, İNB, SÖ; Manuscript Writer: GÖ, İNB, SÖ; Critical Review: GÖ, İNB, SÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Which type of obesity benefits most from endoscopic intragastric balloon application?

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ABSTRACT

Objectives: As obesity poses significant health risks, exploring minimally invasive treatments like intragastric balloons becomes crucial for enhanced accessibility and efficacy in managing this pervasive public health challenge. This retrospective study aimed to evaluate the effectiveness of Intragastric Balloon (IGB) application in weight reduction across various degrees of obesity, providing a comprehensive assessment of its efficacy.

Methods: A total of 187 patients with a BMI >30 kg/m² underwent IGB application and were categorized into three groups based on the degree of obesity. Statistical analyses were conducted to assess weight loss, excess weight loss, and BMI reduction, focusing on the impact of IGB therapy in different degrees of obesity.

Results: IGB application demonstrated significant efficacy in weight reduction across all degrees of obesity. Notably, the highest rates of excess weight loss were observed in patients with Class 1 obesity. Gender-specific analysis revealed variations in the response to IGB therapy, with females exhibiting higher success rates.

Conclusions: The findings of this study highlight the efficacy of IGB application in achieving weight loss, emphasizing its effectiveness across different degrees of obesity. The notable success in Class 1 obesity underscores the potential of IGB as an effective treatment modality.

Keywords: Gastric balloon, obesity, obesity management, weight loss

In recent years, obesity has become a public health problem with increasing frequency worldwide. The diagnosis of obesity is made using the parameter of the Body Mass Index (BMI), which was defined by Adolphus Quetelet in the mid-19th century and later revised [1]. BMI is calculated by dividing body weight in kilograms by the square of height in meters. For adults, a BMI above 30 kg/m² is defined as obesity. Those with a BMI between 30-35 kg/m² are classified as Class 1, those with a BMI between 35-40 kg/m² as Class 2 and those with a BMI above 40 kg/m² as Class 3 obesity [2].

The worldwide prevalence of overweightness and obesity has doubled within the last 40 years and currently one third of the world population is classified as overweight or people with obesity [3]. According to World Health Organization data, 11% of men and 15% of women worldwide are people with obesity [4]. Although obesity is globally observed more often in women, obesity is seen at a higher rate in men in European countries as Germany, Italy, France and Spain and also in Japan [5].

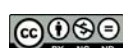
If left untreated, obesity brings with it many complications including hypertension, diabetes, heart dis-

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eases and major depression and it is associated with a lower rates of life expectancy [5].

Although a conservative treatment strategy including a diet tailored to individual needs, physical activity and behavioral changes, is recommended in the first step to achieve weight loss in the treatment of obesity, if individual treatment goals cannot be achieved with this conservative treatment regimen, pharmacotherapy, surgical treatment or endoscopic treatment modalities such as Intra-gastric Balloon (IGB) application should be initiated [5, 6]. Surgical methods may be preferred especially in patients with a BMI >35 kg/m² who do not benefit from conservative treatment methods and pharmacotherapy [7]. Although bariatric surgery is the most effective treatment method for obesity with everlasting results, since it is associated with difficult accessibility, high cost, and higher rates of morbidity and mortality, there is a need for minimally invasive and effective endoscopic treatment methods for obesity such as IGB application [8].

The effect of IGB which occupies space in the stomach is multifactorial. It provides weight loss by reducing food intake and making physiologic and neurohormonal changes. The IGB is placed endoscopically in the stomach and then filled with liquid or air. The IGB is left in the stomach for 6 months and 1 year depending on the type of intra-gastric balloon used. In various randomized controlled studies, excess weight loss varying between 34-50% has been reported with the application of IGB [9-11].

In this study, we have aimed to investigate the effectiveness of IGB application in weight loss according to gender of the patients and different degrees of obesity.

METHODS

In this study, the data of a total of 187 patients aged >18 years, with a BMI of >30 kg/m², without any previous application of bariatric surgery, and any intra-gastric pathology detected during endoscopy, who had undergone IGB application 6 months previously with a diagnosis of obesity in the endoscopy unit of the General Surgery Clinic of Balıkesir University School of Medicine between May 2019 and May 2022 were retrospectively reviewed. Eleven patients whose IGBs were removed because they could not tolerate its application were excluded from the study. The remaining 176 patients were divided into 3 groups according to the degrees of obesity for both genders separately and for the whole patient population and the efficacy of IGB application was evaluated according to the rates of weight loss, excess weight loss and reduction in BMI in these groups. Percentage of excess weight loss is a widely used marker in the literature to determine weight loss in obesity treatment, as recommended by the International Federation for the surgery of Obesity and Metabolic Disorders (IFSO) [12, 13]. In our study, we defined the ideal weight as the weight corresponding to a BMI of 25 kg/m² and calculated the percentage of excess weight loss (%EWL) and percentage of total weight loss (%TWL) according to the formulas in Fig. 1. This study was approved by the Clinical Research Ethics Committee of Balıkesir University School of Medicine (Decision date: 22.11.2023 and no. 2023/179).

Procedural Technique

Informed consent was obtained from all patients

$$\%Total\ weight\ loss = \frac{(Weight\ at\ the\ time\ of\ IGB\ placement) - (Weight\ at\ the\ time\ of\ IGB\ removal)}{Initial\ weight} \times 100$$

$$\%Excess\ weight\ loss = \frac{(Weight\ at\ the\ time\ of\ IGB\ placement) - (Weight\ at\ the\ time\ of\ IGB\ removal)}{(Initial\ weight) - (Ideal\ weight)} \times 100$$

Fig. 1. Formulas for calculating %EWL and %TWL.



Fig. 2. Placement of the IGB into the stomach.

before the application of IGB. After the anesthesiologist administered sedoanalgesia, the esophagus, stomach and duodenum of the patients were carefully evaluated with an endoscope. After endoscopic evaluation, in patients without any detectable pathology such as severe esophagitis, gastritis, peptic ulcer, gastric polyps, Crohn's disease, etc., a non-absorbable silicone-based intragastric balloon was orally advanced into the stomach for 6-month therapy (Fig. 2). After reinsertion of the endoscope into the stomach, the IGB, which was positioned in the corpus-fundus region of the stomach was inflated with approximately 450-600 cc of saline containing methylene blue solution until the endoscope in retrovert position was squeezed between the stomach and the balloon (Fig. 3). Afterwards, the procedure was terminated by pulling the IGB's tube away from its pin. After the procedure, the patients were followed up by the same dietitian team. The patients' balloons were removed after 6 months and their current weights were evaluated.

Statistical Analysis

IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used for statistical analyses of the results obtained in the study. The conformity of the variables to normal distribution was evaluated by Shapiro-Wilk

test, Q-Q graphs and histograms. In addition to descriptive statistical methods (minimum, maximum, mean, standard deviation, frequency, and percentage), Student-t test was used for the comparative evaluation of quantitative data between two groups. One-way Analysis of Variance (ANOVA) was used for the comparative evaluation of quantitative data between more than two groups. Levene's test was used to test the assumption of homogeneity of variances. In the determination of the groups causing differences based on the results of ANOVA test; those with homogeneous variances were evaluated by Tukey HSD and those with non-homogeneous variances by Tamhane T2 post-hoc test. The levels of statistical significance were set at $P < 0.05$ and $P < 0.01$.

RESULTS

The study was conducted with a total of 176 people with obesity including 135 (76.7%) female and 41 (23.3%) male cases to investigate the efficacy of endoscopic IGB application in different groups of people with obesity with a mean age of 38.36 ± 9.84 years (range: 18-62 years). Based on BMI values, 67.6% ($n=119$) of the patients were classified as Group 1

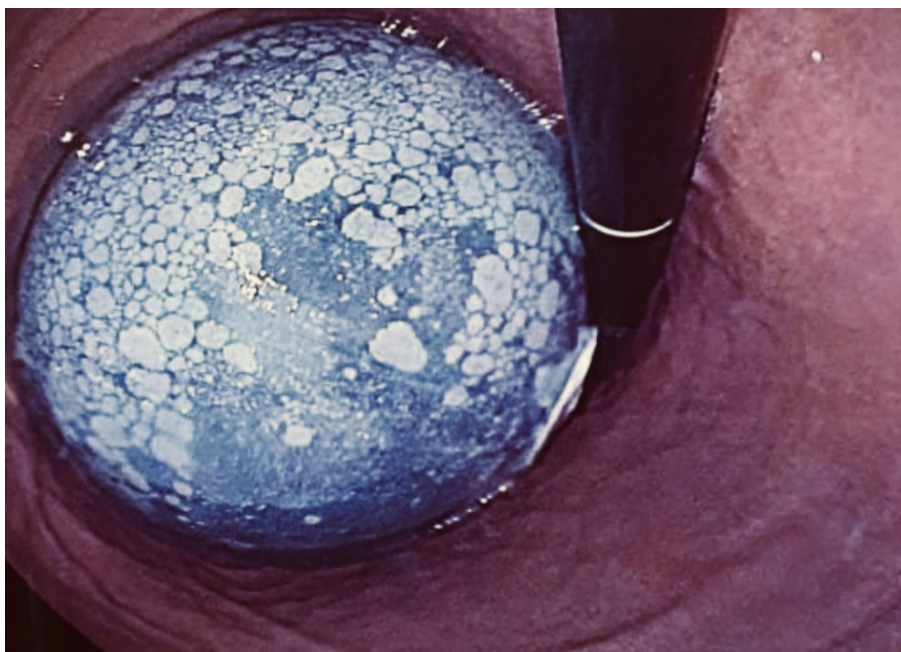


Fig. 3. Inflating of the IGB in the stomach.

(Class 1 obesity), 22.2% (n=39) as Group 2 (Class 2 obesity) and 10.2% (n=18) as Group 3 (Class 3 obesity) (Table 1).

In women, there was no statistically significant

difference between BMI classes in terms of the average rate of achieved weight loss and the amount of decrease in BMI ($P>0.05$), however, a statistically significant difference was detected between BMI

Table 1. Demographic characteristics of the patients before IGB application

		Female (n=135)	Male (n=41)	Total (n=176)
Age (year)		38.99±10.27 (18-62)	36.29±7.99 (18-50)	38.36±9.84 (18-62)
Age groups	18-35 years	46 (34.1)	18 (43.9)	64 (36.4)
	36-45 years	49 (36.3)	15 (36.6)	64 (36.4)
	> 45 years	40 (29.6)	8 (19.5)	48 (27.3)
Body weight (kg)		89.53±10.29 (69-139)	104.83±14.12 (78-144)	93.10±12.99 (69-144)
Excess weight (kg)		23.06±8.77 (13-54)	27.80±10.76 (16-58)	24.16±9.45 (13-58)
BMI (kg/m²)		33.71±3.33 (30.04-42.68)	34.06±3.41 (30.00-42.72)	33.79±3.34 (30.00-42.72)
BMI groups	Group 1	91 (67.4)	28 (68.3)	119 (67.6)
	Group 2	31 (23)	8 (19.5)	39 (22.2)
	Group 3	13 (9.6)	5 (12.2)	18 (10.2)

Data are shown as mean±standard deviation (minimum-maximum) or n (%) where appropriate. BMI=Body Mass Index, IGB=Intra-gastric Balloon.

classes in terms of the average rate of excess weight loss ($P<0.001$) (Table 2). As a result of the statistical evaluations performed to determine the BMI class from which the intergroup differences originated, we found that the average rate of excess weight loss in Group 1 was significantly higher when compared to Groups 2 ($P<0.001$) and 3 ($P<0.001$), while a significant difference was not detected between Groups 2 and 3 in this respect ($P>0.05$).

In men, there was no statistically significant difference between BMI classes in terms of the average rate of achieved weight loss ($P>0.05$), whereas a statistically significant difference was revealed in terms of the average rate of excess weight loss ($P<0.001$) (Table 2). As a result of statistical evaluations performed to determine the BMI class from which the intergroup differences originated, it was found that the average rate of excess weight loss in Group 1 was significantly higher than those in Groups 2 ($P=0.002$) and 3 ($P<0.001$), whereas there was no difference between Groups 2 and 3 in this respect ($P>0.05$). In men, there was a statistically significant difference between BMI

classes in terms of the average amount of decrease in BMI ($P=0.006$) (Table 2). As a result of the statistical evaluations performed to determine from which BMI class the difference originated, we disclosed that the average amount of decrease in BMI of Group 3 was significantly higher than those of Groups 1 ($P=0.022$) and 2 ($P=0.047$) ($P<0.05$), while there was no significant difference between Groups 1 and 2 in this respect ($P>0.05$).

Although a statistically significant difference was not found between BMI classes in terms of average rate of achieved weight loss ($P>0.05$), a statistically significant difference was found in terms of the average rate of achieved excess weight loss ($P<0.001$) (Table 2). As a result of the statistical evaluations performed to determine from which BMI class the difference originated, it was found that the rate of excess weight loss in Group 1 was significantly higher than those estimated for Groups 2 ($P<0.001$) and 3 ($P<0.001$), while any statistically significant difference could not be detected between Groups 2 and 3 in this regard ($P>0.05$). A statistically significant difference was re-

Table 2. Comparison of rates of weight loss, excess weight loss and reduction in BMI according to classes of BMI in patients treated with IGB at the end of six-month follow-up

Classes of BMI	n (%)	Weight Loss (%)	Excess Weight Loss (%)	Decrease in BMI (kg/m ²)
Women	135 (76.7)	15.8±5.82	77.28±38.70	5.32±1.99
Group 1	91 (67.4)	16.03±5.98	91.98±36.77	5.10±1.95
Group 2	31 (23)	15.31±6.20	51.29±22.91	5.56±2.19
Group 3	13 (9.6)	15.33±3.69	36.38±8.53	6.31±1.54
P value		0.801	<0.001**	0.091
Men	41 (23.3)	14.94±4.10	59.27±23.77	5.12±1.55
Group 1	28 (68.3)	14.34±4.38	67.43±23.62	4.61±1.43
Group 2	8 (19.5)	16.82±2.91	47.50±8.52	6.16±1.08
Group 3	5 (12.2)	15.32±3.74	32.40±10.43	6.27±1.55
P value		0.332	<0.001**	0.006*
Total	176 (100)	15.60±5.47	73.09±36.52	5.27±1.90
Group 1	119 (67.6)	15.63±5.67	86.20±35.61	4.98±1.84
Group 2	39 (22.2)	15.62±5.68	50.51±20.74	5.68±2.02
Group 3	18 (10.2)	15.33±3.59	35.28±8.96	6.30±1.50
P value		0.976	<0.001**	0.007**

Data are shown as mean±standard deviation or n (%) where appropriate. BMI=Body Mass Index.

One-Way Analysis of Variance (ANOVA), * $P<0.05$, ** $P<0.01$

vealed between BMI classes in terms of the average amount of decrease in BMI in all patients ($P=0.007$) (Table 2). As a result of the statistical evaluations performed to determine from which BMI class the difference originated, average amount of decrease in BMI of Group 3 was significantly higher than those of Groups 1 ($P=0.015$) and 2 ($P=0.046$), while there was no significant difference between Groups 1 and 2 in this respect ($P>0.05$).

When male, and female patients treated with IGB were compared in terms of rates of weight loss, excess weight loss and the amount of decrease in BMI, the average rate of excess weight loss was found to be statistically significantly higher in women than in men in Group 1 ($P<0.001$) (Table 3).

DISCUSSION

Obesity is a chronic disease associated with different morbidity and mortality rates and its prevalence has been increasing in recent years. Current approaches to the treatment of obesity include lifestyle modifications, pharmacologic treatment and bariatric surgery. Although bariatric surgery is the most effective treatment method with long-lasting favorable results, because of its disadvantages such as difficult accessibility, higher cost, morbidity and mortality rates, there is a need for minimally invasive and effective bariatric treatment methods such as IGB application [8].

A total of 135 female patients included in our

study were compared according to the degrees of their obesity. Statistically significantly higher rates of excess weight loss was detected only in Group 1 ($P<0.001$), while no difference was found between three groups in terms of other parameters (Table 3). In the comparison of the three groups in which 41 male patients were divided according to their degrees of obesity, the rate of excess weight loss was statistically significantly higher in Group 1 ($P<0.001$) and the decrease in BMI was statistically significantly higher in Group 3 ($P=0.006$) (Table 2). We divided the entire patient population into three groups according to the degree of obesity, and observed that the decrease in BMI ($P=0.007$) was higher in Group 3, and the rates of excess weight loss were significantly higher in Group 1 ($P<0.001$) compared to the other groups (Table 2). The reason why the effect of IGB application on excess weight loss was seen especially in class 1 obesity group may be that the initial body weights are comparatively lower in this patient group and therefore the percentage of decrease achieved is proportionally much greater (Fig. 1).

In our study, we observed that the IGB procedure provided an average success rate of 77% in women and 59% in men in achieving the ideal weight. In our opinion, the difference between the rates of achieving the ideal weights between men and women may be that women aim to achieve their ideal weights more strongly as a result of social pressure on them in the context of gender.

Fittipaldi-Fernandez *et al.* [14] reported a weight loss of 19.13 ± 8.86 kg and a significant decrease in

Table 3. Comparison of rates of weight loss, excess weight loss and BMI reduction in male, and female patients treated with IGB application at the end of six-month follow-up period

Classes of BMI	Gender	Weight Loss (%)	Excess Weight Loss (%)	Decrease in BMI (kg/m ²)
Group I	Female	16.03±5.98	91.98±36.77	5.10±1.95
	Male	14.34±4.38	67.43±23.62	4.61±1.43
	P value	0.167	<0.001**	0.155
Group II	Female	15.31±6.20	51.29±22.91	5.56±2.19
	Male	16.82±2.91	47.50±8.52	6.16±1.08
	P value	0.511	0.651	0.461
Group III	Female	15.33±3.69	36.38±8.53	6.31±1.54
	Male	15.32±3.74	32.40±10.43	6.27±1.55
	P value	0.994	0.415	0.965

Data are shown as mean±standard deviation. BMI=Body Mass Index, IGB=Intragastric Balloon.

Student t-Test * $P<0.05$, ** $P<0.01$

BMI from 36.94 ± 5.67 kg/m² to 30.08 ± 5.06 kg/m² in 5444 patients who had undergone IGB application and reported the average rates of total weight loss (18.42 ± 7.25) and excess weight loss (65.66 ± 36.24) as indicated. Similar to our study, the average rate of excess weight loss was highest in class 1 and lowest in class 3 obesity groups (class 1: 76.67%; class 2: 56.01% and class 3: 45.45%) and the rate of excess weight loss was higher in women (69.71%) than in men (53.39%) [14].

In a meta-analysis where fifteen studies were evaluated, the decrease in BMI was reported as 5.7 kg/m², similar to our study; however, the rate of excess weight loss achieved was reported as 32% at a rate much lower than we detected in our study [15].

In a study on 34 patients investigating the efficacy and safety of IGB application in different obesity groups, an average decrease of $6.8\% \pm 7.3\%$ or 7.3 kg in the weight, and an average reduction of 7.0 % or 2.7 kg/m² in BMI of the whole patient group were observed at the end of 6-month follow-up period. Similar results were observed in the subgroup analysis of patients with BMI >40 kg/m², accordingly, the average percentage decreases in mean total body weight (7.2% or 8.9 ± 8.4 kg), and in BMI (6.9% or 3.0 ± 3.3 kg/m²) were achieved [16]. In the aforementioned publication, lower rates of weight loss and BMI reduction were reported compared to our study, which may be due to the smaller number of patients included in the cited study.

In another study in which weight loss achieved with IGB application was evaluated in patients with different degrees of obesity, average rates of weight loss (18.9%), excess weight loss (60.1%), and a decrease of 6.76 kg/m² in BMI were reported as indicated. In the same study, patients were divided into five groups according to the degrees of obesity and each group was compared in terms of their weight before IGB application (T0), at the first (T1), sixth (T2) and sixth (T3) months after removal of IGB. As a result, statistically significant differences were found between T0 and T1 and also between T1 and T2 time points in all groups in terms of all weight loss assessment methods used; however, no significant difference was observed between T2 and T3 time points [17].

Although the retrospective nature of the study, the short-term follow-up of patients after the removal of IGB, the lack of standardization in diet and exercise, the absence of an assessment of the metabolic and hor-

monal effects of IGB, the lack of monitoring of patient compliance and lifestyle changes, and the absence of a comparison between different types of IGB are limitations of this study, the high patient volume relative to similar studies in the literature and the comparison of patients based on gender and degrees of obesity constitute its strengths.

Limitations

The limitations of our study include the lack of evaluation of patients' psychosocial factors, the lack of a comprehensive assessment of side effects and tolerability, and the absence of a comparison with bariatric surgery.

CONCLUSION

Our study has shown that the effect of IGB application on excess weight loss is especially seen in patients with class 1 obesity. In addition, our average success rates of 68% in females, 50% in males, and 64% in all patients in achieving ideal weight were higher than many other success rates reported in the literature for accomplishing ideal body weights. This shows that IGB application is a good and effective treatment option especially for class 1 obesity. We also observed that it could be a method to help lose weight in type 2 and 3 obese patients who have conditions preventing them from undergoing surgery. However, we believe that prospective randomized controlled studies with a higher number of patients are needed to determine the efficacy of IGB application in the treatment of obesity.

Ethical Statement

This study was approved by the Clinical Research Ethics Committee of Balıkesir University School of Medicine (Decision date: 22.11.2023 and no. 2023/179).

Authors' Contribution

Study Conception: AGŞ, EA; Study Design: AGŞ, EA; Supervision: AGŞ, EA; Funding: AGŞ, EA; Materials: AGŞ, EA; Data Collection and/or Processing: AGŞ, EA; Statistical Analysis and/or Data Interpretation: AGŞ, EA; Literature Review: AGŞ, EA; Manuscript Preparation: AGŞ, EA; and Critical Review: AGŞ, EA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Cognitive dysfunction after ischemic stroke

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ABSTRACT

Objectives: One of the most important and common consequences of ischemic stroke is the cognitive impairment observed after stroke. This study aimed to investigate the role of strategic stroke among post-stroke cognitive impairment using the Montreal Cognitive Assessment Scale (MOCA).

Methods: This study was planned as a prospective cross-sectional study. Patients admitted between 3 and 12 months after stroke were included in the study. Patients who had a stroke at least 3 months ago, who had not been admitted for a year after the stroke, and who gave consent to participate in the study were considered as inclusion criteria.

Results: This study included 45 (44.1%) females and 57 (55.9%) males. When evaluated in terms of comorbidity, the frequency of hyperlipidemia was found to be significantly higher in the cognitively impaired group (46.5% vs. 25.4%, $P=0.027$). Thyroid stimulating hormone (TSH) levels were found to be lower in the Cognitive Impairment Group (0.93 μ IU/mL vs. 1.03 μ IU/mL, $P=0.021$). Considering the finding rates and significance level of lesion sites between the groups, the strategic infarction rate was found to be significantly higher in the cognitively impaired group (62.8% vs. 33.9%, $P=0.004$). In cognitive tests, the cognitive impairment group showed significantly lower performance in all areas ($P<0.05$).

Conclusions: It should be kept in mind that the MOCA scale can be a good evaluation scale in detecting patients with cognitive impairment after ischemic stroke.

Keywords: Montreal Cognitive Assessment Scale, Ischemic stroke, hyperlipidemia, cognitive impairment

One of the most important and common consequences of ischemic stroke is the cognitive impairment observed after stroke. This is one of the reasons for decreased quality of life and long-term disability [1]. Post-stroke cognitive impairment can be observed in almost half of stroke patients within the first year [2, 3]. Demographic and vascular risk factors, as well as the burden of the lesion detected on imaging, can predict this disorder [4]. However, the role and relationship of strategic stroke in terms of the presence of post-stroke cognitive impairment has not

yet been clearly established with strong evidence, and it is important to conduct research on this subject.

Cognitive impairment seen after stroke occurs 3 to 6 months after the stroke and affects the patient's cognitive functions. Cognitive dysfunction does not only include neurological deficits, but also includes conditions such as aphasia and memory loss [5]. Depending on the affected regions, visual-spatial, attention and executive dysfunctions are among the other results that cognitive impairment can be seen in patients. These findings can be seen after vascular cog-

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nitive impairment and can sometimes be confused with cognitive impairment after stroke. Strategic stroke is mentioned when cognitive functions originate from regions such as the hippocampus, thalamus and key thalamic [6].

The relationship between the location of stroke and the level of cognition began to be examined with case reports starting from the 19th century [7]. Studies conducted over the last 25 years have been investigating the relationship between some cognitive abilities and neuroanatomy. In most of these studies, analyzes were obtained using modern symptom and lesion mapping techniques [8]. However, very few of these studies state that stroke localization can be predictive in detecting post-stroke cognitive disorders [9]. In particular, predictive modeling created by voxel-based lesion symptom mapping reveals in detail the relationship between ischemic stroke localizations in the left frontotemporal, hippocampus and thalamus and post-stroke cognitive impairment [10]. In recent years, meta-analyses revealing the relationship between strategic infarct location and the risk of cognitive impairment after stroke reveal a very important connection [11].

There is still a need to examine the relationship between stroke localization and post-stroke cognitive impairment. In this study, we aimed to investigate the relationship between post-stroke cognitive impairment and strategic stroke using the Montreal Cognitive Assessment Scale (MOCA).

METHODS

Study Design and Patient Population

This study was planned as a prospective cross-sectional study at Neurology Clinic. This study was approved by the Adana City Training and Research Hospital Clinical Research Ethics Committee (Decision date: 31.08.2023 and no: 2803). This study aimed to include patients who applied to the neurology stroke outpatient clinic after a stroke. Patients admitted between 3 and 12 months after stroke were included in the study. Patients who had a stroke at least 3 months ago, who had not been admitted for a year after the stroke, and who gave consent to participate in the study were considered as inclusion criteria. Exclusion criteria from the study were determined as those who applied within the

first 3 months or more than a year after the stroke, those who did not consent to participate in the study, those with dysarthria, aphasia, or disorders of consciousness that may prevent the evaluation of their level of consciousness, those with a history of recurrent stroke, those with a history of dementia, patients with neurodegenerative diseases such as Parkinsonism, and patients diagnosed with depression.

One hundred and two patients who met the inclusion criteria were included in the study between September 1, 2023 and February 28, 2024. The demographic data of the patients, the medications they used, and the locations of involvement in magnetic resonance imaging (MRI) and diffusion cerebral magnetic resonance imaging results were recorded. Additionally, blood biochemistry tests (blood urea nitrogen, creatinine, liver function tests, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, vitamin B-12, thyroid-stimulating hormone and free T4 levels) were recorded.

Magnetic Resonance Imaging (MRI)

MRI data were acquired on a Philips 3.0-T scanner (Intera; Philips, Best, The Netherlands) using a standardised protocol. In brief, diffusion MRI data were acquired using a single-shot spin echo-planar imaging sequence (TR/TE: 6,638/73 ms; 48 contiguous slices; reconstructed voxel size: 1.72×1.72×2.50 mm), using 45 isotropically distributed diffusion-sensitive gradients with a 90° flip angle, a b-value of 1,200 s/mm² and a b = 0 s/mm². Other sequences included T2-weighted (TR/TE: 1.653/20 ms; reconstructed voxel size: 0.96×0.95×3 mm), FLAIR (TR/TE/TI: 11,000/125/2,800 ms; reconstructed voxel size: 0.96×0.95×3 mm) and 3D T1-weighted sequences (TR/TE: 7.2/2.9 ms; reconstructed voxel size: 1.0×1.0×1.0×1.0 mm).

Montreal Cognitive Assessment Scale (MOCA)

The MOCA scale was applied to the patients by a neurologist at the neurology outpatient clinic. With this scale, visual spatial/executive functions (5 points), naming (3 points), memory (6 points), attention (no points), language (3 points), abstract thinking (2 points), delayed recall (5 points). and orientation (6 points) parameters were evaluated. The evaluation was made out of a total of 30 points. Patients with a MOCA score of 21 and above were determined as the

group with normal cognitive function. Patients with a MOCA score of 20 and below were grouped as patients with abnormal cognitive function.

Statistical Analysis

The data obtained from the study were recorded in SPSS 26.0 (Armonk, NY: IBM Corp.). Categorical measurements were recorded as numbers and percentages; continuous measurements were recorded as mean and standard deviation. The suitability of continuous variables to normal distribution was examined with the Shapiro Wilk test. In comparisons of contin-

uous variables between groups, the Student-t test was used for normally distributed parameters and the Mann-Whitney U test was used for non-normally distributed parameters. Chi-Square test or Fisher test was used to analyze categorical variables. Univariate and multivariate regression analysis was used to identify variables that predict cognitive impairment and their significance levels. The prognostic value of AST level on cognitive impairment was evaluated by ROC (Receiver Operating Characteristic) analysis. Within the scope of the analysis, the predictive value for the AST level was determined and the sensitivity and speci-

Table 1. Clinical characteristics of the study population

Variable	Cognitively normal group (n=59)	Cognitive impairment group (n=43)	P value
Age (years)	53.4 ± 8.1	57.0 ± 8.4	0.036
Sex, female, n (%)	26 (44.1)	19 (44.2)	0.991
HT, n (%)	51 (44.1)	39 (44.2)	0.510
DM, n (%)	32 (54.2)	16 (37.2)	0.089
CAD, n (%)	14 (23.7)	12 (27.9)	0.633
HL, n (%)	15 (25.4)	20 (46.5)	0.027
AF*, n (%)	2 (3.4)	6 (14.0)	0.067
Smoking, n (%)	23 (39.0)	16 (37.2)	0.856
Family history of dementia, n (%)	12 (20.3)	8 (18.6)	0.828
Statin use, n (%)	18 (30.5)	16 (37.2)	0.478
PPI use, n (%)	12 (20.3)	9 (20.9)	0.942
BUN (mg/dL), median (IQR)	28.0 (12.0)	34.0 (11.6)	0.022
Creatinine (mg/dL), median (IQR)	0.76 (0.2)	0.79 (0.2)	0.949
ALT (IU/I), median (IQR)	18.0 (14.0)	21.0 (16.0)	0.378
AST (IU/I), median (IQR)	24.0 (8.0)	26.0 (10.0)	0.039
Total cholesterol (mg/dL), median (IQR)	175.0 (78.0)	180.0 (59.3)	0.535
LDL (mg/dL), median (IQR)	111.0 (40.0)	120.0 (45.0)	0.533
HDL (mg/dL), median (IQR)	42.0 (11.0)	45.0 (9.0)	0.409
Triglyceride (mg/dL) median (IQR)	160.0 (184.0)	160.0 (108.0)	0.569
Vitamin B12 level (pmol/L), median (IQR)	257.0 (167.0)	302.0 (240.0)	0.130
TSH (μIU/mL), median (IQR)	1.03 (0.9)	0.93 (0.4)	0.021
ftT4 (ng/dL), median (IQR)	0.95 (0.1)	0.88 (0.1)	0.143

Data are showed as mean±standard deviation or median (interquartile range) or n (%) where appropriate. CAD=Coronary artery disease, HL=Hyperlipidemia, AF=Atrial Fibrillation, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, DM=Diabetes mellitus, HDL=High density lipoprotein, HT=Hypertension, LDL=Low density lipoprotein, PPI=Proton pump inhibitors, BUN=Blood urea nitrogen, ftT4=Free thyroxine, TSH=Thyroid stimulating hormone.

*Fisher's exact test

ficity rates of this value were calculated. P values <0.05 were considered statistically significant.

RESULTS

The study, which was examined in two groups as cognitively normal group (n=59) and cognitively impaired group (n=43), was conducted on a total of 102 cases. Of those included in the study, 44.1% (n=45) were women and 55.9% (n=57) were men. The average age of the participants was 54.9±8.4 years, and the average age of the cognitively impaired group was found to be significantly higher than the cognitively normal group (57.0±8.4 vs. 53.4±8.1, P=0.036). When evaluated in terms of comorbidity, the frequency of hyperlipidemia was found to be significantly higher in the cognitively impaired group (46.5% vs. 25.4%, P=0.027). In labo-

ratory parameters, blood urea nitrogen (BUN) levels were found to be significantly higher in the cognitively normal group (34.0 mg/dL vs. 28.0 mg/dL, P=0.022), while aspartate aminotransferase (AST) levels were also found to be higher in this group (26.0 IU/L vs. 24.0 IU/L, P=0.039). Thyroid stimulating hormone (TSH) levels were found to be lower in the Cognitive Impairment Group (0.93 µIU/mL vs. 1.03 µIU/mL, P=0.021) (Table 1).

Considering the finding rates and significance level of lesion sites between the groups, the strategic infarction rate was found to be significantly higher in the cognitively impaired group (62.8% vs. 33.9%, P=0.004). In cognitive tests, the cognitive impairment group showed significantly lower performance in all areas (P<0.05) (Table 2). The results of univariate and multivariate logistic regression analysis applied to determine the risk factors of cognitive impairment are

Table 2. Comparison of MOCA scale parameters and lesion locations in patient groups with and without cognitive impairment.

Variable	Cognitively normal group (n=59)	Cognitive impairment group (n=43)	P value
NIHSS, median (IQR)	1.0 (2.0)	0.0 (2.0)	0.350
MRS, median (IQR)	0.0 (1.0)	0.0 (1.0)	0.646
Lesion side, right, n (%)	33 (55.9)	22 (51.2)	0.633
Strategic infarction, n (%)	20 (33.9)	27 (62.8)	0.004
Thalamic*, n (%)	4 (6.8)	6 (14.0)	0.315
Internal capsule, n (%)	4 (6.8)	4 (9.3)	0.718
Caudate*, n (%)	6 (10.2)	6 (14.0)	0.558
Angulargyrus*, n (%)	8 (13.6)	7 (16.3)	0.702
Hippocampus*, n (%)	40 (67.8)	26 (60.5)	0.444
Anterior circulation, n (%)	12 (20.3)	8 (18.6)	0.828
Posterior circulation, n (%)	19 (32.2)	17 (39.2)	0.444
Visuospatial executive function, median (IQR)	5.0 (1.0)	3.0 (2.0)	<0.001
Naming, median (IQR)	3.0 (1.0)	2.0 (2.0)	<0.001
Attention, median (IQR)	4.0 (1.0)	4.0 (2.0)	0.119
Language, median (IQR)	2.0 (0.0)	1.0 (1.0)	<0.001
Intangible thinking, median (IQR)	2.0 (1.0)	1.0 (1.0)	0.007
Delayed recall, median (IQR)	2.0 (2.0)	0.0 (1.0)	<0.001
Orientation, median (IQR)	6.0 (0.0)	6.0 (1.0)	0.001

Data are showed as median (interquartile range) or n (%) where appropriate.

*Fisher's exact test

Table 3. Univariate and multivariate logistic regression analysis

Variable	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	1.053 (1.002-1.107)	0.040	1.071 (1.003-1.143)	0.040
Hyperlipidemia	2.551 (1.103-5.897)	0.029	2.467 (0.905-6.723)	0.078
Atrial fibrillation	4.622 (0.885-24.135)	0.070		
Diabetes mellitus	0.500 (0.224-1.116)	0.091		
Aspartate aminotransferase	1.069 (1.004-1.138)	0.037	1.107 (1.021-1.199)	0.014
Thyroid stimulating hormone	0.510 (0.265-0.984)	0.045	0.466 (0.226-0.962)	0.039
Blood urea nitrogen	1.029 (0.993-1.067)	0.114		
Strategic infarction	3.291 (1.449-7.474)	0.004	5.092 (1.855-13.978)	0.002

shown in Table 3. Among the age, hyperlipidemia, AST, TSH and strategic infarct values found to be significant in univariate analysis, only age (OR: 1.071, P=0.040), AST (OR: 1.107, P=0.014), TSH (OR: 0.466, P=0.039) were found to be significant in multivariate analysis and strategic infarction (OR: 5.092, P=0.002) independent risk were determined as factors.

DISCUSSION

Our study has some important findings. The first of these is that there is a significant relationship between strategic stroke and cognitive impairment. We found that strategic stroke localization is more common in patients with cognitive impairment. Other important findings are the presence of hyperlipidemia and low TSH levels in patients with cognitive dysfunction.

Post-ischemic stroke lesion symptom mapping studies have often been used as an outcome measure on cognitive function. A recent meta-analysis study showing that there is a relationship between strategic infarct areas in predicting post-stroke cognitive impairment shows very important results. This meta-analysis reveals that truly strategic infarct localizations are significantly effective in predicting post-stroke cognitive impairment [11]. Although the vascular etiology of stroke and the extent and volume of involvement are important, it is emphasized that there is a strong connection with the localization of the lesion in terms of post-stroke cognitive functions [4]. It is known that supratentorial infarctions have a different infarct area distribution than cortical and larger sub-

cortical infarcts [12]. While left thalamic strokes may predict post-stroke cognitive impairment, the situation may be different for subcortical regions including the basal ganglia. It is emphasized that these regions should have a larger infarct area in order to predict cognitive dysfunction after stroke [11].

Although these studies reveal that localizations determined by modern mapping methods are effective in predicting cognitive impairment, it is important to consider some confounding factors. Among these, the most important issues are issues such as the patients' previous cognitive levels, the presence of previous lesions, and the presence of depression [13]. In this study, we aimed to eliminate bias in the selection of patients, especially on these issues. Patients with a previous history of depression or previous stroke lesions were excluded from the study to eliminate these confusing situations. As far as we have researched, we have not found sufficient literature data using the MOCA scale to evaluate cognitive functions based on lesion localization.

In our study, we found that the frequency of strategic stroke was significantly higher in patients with cognitive dysfunction as a result of MOCA measurements. In this respect, our study confirms studies showing that strategic stroke is effective in predicting post-stroke cognitive impairment. In this way, identifying and early evaluation of patients with cognitive impairment according to the MOCA scale can guide clinicians regarding rehabilitation treatment strategies. In addition, it may contribute to the correct use of resources in these patients by determining them.

Advanced age is a major risk factor for cognitive

dysfunction after stroke. According to the results of the REGARDS study, each year of advancing baseline age increases the odds of cognitive dysfunction by 17% per subsequent year [14]. This emphasis suggests that advanced age is a strong risk factor for cognitive dysfunction after stroke. Although the mean age of our patients in our study was less than 65 years, we found that the mean age of patients with cognitive impairment was higher than that of patients without cognitive impairment. Considering that increasing age increases the risk of cognitive dysfunction, cognitive dysfunction after stroke cannot be considered independent of age.

Hyperlipidemia is one of the risk factors leading to adverse outcomes, especially cardiovascular. One of these undesirable consequences is ischemic strokes [15]. Hyperlipidemia is known to be a risk factor that can lead to thrombotic consequences. One of the important results of our study is that hyperlipidemia is significantly present in patients with impaired cognitive functions compared to patients without impairment. Although our study revealed that hyperlipidemia may be associated with cognitive dysfunction, it also shows that statin treatments alone are not effective in improving these cognitive functions. Although studies emphasize the preventive effects of statin treatments, further research is needed to reveal whether they are effective in preventing cognitive dysfunction.

Another important finding of our study is that TSH values were found to be significantly lower in patients with cognitive dysfunction compared to those without. The results of two meta-analyses analyzing prospective cohort studies reveal an association between subclinical hyperthyroidism and coronary artery disease [16, 17]. These cardiac effects include atrial fibrillation. Atrial fibrillation is one of the conditions that increases the risk of ischemic stroke [18, 19]. For this reason, it is necessary to emphasize that subclinical thyroid disorder is a risk factor for ischemic stroke. There is not enough literature data revealing the relationship between cognitive dysfunction and subclinical thyroid disorder and stroke. According to the results obtained in our study, it can be said that there may be a relationship between post-stroke cognitive impairment and subclinical hyperthyroidism. In light of the data we obtained, the need to investigate subclinical thyroid disorder in patients with impaired cognitive functions after stroke makes it important for clinicians. It is clear that further research is needed to clearly.

Limitations

Our study has some limitations. The first of these is that the study was conducted in a single center. Another limiting step is the small number of patients included in the study. In our study, we found that there was a statistically significant difference between the two groups in the analysis of the total infarcts of the strategic infarct area. However, we found that there was no statistically significant difference in the analysis of the individual infarct areas between the groups. We would like to state that this situation is due to the limited number of patients included in the study. The number of cases is even more limited in the analysis of individual area involvements. This situation is another limitation of our study. Multicenter prospective studies involving a larger number of patients are needed.

CONCLUSION

It is important for clinicians to evaluate patients with cognitive impairment after ischemic stroke early, to prioritize rehabilitation treatment strategies, and to contribute to the correct use of resources by determining them according to priorities. According to the results of our study, we would like to emphasize that clinicians can use the MOCA scale in the evaluation of cognitive functions after ischemic stroke. We believe that the results we obtained can be supported by future multicenter studies in which a larger number of patients will be analyzed.

Ethical Statement

This study was approved by the Adana City Training and Research Hospital Clinical Research Ethics Committee (Decision date: 31.08.2023 and no: 2803). Written informed consent was obtained from the patient. This manuscript was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Authors' Contribution

Study Conception: DO, ME; Study Design: DO, ME; Supervision: DO, ME; Funding: None; Materials: DO, ME; Data Collection and/or Processing: DO, ME; Statistical Analysis and/or Data Interpretation: DO, ME; Literature Review: DO, ME; Manuscript Preparation: DO, ME and Critical Review: DO, ME.

Availability of data and materials

Data and materials are reachable from hospital automation information systems.

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All statements made in this article are solely those of the authors and do not represent the views of their affiliates or the publisher, editors, or reviewers. Any claims made by any product or manufacturer that may be evaluated in this article are not guaranteed or endorsed by the publisher.

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Massive transfusion in obstetric hemorrhage: What are the risk factors and can they be predicted?

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ABSTRACT

Objectives: This study aims to identify the risk factors associated with massive transfusion in obstetric hemorrhage and evaluate their predictive value to facilitate early intervention and improve maternal outcomes.

Methods: A retrospective cohort study was conducted on 1305 women who received blood transfusions for obstetric hemorrhage at Etlik City Hospital between October 2022 and December 2024. Patients were categorized into two groups: those who required massive transfusion (≥ 10 units of blood products) and those who received at least one unit of transfusion. Demographic, clinical, obstetric, and hematological parameters were analyzed. Statistical comparisons were performed using chi-square, Fisher's exact, Mann-Whitney U, and independent sample t-tests.

Results: A history of recurrent miscarriage, two or more previous cesarean sections, congenital uterine abnormalities, and uterine rupture were significantly associated with massive transfusion ($P < 0.01$). Severe anemia ($Hb < 9$ g/dL) and thrombocytopenia were also identified as critical hematological predictors ($P < 0.001$). Socioeconomic factors, including low educational attainment and unemployment, were significantly correlated with the need for massive transfusion ($P < 0.001$). Obstetric complications such as postpartum atony ($P < 0.001$) and premature rupture of membranes ($P = 0.04$) also contributed to increased transfusion risk.

Conclusions: Identifying key risk factors for massive transfusion can aid in early recognition and timely intervention for obstetric hemorrhage. Integrating these predictors into clinical protocols may enhance maternal care by improving preparedness and reducing maternal morbidity and mortality.

Keywords: Obstetric hemorrhage, massive transfusion, risk factors, postpartum atony, anemia, cesarean section, maternal morbidity

Postpartum hemorrhage and associated maternal morbidity and mortality remain significant challenges for obstetricians globally. Maternal

mortality rates vary between industrialized and poor nations. Despite a dramatic decline from 1 in 73 to 1 in 180, this rate remains one of the highest in devel-

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oping nations. 99% of total maternal mortality occurs in developing countries [1]. The primary etiologies of antepartum bleeding are placental abruption, placenta previa, and uterine rupture. This disease is the most common cause of blood and blood product transfusions [2].

Severe postpartum hemorrhage is typically described as bleeding exceeding 1000 ml within 24 hours, despite varying interpretations of the diagnosis [3]. The Royal College of Obstetricians and Gynaecologists (RCOG) defines moderate bleeding as 500-1000 ml, major bleeding as exceeding 1000 ml, and severe postpartum hemorrhage as ranging from 1500 to 2000 ml [4]. Signs of massive hemorrhage, such as tachycardia and hypotension, may be noticed late, even if the blood loss is 25% (corresponding to approximately 1.5 liters of bleeding for a pregnant woman), and may cause a delay in the intervention time. Therefore, when bleeding occurs, active management should be initiated immediately [5, 6]. The active management of the third stage of labor is the key approach for mitigating postpartum hemorrhage. This treatment encompasses many medical interventions and invasive techniques that persist until hemostasis is achieved. The medical components of these procedures include fluid resuscitation, placental extraction, bimanual uterine massage, administration of uterotonics, tranexamic acid, and transfusion of blood products. The surgical procedure includes the treatment of genital tract injury, insertion of balloon tamponade into the uterus, laparotomy, uterine devascularization, application of compression sutures, and hysterectomy [7].

The transfusion of blood and blood products is a crucial intervention for postpartum hemorrhage. Massive transfusion is characterized by the administration of 10 or more units of red blood cell suspensions during 24 hours [8]. Accurately assessing blood loss at the proper time is essential for selecting, preparing, and providing suitable blood and blood products to the patient, thereby preventing maternal mortality. Despite insufficient evidence, it has been proposed that early aggressive replacement of blood and blood products during bleeding may yield superior outcomes compared to conventional methods [9, 10]. Despite inadequate prospective data, numerous institutions in the United States have implemented massive transfusion protocols for patients experiencing acute hemorrhage

[10]. In cases where maternal hemorrhage is very severe, a few blood and blood product transfusions may not be sufficient to prevent morbidity and mortality. Interventions within the initial 48 hours are crucial for mitigating morbidity and death in both the mother and the newborn. Nearly fifty percent of maternal and neonatal fatalities transpire within this 48-hour timeframe [11].

In planning our study, we aimed to investigate the predictors of maternal massive blood transfusion, identify preventative measures, and establish preliminary protocols for blood and blood product transfusion in obstetric emergencies. This approach could facilitate clinicians in making expedited and informed decisions, thereby enhancing patient referral to appropriate higher-level care facilities. Therefore, we aimed to identify the factors that predict massive transfusion.

METHODS

Study Design

This study encompassed patients who received blood transfusions for obstetric hemorrhage at Etlik City Hospital from October 2022 to December 2024. This research adhered to the Helsinki Declaration on Research Involving Human Subjects and received clearance from the hospital's Ethics Committee (approval number: AESH-BADEK-2024-1198).

Study Participants

The study consisted of 1,305 women who either gave birth after the 24th week of pregnancy or were within the first 6 weeks postpartum and received blood transfusions owing to obstetric hemorrhage. These women were divided into 2 groups: those who received massive blood transfusion and those who received at least 1 unit of blood transfusion. A total of 49 patients received massive blood transfusions, while 1,256 patients received at least 1 blood and/or blood product transfusion. Women experiencing bleeding necessitating transfusion, except those with maternal hemorrhage, were omitted from the study. Cases with a gestational age under 24 weeks or those undergoing transfusion owing to ectopic pregnancy were likewise excluded. Furthermore, individuals who did not deliver at our hospital and possessed inadequate data

were excluded from the study. Demographic, clinical, laboratory, and ultrasonographic data of the cases were retrospectively acquired through the hospital data management system.

Obstetric hemorrhage is characterized by a recorded estimated blood loss over 1500 ml (milliliters) or a reduction in hemoglobin concentration greater than 3 g/L (grams/deciliter) necessitating blood transfusion [12].

A massive blood transfusion is defined as the administration of 10 or more units of blood and blood products during a 24-hour period [13].

Statistical Analysis

IBM Corporation SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) was used to conduct the statistical analysis. The conformance to the normal

distribution was examined using the Kolmogorov-Smirnov test. For continuous variables having a normal distribution, descriptive statistics are displayed as "mean±standard deviation". Fisher's exact test or the chi-squared test was used to compare categorical variables. The independent samples t-test was used to compare continuous variables that were regularly distributed. For all tests, a P-value of less than 0.05 was considered statistically significant.

RESULTS

Our study evaluated the demographic and clinical characteristics, pregnancy problems, birth outcomes, and hematological parameters of pregnant women who required ≥10 units of blood transfusion and re-

Table 1. Comparison of characteristics of the pregnant women included in the study

	Transfusion ≥10 units		P value
	Yes (n=49)	No (n=1256)	
Maternal age (year)	29.6±6.6	28.5±6	0.2 ^a
BMI>30 (kg/m ²)	2 (4.2)	143 (11.3)	0.1 ^b
Gravida	2.3±1.5	2.4±1.6	0.8 ^a
Parity	1±1.4	1.1±1.3	0.8 ^a
History of abortion	33 (67.3)	380 (30.2)	<0.01 ^c
Recurrent abortion	9 (18.3)	78 (6.2)	<0.01 ^c
Congenital uterine anomalies	2 (4.1)	0 (0)	<0.01 ^b
Previous cesarean section	2±2.2	0.5±0.9	<0.01 ^a
Education status, n (%)			<0.01 ^c
Illiterate	7 (14.2)	111 (8.8)	
Primary school	13 (26.5)	105 (8.3)	
Secondary school	16 (32.6)	186 (14.8)	
High school	13 (26.5)	739 (58.8)	
University	0 (0)	115 (9.1)	
Tobacco use	5 (10.2)	106 (8.4)	0.1 ^c
Working Status			
Housewife/Unemployment	49 (100)	841 (66.9)	<0.001 ^b
Duration of hospitalization (days)	3.4±4	3.5±3.5	0.8 ^a
Duration of hospital readmission	1 (2)	21 (1.6)	0.8 ^b

Data are shown as mean±standard deviation or n (%) where appropriate.

^aIndependent samples t-test, ^bFisher's exact test, ^cPearson chi-square.

ceived at least one blood and/or blood product transfusion. Although the average age of pregnant women requiring massive blood transfusion was higher than the other transfused groups, this difference was not found to be statistically significant ($P=0.2$). Despite a reduced number of patients with a body mass index (BMI) >30 kg/m² in the cohort receiving ≥ 10 units of blood transfusion, no statistically significant change was seen ($P=0.1$). It was concluded that there was no significant difference between the two groups for gravida and parity ($P>0$). Nevertheless, the incidence of miscarriage and repeated miscarriage rates were markedly elevated in the cohort necessitating massive transfusion ($P<0.01$ and $P<0.01$, respectively). Nonetheless, congenital uterine abnormalities and a history of two or more prior cesarean sections were markedly elevated in the massive transfusion cohort ($P<0.01$) (Table 1). Upon assessment of educational attainment, it was noted that none of the women who got ≥ 10 units of blood transfusion were university graduates, with the majority being primary and secondary school graduates. When the employment status

was examined, it was determined that all patients who received massive transfusions were unemployed or housewives ($P<0.001$). No significant difference was found between the two groups in terms of tobacco use ($P=0.1$) (Table 1).

Upon evaluating pregnancy problems, the incidence of gestational diabetes was elevated in the group necessitating massive transfusion; nevertheless, no statistically significant difference was observed ($P=0.07$). No notable difference was observed between the two groups regarding fetal growth retardation, hypertensive disorders (gestational hypertension, chronic hypertension, preeclampsia, and eclampsia), and placental abnormalities ($P>0.05$).

The incidence of anemia was markedly reduced in individuals who had ≥ 10 units of blood transfusion ($P<0.001$). Moreover, the incidence of Premature Rupture of Membrane (PROM) and uterine rupture was markedly elevated in the massive transfusion cohort ($P=0.04$ and $P<0.001$, respectively) (Table 2).

No significant difference was found between the two groups in terms of birth week ($P=0.7$). Upon eval-

Table 2. Pregnancy complications of the women included in the study

	Transfusion ≥ 10 units		P value
	Yes (n=49)	No (n=1256)	
Gestational diabetes mellitus, n (%)	5 (10.2)	59 (4.6)	0.07 ^a
Fetal growth restriction, n (%)	2 (4.1)	81 (6.4)	0.5 ^b
Hypertension, n (%)			
Gestational hypertension	0	50 (3.9)	0.2 ^b
Chronic hypertension	0	17 (1.3)	
Preeclampsia	1 (2)	43 (3.4)	
Eclampsia	1 (2)	3 (0.02)	
Anemia, n (%)	3 (6.1)	568 (45.2)	<0.001^b
Preterm birth, n (%)	6 (12.2)	272 (21.6)	0.1 ^a
EMR, n (%)	3 (6.1)	24 (1.9)	0.04^b
Uterine rupture, n (%)	18 (36.7)	12 (0.9)	<0.001^a
IUFD, n (%)	1 (2)	21 (1.6)	0.8 ^b
Placenta Previa, n (%)	3 (6.1)	90 (7.1)	0.9 ^b
Placental abruption, n (%)	1 (2.1)	54 (4.2)	0.7 ^b
Placenta accreta spectrum, n (%)	1 (2)	36 (2.8)	0.9 ^b

EMR=Early Membrane Rupture, IUFD=Intrauterine Fetal Demise

^aPearson chi-square, ^bFisher's exact test.

Table 3. Birth characteristics and neonatal outcomes of the newborns

	Transfusion ≥ 10 units		P value
	Yes (n=49)	No (n=1256)	
Gestational age at delivery (week)	37.2 $\pm$ 3.8	36.5 $\pm$ 4.2	0.7 ^a
Mode of delivery			
Normal spontaneous vaginal birth	44 (89.7)	346 (27.5)	<0.01^b
Cesarean section	5 (10.2)	890 (70.8)	<0.01^b
Operative delivery	0 (0)	20 (1.6)	0.3 ^c

Data are shown as mean $\pm$ standard deviation or n (%) where appropriate.

^aIndependent samples t-test, ^bPearson chi-square, ^cFisher's exact test.

uating the method of delivery, it was shown that the rate of normal spontaneous vaginal delivery was significantly elevated in the group receiving ≥ 10 units of blood transfusion ($P < 0.01$), whereas the rate of cesarean sections was dramatically reduced ($P < 0.01$). There was no significant difference between the two groups in terms of operative vaginal delivery ($P = 0.3$) (Table 3).

Upon analysis of hematological parameters, hemoglobin levels in patients necessitating massive transfusion were comparable to those in the transfusion group ($P = 0.7$). The incidence of severe anemia ($Hb < 9$ g/dL) was markedly elevated in the massive transfusion group ($P < 0.01$). Additionally, the incidence of thrombocytopenia was significantly higher in the massive transfusion group ($P < 0.001$) (Table 4).

Analysis of obstetric emergencies necessitating blood transfusion revealed a significantly elevated requirement due to postpartum atony, uterine rupture,

and miscarriage (all $P < 0.001$). No substantial difference was observed between the two groups regarding causes such as placental abruption, placenta accreta spectrum, and trauma ($P > 0.05$) (Table 5).

DISCUSSION

Our investigation showed significant risk variables related to the necessity for large blood transfusion in cases of postpartum hemorrhage. Specifically, we identified that a history of recurrent miscarriage, two or more prior cesarean sections, congenital uterine abnormalities, and uterine rupture were significantly correlated with the necessity for massive transfusion ($P < 0.01$). Moreover, severe anemia ($Hb < 9$ g/dL) and thrombocytopenia were identified as crucial hematological factors influencing the necessity for massive transfusion ($P < 0.001$). In the assessment of obstetric complications, preterm mem-

Table 4. Hematological Parameters at the time of hospital admission

	Transfusion ≥ 10 units		P value
	Yes (n=49)	No (n=1256)	
Hemoglobin (g/dL)	10 $\pm$ 1.1	9.8 $\pm$ 1.7	0.7 ^a
Severe anemia ($Hb < 9$ g/dL)	34 (69.3)	348 (27.7)	<0.01^b
Hematocrit (%)	31.5 $\pm$ 3.6	31.6 $\pm$ 4.5	0.9 ^a
Platelet count ($\times 10^9/L$)	247 $\pm$ 73	254 $\pm$ 84	0.7 ^a
Thrombocytopenia	15 (30.6)	28 (2.2)	<0.001^b

Data are shown as mean $\pm$ standard deviation or n (%) where appropriate.

^aIndependent samples t-test, ^bPearson chi-square.

Table 5. Main triggering event for blood transfusion

	Transfusion ≥ 10 units		P value
	Yes (n=49)	No (n=1256)	
Postpartum atonia, n (%)	16 (32.6)	1124 (89.4)	$<0.001^a$
Placental abruption, n (%)	1 (2.1)	54 (4.2)	0.7 ^b
Uterine rupture, n (%)	18 (36.7)	12 (0.9)	$<0.001^a$
Placenta accreta spectrum, n (%)	1 (2)	36 (2.8)	0.9 ^b
Abortion, n (%)	12 (24.4)	15 (1.1)	$<0.001^a$
Ectopic pregnancy, n (%)	0 (0)	3 (0.02)	1 ^b
Trauma, n (%)	1 (2)	12 (0.9)	0.4 ^b

^aPearson chi-square, ^bFisher's exact test.

brane rupture ($P=0.04$) and particularly postpartum atony ($P<0.001$) emerged as significant determinants for massive transfusion. Furthermore, an assessment of work status revealed that all patients necessitating massive transfusion were either unemployed or housewives ($P<0.001$), indicating that socioeconomic considerations may exert an indirect influence. Our findings indicate that these characteristics may significantly influence the prediction of obstetric hemorrhage and the necessity for massive transfusion, underscoring the critical relevance of early diagnosis of at-risk pregnancies for maternal health.

Despite numerous research aimed at predicting postpartum hemorrhage and transfusion, it remains a reality that this obstetric emergency might arise in the absence of risk factors and preventive measures. It is essential to assess the necessity for transfusion by identifying discernible risk factors and implementing appropriate safeguards. Results of a recently published 20-year analysis showed that the most common causes of postpartum hemorrhage and transfusion were placental disorders (previa, accreta spectrum, and abruption) and several previous cesarean deliveries [14]. In their study in 2019, Ouh *et al.* [15] found that the risk factors requiring transfusion were maternal age, increased gravida and cesarean section, fetal gender, preterm birth, and preeclampsia. They also found factors that elevate the risk of transfusion, including placental abruption, and aberrant placentation such as previa, anemia, and smoking [15]. One of the most significant consensus identifies risk factors for postpartum hemorrhage, which include multiple pregnan-

cies, a prior history of postpartum hemorrhage, chorioamnionitis, genital tract injuries, operative vaginal delivery, emergency cesarean section, and pregnancy-induced hypertension [16]. Another study identified anemia during pregnancy, a higher incidence of cesarean sections, severe preeclampsia, emergency cesarean sections, and placental abnormalities as significant risk factors for transfusion [17]. Oya *et al.* [18] discovered in their research that, with placenta previa and maternal age, a history of recurrent dilatation and curettage may constitute a risk factor for transfusion. The RCOG guidelines for managing postpartum hemorrhage emphasize that the platelet count must be sustained at 50,000 or more, and prenatal hemoglobin levels should be preserved at 10 or above to treat anemia [19]. In our analysis, while the number of prior cesareans was 2 or more, a history of recurrent miscarriage and uterine anomalies were related to massive transfusion, only uterine rupture was found to be associated with massive transfusion among obstetric complications. Again, in the literature, hematological markers such as Hb values of 9 and less and the presence of thrombocytopenia were analyzed as predictors of major transfusion.

Wu *et al.* [20] conducted a study examining postpartum hemorrhage and transfusion from an alternative perspective, revealing that pre-birth cross-matching of patients with certain risk factors and the preparation of blood at a blood bank influenced and decreased the transfusion rate. In a separate study, preoperative blood preparation was advised just in the presence of risk factors associated with cesarean sec-

tion. The fatality rate from maternal hemorrhage is notably low in women without other risk factors undergoing elective cesarean sections [21]. Numerous investigations have assessed that elective cesarean birth does not elevate the risk of transfusion or postpartum hemorrhage, and it has been determined that cesarean delivery alone does not heighten the necessity for postpartum hemorrhage management or transfusion. Factors including the presence of risk factors associated with cesarean delivery, placenta previa, preeclampsia, and emergency cesarean delivery in patients monitored for normal delivery have been demonstrated in numerous studies to elevate the necessity for transfusion [17, 21]. Breyman [22] asserted in their study that the risk of maternal mortality during cesarean birth is minimal, with only concomitant conditions potentially leading to significant maternal bleeding. Our study indicated that the number of cesarean sections, specifically two or more, rather than cesarean section alone, was a risk linked to massive transfusion. These results underscore the significance of adopting prompt precautions by predicting postpartum hemorrhage and boost the importance of our study. We believe that the absence of placental anomalies as a contributing factor to the risk of massive transfusion in our study can be ascribed to our institution's status as a tertiary center, the prompt accessibility of the blood center, the routine communication with our blood bank upon patient admission for blood and blood product reservations with cross-matching, and our center's expertise in managing surgical conditions, particularly those related to placenta previa and the accreta spectrum.

The occurrence of preoperative anemia has been significantly correlated with bleeding and the necessity for transfusion in numerous investigations [17, 21]. During pregnancy, Hb <11 mg/dl is defined as anemia, and <9 mg/dL is defined as severe anemia [22, 23]. Alongside the management of anemia, a significant predictor of transfusion and a contributor to the risk of postpartum hemorrhage during pregnancy, research has indicated that anemia, postpartum hemorrhage, and transfusion are correlated with socioeconomic status and educational attainment [24]. However, in one study, they did not find a higher rate of maternal death in women with anemia [25]. Tort *et al.* [26] indicated in their study that the mortality risk

from postpartum hemorrhage is sevenfold greater in pregnant women with anemia. A significant correlation exists between anemia and depression during pregnancy, which is a critical factor for postpartum hemorrhage and postpartum depression, and this link is also influenced by women's socioeconomic situation and educational attainment. The prevalence of fatalities resulting from anemia and postpartum hemorrhage is significantly greater in underdeveloped nations compared to developed nations [27, 28]. Our research indicated that the incidence for massive transfusion was markedly elevated among women with severe anemia, homemakers, and individuals with limited educational attainment. Furthermore, the correlation between the rise in pregnancy rates and miscarriage rates with women's education and socioeconomic status elucidates the elevated incidence of massive transfusion among these women, corroborating existing literature.

Limitations

Our research possesses several limitations. Firstly, the retrospective methodology of the study may result in missing data and recording errors, hence limiting the generalizability of the results, which require validation in diverse populations. Nonetheless, the advantages of our investigation encompass a substantial patient cohort, a thorough examination of the determinants necessitating massive transfusion owing to maternal hemorrhage, and alignment with previously established risk variables in the literature. Our data highlight the correlation between socioeconomic and hematological factors and excessive transfusion, which may inform clinical treatment. Furthermore, our center's expertise in obstetric emergency management and adherence to established blood reserve protocols enhance the dependability of the results achieved.

CONCLUSION

These findings show that the need for massive transfusion due to obstetric hemorrhage has a strong relationship with a history of miscarriage, uterine rupture, postpartum atony, education and employment status. It supplies critical information for forecasting obstetric hemorrhage and discerning patients necessitating massive transfusion at an early stage, hence enabling the

implementation of requisite safeguards. This study may assist clinicians in managing obstetric emergencies and aid in formulating preventive programs for at-risk populations to enhance maternal health.

Ethical Statement

The Ankara Etlik City Hospital's Ethics Committee gave its permission to the study protocol (approval number: AESH-BADEK-2024-1198). The Declaration of Helsinki's guidelines were followed in the conduct of this study.

Authors' Contribution

Study Conception: GA; Study Design: GA, GK; Supervision: ŞÇ, ÇS; Funding: N/A; Materials: ŞÇ, EY, KÖ; Data Collection and/or Processing: GA, GK, NY, ÖDÇ; Statistical Analysis and/or Data Interpretation: ŞÇ, YC; Literature Review: GA, GK, ŞÇ, ÇS; Manuscript Writer: GA; Critical Review: GA, GK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Editor's note

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