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Effects of COVID-19 Lockdown on Time in Therapeutic Range (TTR) for Warfarin Users

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Abstract:

Objective: This study investigated the impact of COVID-19 lockdown measures on Time in Therapeutic Range (TTR) for patients receiving warfarin therapy.

Methods: warfarin for at least one year before and after March 11th, 2020 (the start of pandemic) were included (n=112). Demographic data, comorbidities, medications, and International Normalized Ratio (INR) results were collected. TTR was calculated using the Rosendaal method.

Results: The mean TTR before the pandemic was 56.91%, significantly higher than the 40.23% observed during the pandemic ($P<0.001$). INR measurement intervals also increased significantly during the pandemic (34.2 days pre-pandemic vs. 50.9 days during the pandemic, $P<0.001$). This effect was most pronounced in patients over 65 years old ($P<0.001$).

Conclusion: COVID-19 lockdown measures significantly decreased TTR and extended INR monitoring intervals for warfarin users. These findings were particularly concerning in the elderly population. Strategies to ensure optimal warfarin monitoring during pandemics or disasters are crucial to prevent complications.

Keywords: COVID Lockdown, Warfarin, Time in Therapeutic Range, INR Monitoring

Oral anticoagulant therapy, particularly with the anti-vitamin K agent warfarin, plays a crucial role in both primary and secondary antithrombotic prophylaxis for patients with venous thromboembolism, atrial fibrillation (AF), and cardiac mechanical valves [1]. Careful monitoring of coagulation status is essential to prevent potentially life-threatening major haemorrhagic complications. Warfarin therapy presents a unique challenge due to its narrow therapeutic window. To mitigate this challenge and ensure optimal outcomes, patients on warfarin therapy require close follow-up and meticulous dose adjustments. This vigilance is crucial to minimise the risk of both bleeding and thrombotic complications [2]. An International Normalized Ratio (INR) below 2.0 is associated with an increased risk of stroke, while an INR exceeding 4.0 is linked to a higher risk of major bleeding events [3]. For stable oral anticoagulant therapy patients, the interval between INR measurements should not exceed four weeks [4]. Time in therapeutic range (TTR) has become valuable for assessing warfarin therapy quality. Numerous studies have consistently demonstrated a strong correlation between TTR and

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adverse event rates, solidifying TTR's role as a valid and practical tool for quality control evaluation.

The COVID-19 pandemic, declared in March 2020, prompted widespread lockdowns and social distancing measures that substantially transformed healthcare delivery [5]. Fear of infection and mobility restrictions, particularly among individuals over 65 years of age, led to a decline in outpatient visits.

This study examined how the COVID-19 pandemic influenced healthcare utilization patterns among warfarin users, specifically focusing on the impact of public apprehension towards hospital visits and the restrictions imposed by lockdowns.

METHODS

Study Population

We completed this study as a retrospective cohort study of patients receiving warfarin in the outpatient clinics of Malatya Training and Research Hospital, one of the region's leading tertiary care hospitals. We included patients who continued consecutive warfarin treatment for at least one year, six months before and six months after 11/03/2020, the turning point of the pandemic for our country.

This study investigated the impact of the COVID-19 pandemic on warfarin management among patients receiving follow-up care at our hospital. We included patients who utilized warfarin for various indications and were actively followed up from January 1st, 2019, to December 31st, 2020. Patients who did not have a pre-pandemic follow-up history at our institution or who discontinued follow-up after the pandemic began were excluded. The COVID-19 pandemic's official start in Turkiye, marked by the first reported case on March 11th, 2020, served as the demarcation point for this study. The preceding six months, from January 1st, 2020, to March 10th, 2020, were designated as the pre-pandemic period. Conversely, the subsequent six months, from March 11th, 2020, to December 31st, 2020, were defined as the pandemic period. This study retrospectively analyzed the hospital admissions of warfarin users within our institution for one year, encompassing the six months before and after March 11th, 2020 (the date of the first reported COVID-19 case and subsequent restrictions in Turkiye). Demographic characteristics, co-morbidities, and medication use were extracted from patients' electronic medical records. Additionally, the CHA2DS2-VASc score was calculated for each participant [6]. We evaluated the frequency of INR monitoring and the distribution of INR results during the pre-pandemic and pandemic periods, for patients with isolated mitral valve replacements (MVR) or combined aortic and mitral valve replacements (AVR+MVR), a therapeutic INR was defined as a value between 2.5 and 3.5. In contrast, for patients with AF or isolated aortic valve replacements (AVR), the target INR range was set between 2.0 and 3.0 [7]. TTR was calculated using the Rosendaal linear interpolation method, which assumes a linear change between consecutive INR measurements [TTR = (Days in range / Total days observed) × 100]. Employing the Rosendaal method, we calculated the TTR for patients before and after the pandemic period [8]. The National Institute for Health and Care Excellence (NICE) criteria were used to assess anticoagulation status, with TTR below 65% signifying poor control [9].

The local clinic's ethics committee approved all procedures used in the study, which was conducted in accordance with the Declaration of Helsinki. Written and signed consent was obtained from each participant.

Statistical Analysis

Statistical analyses were conducted using SPSS software (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY, USA, IBM Corp.). Prior to conducting parametric statistical tests, the normality of the data distribution was evaluated. The Kolmogorov-Smirnov test, appropriate for sample sizes exceeding 50, was employed to assess the normality of TTR values. The test results indicated no significant deviations from normality (P=0.16), suggesting that the data distribution closely approximates a normal distribution. This finding supported the utilization of parametric statistical tests for further analysis. Skewness and kurtosis values were also examined to substantiate the normality assumption further. Both skewness and kurtosis fell within the acceptable range of ±1, further confirming the normality of the data distribution. A paired t-test was employed to compare TTR values between the

pre-pandemic and pandemic periods to investigate the impact of the pandemic on TTR values. Independent t-tests were utilized to examine the relationship between TTR and maximum days without INR values across different age groups. Cohen's d values were calculated to measure the effect size of the observed differences. Cohen's d values of 0.02, 0.05, and 0.08 were interpreted as small, medium, and large effects, respectively (Cohen, 1988). The significance level for all statistical tests was set at α=0.05.

RESULTS

This study included 112 patients receiving warfarin therapy, 61 (54.5%) women. The mean age was 61±14 years. Notably, 52 (46.4%) patients fell within the 65+ age group, where stricter restrictions were implemented. Warfarin use was primarily for mechanical heart valves in 92 (82.1%) patients, while 20 (17.9%) used it solely for AF. Among the AF patients, eleven lacked valve disease that would preclude direct oral anticoagulants (DOAC). The average CHA2DS2-VASc score was 2.48±1.59. Comorbidities included diabetes mellitus (33 patients, 29.5%), hypertension (56 patients, 50%), coronary artery disease (24 patients, 21.4%), heart failure (32 patients, 28.6%), and atrial fibrillation (40 patients, 35.7%). Additionally, 14 patients (12.5%) had a history of cerebrovascular events, and 15 (13.4%) had a glomerular filtration rate below 50 mL/min. Lastly, 23 patients (20.5%) used statins, proton pump inhibitors, amiodarone, and carbamazepine, which can interact with warfarin. A detailed breakdown of baseline patient characteristics is provided in Table 1. Analysis revealed a significant decrease in the frequency of INR monitoring during the pandemic period compared to the Pre- pandemic period. On average, patients underwent blood tests for INR measurement every 34.2±0.95 days in the Pre-pandemic period, whereas this interval increased to 50.9±0.99 days in the pandemic period (P<0.001). This translates to a decrease in the average number of blood tests from 5.45±0.95 in the Pre-pandemic period to 3.79±0.99 in the pandemic period. Stringent restrictions were implemented in our country during the COVID-19 pandemic due to the increased mortality risk observed in the over-65 age group. Table 2 details the pre-pandemic and pandemic INR monitoring frequencies stratified by patient age categories. The analysis revealed statistically significant longer INR measurement intervals in the over-65 age group (P<0.001).

Before March 11th, 2020 (considered the start of the COVID-19 pandemic in Turkiye), 42.8% of patients achieved their target INR range at their last measurement. However, following the pandemic's onset, the first INR measurement obtained for these patients fell outside the target range. The analysis revealed a significant increase in the time interval between INR measurements during the pandemic. On average, patients waited 80.8 days between their last pre-pandemic INR and their first INR measurements

TABLE 1. Baseline Characteristics of the Patients Using Warfarin

Age (years)	61±14
Female gender	61 (54.5 %)
Diabetes mellitus	33 (29.5 %)
Hypertension	56 (50 %)
Heart failure	32 (28.6 %)
Stroke	14 (12.5 %)
Coronary artery disease	24 (21.4 %)
Hemoglobin (g/dL)	12.2±1.4
Platelets, ($\times 10^9$/)L	228±56
AST (U/L)	32±24
ALT (U/L)	28±10
Creatinine (mg/dL)	1.03±0.4
GFR<50 (mL/min/1.73 m^2)	15 (13.4 %)
CHA_2DS_2-VASc score	2.48±1.59
Atrial fibrillation	40 (35.7 %)
Drug interactions	23 (20.5 %)
Indication of Vitamin K antagonist	
Mechanical valve	92 (82 %)
Non-valvular AF	11 (10 %)
Valvular AF	9 (8 %)

Data are shown as mean±standard deviation or n (%) where appropriate. AF, atrial fibrillation; ALT, alanine amino transferase; AST, aspartate amino transferase; CHA2DS2-VAScscore, congestive heart failure, hypertension, age (>65:1point, >75:2points), diabetes, previous stroke/transient ischemic attack (2 points), vascular disease and female gender; GFR, glomerular filtration rate.

TABLE 2. Average Days Between INR Measurements by Age Group

Period	<65-year-olds (n=60)		>65-year-olds (n=52)		t(110)	Cohen's d
	M	SD	M	SD		
Pre-pandemic period	32.91	6.87	35.75	7.66	-2.07*	-0.39
Pandemic period	45.60	11.98	57.06	14.26	-4.62***	-0.88
All period	37.45	6.13	43.28	7.76	-4.44***	-0.84

INR, international normalized ratio; M, mean; SD, standard deviation.
*P<0.01, ***P<0.001.

while the pandemic was ongoing. This interval was even longer in the over-65 age group, averaging 102.8 days (P<0.001), compared to younger patients. Analysis of time in TTR revealed a significant decrease during the pandemic period compared to the Pre-pandemic period. The average TTR in the Pre-pandemic period was 56.91%, whereas it dropped to 40.23% in the pandemic period (Table 3). Further evaluation stratified by age categories (Figure 1) demonstrated that patients over 65, a group with stricter pandemic restrictions, exhibited lower TTR values than younger patients in both Pre- pandemic period and pandemic period.

DISCUSSION

Warfarin remains the cornerstone of stroke prevention strategies. However, its narrow therapeutic window presents a significant challenge in achieving optimal clinical use. Multiple factors influence the quality of anticoagulation with warfarin, including patient characteristics (diet, age), comorbidities, concomitant medications, and the drug's pharmacokinetic and pharmacodynamic properties. TTR serves as a critical metric for assessing anticoagulation quality and has been demonstrably linked to adverse outcomes such as stroke, haemorrhage, and mortality. Randomized controlled trials reveal that only approximately 60% of patients achieve the desired TTR threshold with warfarin treatment [10]. This study investigated the impact of the COVID-19 pandemic on TTR for warfarin users. We observed a significant decrease in average TTR during the pandemic period compared to the pre-pandemic period (P<0.001). This decline can be attributed, in part, to a reduction in outpatient clinic visits for INR monitoring during the pandemic's initial stages. Hospitals prioritized COVID-19 diagnosis and treatment, leading to fewer patients seeking clinic INR monitoring. Additionally, concerns about nosocomial transmission likely discouraged patients from frequent hospital visits, particularly those worried about COVID-19 infection.

Consistent with previous findings, our study demonstrated lower TTR values in the over-65 age group, both pre-pandemic and during the pandemic (P< .001). The VARIA study reported lower TTR in warfarin users exceeding 55 years of age, and similar age-related TTR reductions have been observed in patients with atrial fibrillation [11,12]. Potential explanations for this negative correlation between age and TTR include age-related changes in drug

TABLE 3. Age-Stratified Comparison of TTR

Age	Pre-pandemic TTR		Pandemic TTR		t	Cohen's d
	M	SD	M	SD		
<65-year-olds (n=60)	59.74	19.66	47.49	22.33	3.80***	0.49
>65-year-olds (n=52)	53.65	22.93	31.85	21.13	5.57***	0.77
Full group (n=112)	56.91	21.36	40.23	23.06	6.57***	0.62

M, mean; SD, standard deviation; TTR, time in therapeutic range.
***P<0.001.

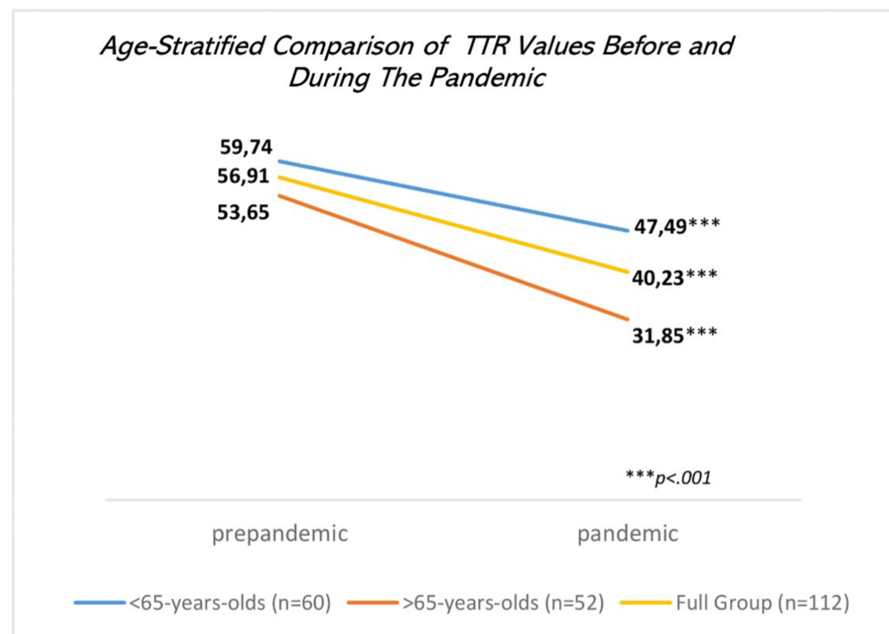

FIGURE 1. Target TTR values before (6 months) and during (6 months) the pandemic.

metabolism, increased comorbidities in elderly patients, and cognitive decline.

However, our study not only confirms lower TTR in the over-65 population pre-pandemic and pandemic but also reveals that this age group experienced the most significant TTR decline during the pandemic. This finding can likely be attributed to two key factors: heightened reluctance among elderly patients to visit crowded environments like hospitals due to their increased vulnerability to COVID-19 mortality, and stricter enforcement of pandemic restrictions for individuals over 65 in our country. A prospective study by Turk *et al*. [13] investigating TTR in Turkish AF patients reported an average TTR of 42%. Our analysis revealed a pre-pandemic period TTR of 56.91% for all warfarin-treated patients, significantly decreasing to 40.23% during the pandemic period.

Current guidelines recommend INR testing intervals no longer than 4-6 weeks for stable patients on warfarin [14]. Our study revealed a significant increase in INR monitoring intervals during the pandemic compared to the pre-pandemic period (34.2 days vs. 50.9 days, $P<0.05$). Notably, the longest intervals were observed in the over-65 age group, where stricter pandemic restrictions were implemented. In this group, INR measurements were performed every 57 days on average during the pandemic. These extended intervals significantly exceeded the recommended guidelines. Subtherapeutic INR levels are known to elevate the risk of both thromboembolic events and bleeding complications [15]. A study by Shalev *et al*. [16] involving 4408 chronic AF patients demonstrated superior TTR with frequent, regular INR monitoring (intervals ≤ 3 weeks with 7-day multiples) compared to less frequent or irregular schedules.

Our analysis identified a concerning gap of 80.8 days between the last pre-pandemic INR test and the first INR test performed after the pandemic's onset. This interval further extended to 102.8 days in the over-65 age group. These extended periods significantly exceed the recommended 1-month interval and pose a potential risk of severe complications.

Furthermore, only 33% of the first INR measurements obtained following the pandemic fell within the target range. Additionally, while patients were expected to undergo an average of 5-6 INR tests during the first six months of the pandemic, the average number of examinations during this period was only 3.79.

Our findings highlight a concerning trend: pre-existing suboptimal TTR levels in the Turkish

population are further declining during the COVID-19 pandemic to a degree potentially compromising patient safety. As previously established, inadequate TTR is associated with increased risks of both thromboembolic and bleeding complications [15]. While this study, due to its observational design, did not capture the incidence of adverse events associated with suboptimal TTR, other studies have documented the significant morbidity and mortality associated with poor TTR control. Notably, our data reveal a disproportionate impact on the over-65 age group, a population subject to stricter pandemic restrictions. This vulnerability emphasizes the potential dangers posed by disruptions to healthcare access during pandemics or other public health emergencies.

The results of this study underscore the urgent need for healthcare providers to develop strategies to mitigate the risks identified. Educational initiatives aimed at patients, particularly those over 65, are crucial to emphasize the importance of INR monitoring and the potential consequences of non-adherence. For non-valvular atrial fibrillation patients, a temporary shift towards newer, more user-friendly DOAC compared to warfarin may be warranted during pandemic periods. Additionally, further development of home INR monitoring systems is crucial. These systems could involve either point-of-care devices for patients' home use or healthcare provider-initiated home blood sampling for laboratory analysis. Ultimately, a heightened awareness of these pandemic-related risks among patients and healthcare professionals is essential for optimal patient outcomes.

Strengths and Limitations

A major strength of this study is that it provides empirical evidence of the 'collateral damage' caused by the pandemic, demonstrating that public health restrictions negatively impacted chronic disease management independently of the virus itself.

This study has limitations. The retrospective design prevented us from capturing data on patient outcomes, such as bleeding and thrombosis. Additionally, the single-centre design resulted in a relatively small sample size, potentially limiting the generalizability of our findings.

CONCLUSION

This study investigated the impact of pandemic-related restrictions on warfarin users. We observed a significant decline in TTR during the pandemic, potentially leading to adverse consequences for patients with subtherapeutic INR levels. Additionally, INR monitoring intervals were significantly extended. These findings were particularly concerning in the elderly population. This study highlights patients' challenges in maintaining therapeutic warfarin levels during the pandemic. Our findings underscore the potential risks associated with disruptions to healthcare access during public health emergencies like pandemics or natural disasters. It is crucial to develop strategies, informed by data from this study, to ensure optimal warfarin monitoring during such events.

Ethics Approval and Consent to Participate

This study was approved by the Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee (Decision No:2025/7288; date: 25.03.2025). All procedures were conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all individual participants included in the study.

Data Availability

All data generated or analyzed during this study are included in this published article. The data that support the findings of this study are available on request from the corresponding author, upon reasonable request.

Authors' Contribution

Study Conception: İA; Study Design: İA; Supervision: EY; Funding: GS, İA; Materials: İ.A, GS; Data Collection and/or Processing: İA, EY, GS; Statistical Analysis and/or Data Interpretation: EY, İA; Literature Review: EY; Manuscript Preparation: GS; and Critical Review: İA, EY, GS.

Conflict of Interest

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

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Generative Artificial Intelligence Statement

The author(s) declare that no artificial intelligence-based tools or applications were used during the preparation process of this manuscript. The all content of the study was produced by the author(s) in accordance with scientific research methods and academic ethical principles.

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