ORIGINAL ARTICLE

SARS-CoV-2 and Warfarin Dose Interaction in Patients with Non-Valvular Atrial Fibrillation

Poramate Rungrattanawilai, MD[1], Phanthaphan Sureeyatanaphat, MD[1], Pattama Sahasoonthorn, PharmD[2], Warisara Pangprasert, PharmD[2], Teetouch Ananwattanasuk, MD[1], Padoemwut Teerawongsakul, MD, MSc[1]

[1] Department of Internal Medicine, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

[2] Department of Pharmacy, Vajira Hospital, Bangkok, Thailand

Objective: Warfarin is commonly used to prevent cardioembolic illness in patients with atrial fibrillation (AF). However, warfarin has a narrow therapeutic range and requires continuous monitoring for safety and effectiveness. Numerous factors, including infection and inflammation, can affect the dose of warfarin. SARS-CoV-2 infection involves multiple inflammatory pathways leading to hyperinflammation. This study explored warfarin dosing in patients hospitalized with SARS-CoV-2 infection and other factors that affect warfarin dosing.

Materials and Methods: The authors performed a retrospective descriptive study among adult patients with AF receiving warfarin treatment 180 days before and after being infected with SARS-CoV-2 who were admitted to Vajira Hospital between January 2020 and June 2022. The primary outcome was a difference in average warfarin daily dose (WDD) between pre-infection and inpatient SARS-CoV-2 infection. Secondary outcomes were a difference in the average WDD between pre- and postinfection, a difference in time to therapeutic range (TTR) between pre- and postinfection, and factors affecting warfarin dosage after infection.

Results: Twenty patients were included in the present study. The average inpatient WDD was significantly lower than the average WDD before SARS-CoV-2 infection (2.10±1.11 mg vs. 3.01±1.34 mg, p<0.001), and the mean reduction in WDD was 28.3%. The mean average WDD after infection was significantly lower than the mean average WDD before infection (2.62±1.19 mg vs. 3.01±1.34 mg, p=0.002), and the mean reduction in WDD was 11.5%. There was no difference between mean pre- and postinfection TTR (46.7 vs. 44.9, p=0.794). Consumption of green chiretta was associated with a significantly higher warfarin dosage following SARS-CoV-2 infection (p=0.046).

Conclusion: SARS-CoV-2 infection may interact with the warfarin level. Adults hospitalized with SARS-CoV-2 infection and following postdischarge follow-up had considerably lower average WDDs.

Keywords: Warfarin; Vitamin K antagonist; SARS-CoV-2; COVID-19

Received 14 May 2024 | Revised 25 August 2024 | Accepted 10 September 2024

J Med Assoc Thai 2025;108(Suppl.1):S64-70

Website: http://www.jmatonline.com

Atrial fibrillation (AF) is associated with a significantly increased risk of both thromboembolic stroke and mortality[1]. Consequently, in patients diagnosed with AF, oral anticoagulants are widely recommended as a preventive strategy for stroke[2,3]. Warfarin, a widely used oral anticoagulant, demonstrably reduces the risk of thromboembolic stroke by up to 64% and mortality rates by 26%[4]. However, this efficacy is offset by potential adverse effects. To ensure optimal balance, warfarin therapy is monitored through the international normalized ratio (INR), with the target range dependent on the specific indication for anticoagulation[2,3]. An important drawback of warfarin is its narrow therapeutic range, which means careful monitoring of the INR is required to adjust the dosage properly[5]. Many factors, such as infection and inflammation, can affect the appropriate warfarin dose. Specifically, infection with SARS-CoV-2 triggers various inflammatory responses that lead to excessive inflammation.

The global pandemic of SARS-CoV-2, also known as COVID-19, has spread rapidly since its initial detection on November 17, 2019, in Wuhan, China. Thailand confirmed its first case on January 13, 2020, marking it as the first confirmed case outside of China[6]. Patients hospitalized with SARS-CoV-2 infection commonly exhibit abnormal blood-clotting parameters, including elevated levels of fibrinogen and D-dimer. A systematic review discovered that the occurrence of pulmonary embolism and deep

Correspondence to:

Teerawongsakul P.

Cardiology Division, Department of Internal Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok 10300, Thailand.

Phone: +66-2-2443066

Email: padoemwut@nmu.ac.th

How to cite this article:

Rungrattanawilai P, Sureeyatanaphat P, Sahasoonthorn P, Pangprasert W, Ananwattanasuk T, Teerawongsakul P. SARS-CoV-2 and Warfarin Dose Interaction in Patients with Non-Valvular Atrial Fibrillation. J Med Assoc Thai 2025;108(Suppl.1):S64-70.

DOI: 10.35755/jmedassocthai.2025.S01.S64-S70

vein thrombosis increases in patients with SARS-CoV-2 infection, particularly among those receiving treatment in intensive care units[7]. A minor elevation in prothrombin time and activated partial thromboplastin time levels have been noted. These abnormal blood-clotting parameters are associated with disease severity, including mortality rate and the requirement for mechanical ventilation[8,9].

A retrospective study identified eight patients who were receiving warfarin treatment before contracting SARS-CoV-2 infection. Before infection, these patients had an average warfarin dose of 6.2 mg/day. During hospitalization for SARS-CoV-2 infection, there was a noticeable decrease in the average warfarin dose to 1.3 mg/day, representing a 68.8% reduction from pre-infection levels. One patient was suspected of having acute pulmonary embolism despite having INR levels above the target range during hospitalization. Another patient experienced abnormal bleeding, necessitating discontinuation of warfarin. Interestingly, both patients had INR levels within the target range on the first day of hospitalization[10]. Previous studies have shown that administering warfarin to patients with AF can reduce the occurrence of ischemic strokes. Various factors, including medication dosage, renal function, patient age, underlying medical conditions, concomitant use of other medications, acute illnesses, and even SARS-CoV-2 infection, can lead to fluctuations or deviations from the target INR range[9-11].

Throughout the SARS-CoV-2 pandemic, numerous patients diagnosed with AF were prescribed warfarin to prevent stroke. Many of these patients also underwent treatment for SARS-CoV-2 infection. As a result, our study aims to analyze the warfarin dosage administered to these patients and compare their INR levels before and during the period of SARS-CoV-2 infection, with a focus on determining the time in therapeutic range (TTR) over 180 days before and after the occurrence of SARS-CoV-2 infection.

Materials and Methods

Study design and population

The authors conducted a retrospective descriptive study involving adult patients with AF who were receiving warfarin treatment both 180 days before and after being infected with SARS-CoV-2 and who were admitted to the Faculty of Medicine Vajira Hospital, Navamindradhiraj University, from January 2020 to June 2022. The investigators meticulously reviewed and compiled data from electronic medical record databases. The inclusion criteria were that patients must be 1. age >18 years, 2. diagnosed with AF, and 3. They received a prescription for warfarin, 4. Confirmed diagnosis of SARS-CoV-2 infection, as determined based on an antigen or real-time reverse transcriptase-polymerase chain reaction testing and receiving treatment at the hospital, and 5. have been followed-up for warfarin-related therapy for at least 180 days before and after the SARS-CoV-2 infection diagnosis. The exclusion criteria included a diagnosis of moderate-to-severe mitral stenosis or mechanical prosthetic valve replacement, end-stage renal disease and receiving renal replacement dialysis therapy and switching from warfarin to either unfractionated heparin or low-molecular-weight heparin during hospitalization.

Data collection

The authors examined the electronic medical records for baseline characteristics, including age, sex, body mass index (BMI), underlying diseases, current medications, CHA2DS2-VASc score, HAS-BLED score, laboratory results, and SARS-CoV-2 treatment. The daily dose of warfarin calculation is based on a stable INR without further adjustments. If different dosages are used each day of the week, the daily dose of warfarin is averaged by dividing the weekly total dose by 7.

Endpoints

The primary outcome assessed was the variance in average warfarin daily dose (WDD) between pre-infection and during hospitalization for SARS-CoV-2 infection. Secondary outcomes included the variance in average WDD between pre-infection and post-SARS-CoV-2 infection, the difference in TTR between pre- and post-SARS-CoV-2 infection, and the factors influencing warfarin dosage after SARS-CoV-2 infection.

Statistical analysis

The authors calculated the sample size based on a prior study that compared the average daily dose of warfarin before hospital admission and during inpatient treatment for SARS-CoV-2. The present study revealed a difference between the average daily doses of warfarin before admission and during inpatient care, showing a mean decrease in dose requirement of 68.8%[10]. We established a significance level of α=0.05, along with a power of 80% (power=0.8). The sample size calculation indicated a minimum sample size of seven for both the pre- and post-infection groups. However, because the two groups were not independent, we assigned a minimum sample size of seven to each group to avoid bias. To mitigate the risk of patient dropout, we increased the sample size by 20%, resulting in a sample size of nine for each group.

Qualitative data, including sex, comorbid diseases, and SARS-CoV-2 treatment, were presented as frequencies and percentages. Quantitative data, such as age, BMI, CHA2DS2-VASc score, HAS-BLED score, and laboratory

results, were reported as mean and standard deviation values in normal distribution data. In the case of nonnormal distribution data, the median with an interquartile range was presented. We compared the average WDD before and during inpatient SARS-CoV-2 infection using the Wilcoxon signed-ranks test. The results reported as mean, standard deviation, mean difference, and statistical significance were considered for $p<0.05$. We assessed the correlation between WDD and associated factors and subgroup analysis using univariate analysis. Statistical analysis was conducted using STATA/BE Software, version 17.0 (Stata Corp, College Station, TX, USA).

Ethical considerations

The present study received approval from the Human Research Ethics Committee at Navamindradhiraj University (COA 096/2565).

Results

Patient characteristics

From January 2020 to June 2022, a total of 20 adult patients with AF receiving warfarin treatment were included in the present study. The average age of the patients was 73.30±8.49 years, with 11 male patients making up 55% of the study population. The average BMI was 25.67±6.13 kg/m^2. The incidence of comorbidities was as follows: diabetes mellitus, 40%; hypertension, 95%; dyslipidemia, 45%; chronic kidney disease stage III-V, 45%; ischemic heart disease, 20%; congestive heart failure, 35%; history of stroke, 35%; and cancer, 15%. The average CHA2DS2-VASc score was 4.40±1.31, and the average HAS-BLED score was 2.30±1.30. Upon admission, the mean values for absolute lymphocyte count, INR, estimated glomerular filtration rate, C-reactive protein, and D-dimer were 1,462.89±616.98 cells/mL, 2.19±0.58, 44.15±25.13 mL/min, 15.69±13.94 mg/L, and 0.58±0.50 ng/mL, respectively. During inpatient treatment for SARS-CoV-2, most patients had mild symptoms. Three patients required an oxygen mask with a reservoir bag, and only one patient needed a high-flow nasal cannula. The medications used were favipiravir, 65%; remdesivir, 15%; molnupiravir, 10%; dexamethasone, 40%; and green chiretta, 5%. The average length of stay was 10.40±5.40 days. Table 1 presents the baseline characteristics, current medication, and admission laboratory values.

Dosage of Warfarin between Before and After admission

The mean inpatient WDD was significantly lower than the mean pre-SARS-CoV-2 infection dose (2.10±1.11 mg vs. 3.01±1.34 mg, $p<0.001$), with a mean reduction of 28.3%, as displayed in Table 2.

Table 1. Baseline characteristics and laboratory values

	n=20
Mean age (SD) (years)	73.30 (8.49)
Sex, male, n (%)	11 (55)
Mean BMI (SD) (kg/m^2)	25.67 (6.13)
Comorbid conditions, n (%)	
Diabetes mellitus	8 (40)
Hypertension	19 (95)
Dyslipidemia	9 (45)
Chronic kidney disease stage III-V	9 (45)
Ischemic heart disease	4 (20)
Congestive heart failure	9 (45)
Stroke	7 (35)
Cancer	3 (15)
Mean CHA2DS2-VASc score (SD)	4.40 (1.31)
Mean HAS-BLED (SD)	2.25 (1.29)
Mean Admission Laboratory (SD)	
INR	2.19 (0.58)
eGFR (ml/min)	44.15 (25.13)
CRP (mg/l)	15.69 (13.94)
D-dimer (ng/ml)	0.58 (0.50)
SARS-CoV-2 treatment, n (%)	
Antiviral Drug	
Favipiravir	13 (65)
Remdesivir	3 (15)
Molnupiravir	2 (10)
Dexamethasone	8 (40)
Green chiretta	1 (5)
O_2 supplement, n (%)	
Room air	10 (50)
O_2 cannula	6 (30)
O_2 mask with bag	3 (15)
High-flow nasal cannula	1 (5)
Mean Length of stay (SD) (days)	10.40 (5.40)

BMI=body mass index; CRP=C-reactive protein; eGFR=estimated glomerular filtration rate; INR=international normalized ratio; SD=standard deviations.

Secondary outcome

The average WDD after SARS-CoV-2 infection was significantly lower than the WDD before infection (2.62±1.19 mg vs. 3.01±1.34 mg, $p=0.002$), resulting in a mean reduction of 11.5%. In addition, the mean inpatient WDD was significantly lower than the mean WDD after SARS-CoV-2 infection (2.10±1.11 mg vs. 2.62±1.19 mg, $p=0.019$), revealing a mean reduction of 41.6%. As illustrated in Table 2, the authors found no significant difference in the mean TTR before and after SARS-CoV-2 infection (46.7±38.5 vs. 44.9±33.5, $p=0.794$). Table 3 presents the correlation between WDD and potential affecting factors. The authors found that consumption of green chiretta had a significant positive correlation with the change in pre- to post-hospital daily warfarin dose ($r=0.59$, $p=0.006$). The

Table 2. Warfarin Characteristics

	Pre-infection	In-patient	Post-infection	Difference	Percentage change	p-value
Average warfarin daily dose (mg/day)						
Total	3.01 (1.34)	2.10 (1.11)	2.62 (1.19)	[a] 0.91 (0.94)	[a] 28.30 (25.45)	[a] <0.001
				[b] 0.39 (0.49)	[b] 11.54 (13.68)	[b] 0.002
				[c] -0.51 (0.99)	[c] -41.56 (63.53)	[c] 0.019
Day 1 to 60			2.59 (1.37)			
Day 61 to 120			2.60 (1.14)			
Day 121 to 180			2.64 (1.17)			
TTR*	45.65 (38.45)		44.90 (33.50)	[b] 0.74 (47.03)		[b] 0.794
Test in range		25.45 (25.01)				
Average INR	2.19 (0.58)	2.49 (0.83)	2.09 (0.46)	[a] -0.30 (0.92)		[a] 0.167
				[b] 0.11 (0.77)		[b] 0.538
				[c] 0.40 (0.87)		[c] 0.052

INR=international normalized ratio; TTR=Time in therapeutic range.

Data are presented as mean (standard deviation), * INR target is 2.0 to 3.0

[a] Comparison of pre-infection and in-patient; [b] Comparison of pre-infection and post-infection 180 days; [c] Comparison of in-patient and post-infection 180 days,

Table 3. The correlation between warfarin daily dose and potential affecting factors

Correlations	% change pre-/in-hospital daily dose		% change pre-/post-infection daily dose	
	r	p-value	r	p-value
Sex	0.310	0.183	0.131	0.581
Favipiravir	0.235	0.318	0.157	0.508
Remdesivir	-0.191	0.419	-0.330	0.155
Molnupiravir	-0.264	0.261	0.134	0.575
Green Chiretta	0.396	0.084	0.594**	0.006
Dexamethasone	0.421	0.065	0.181	0.446
Age ≥75 years old	-0.264	0.261	-0.309	0.185
BMI ≥25 kg/m^2	-0.669**	0.001	0.145	0.542
ALC ≥1,500 cells/mm^3	0.139	0.569	0.318	0.184
eGFR ≥60 ml/min	0.145	0.555	-0.524*	0.021
CRP ≥10 mg/l	-0.119	0.650	-0.409	0.103
D-dimer ≥0.5 ng/ml	-0.137	0.612	-0.063	0.818

* Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed).

eGFR ≥60 ml/min had a significant negative correlation with the change in pre- to post-hospital daily warfarin dose (r=-0.52, p=0.021). BMI ≥25 kg/m^2 had a significant negative correlation with change in pre- to in-hospital daily warfarin dose (r=-0.67, p=0.001). Furthermore, consumption of green chiretta was associated with a significantly higher warfarin dosage following SARS-CoV-2 infection (odds ratio=33.32, 95% confidence interval 0.92 to 65.72, p=0.046). However, BMI ≥25 kg/m^2 was associated with a significantly lower warfarin dosage during in-hospital SARS-CoV-2 infection, compared with pre-hospital dosage (odds ratio=-35.00, 95% confidence interval -65.66 to -4.34, p=0.031) but not after hospital discharge, as displayed in Table 4. None of the other factors showed a statistically significant effect on warfarin dosage. Figure 1 presents the distribution of WDD for each individual in the population, categorized by days 60, 120, and 180 before SARS-CoV-2 infection, during hospitalization, and after discharge.

Discussion

In the present study, the authors focused on patients with AF who were taking warfarin to prevent thromboembolic stroke and were also infected with SARS-CoV-2 and receiving treatment in the hospital. Our goal was to examine the pattern of changes in warfarin dosage during SARS-CoV-2 infection, including the influence of drugs for SARS-CoV-2 treatment on the required warfarin dosage during hospitalization. We also looked at basic patient factors such as BMI, comorbidities, and prior medications to understand their impact. In addition, we investigated the

Table 4. Univariate analysis in warfarin daily dose with potential affecting factors

Factors	% change pre-/in-hospital daily dose			% change pre-/post-infection daily dose		
	B*	p-value	95% CI	B	p-value	95% CI
Sex	2.316	0.808	-20.035 to 24.667	-3.343	0.547	-16.178 to 9.492
Remdesivir	-23.598	0.194	-63.045 to 15.850	-6.389	0.516	-29.042 to 16.264
Molnupiravir	-7.309	0.656	-45.545 to 30.926	-5.260	0.579	-27.217 to 16.697
Green chiretta	26.361	0.297	-30.061 to 82.783	33.322	0.046	0.921 to 65.723
Dexamethasone	8.679	0.443	-17.175 to 34.532	5.281	0.418	-9.565 to 20.127
Age ≥75 years old	-20.746	0.187	-54.809 to 13.317	-9.884	0.262	-29.445 to 9.677
BMI ≥25 kg/m^2	-35.000	0.031	-65.657 to -4.344	8.246	0.295	-9.359 to 25.850
ALC ≥1,500 cells/mm^3	-0.549	0.955	-23.567 to 22.469	3.150	0.581	-10.068 to 16.368
eGFR ≥60 ml/min	7.842	0.618	28.689 to 44.372	-3.722	0.679	-24.700 to 17.256
D-dimer ≥0.5 ng/ml	-7.674	0.455	-31.160 to 15.813	-10.444	0.107	-23.931 to 3.043

* B-value is the coefficient of a predictor variable in a simple linear regression model. It represents the slope of the regression line, indicating the change in the dependent variable (outcome) for each unit change in the independent variable (predictor)

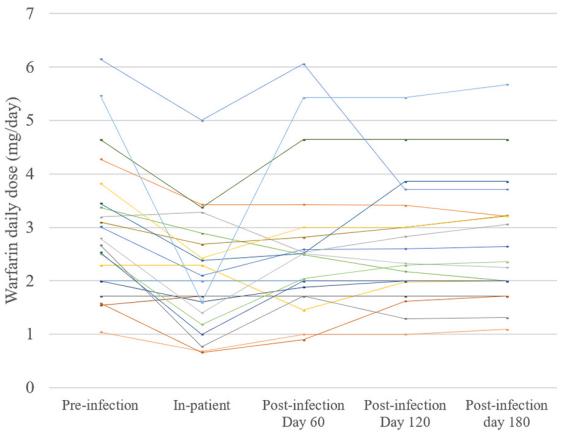

Figure 1. Average warfarin daily dose in all population.

occurrence of complications such as bleeding or thrombosis during hospitalization. Furthermore, the authors followed-up with patients for 180 days after discharge to observe any differences in the trend of warfarin dosage as compared with the period before SARS-CoV-2 infection. This information is crucial for optimizing warfarin therapy in patients with SARS-CoV-2 and preventing potential complications.

The authors found in our study that the average participant was overweight (average BMI of 25.67 kg/m^2) based on the WHO Asian BMI classification. Patients had a high risk of stroke (average CHA2DS2-VASc score of 4.40) and a moderate risk of bleeding (average HAS-BLED score of 2.25). Most participants had mild COVID-19 symptoms and did not require much oxygen support (i.e., only half of the patients needed oxygen), and very few (5%) required a high-flow nasal cannula. None needed to be put on a ventilator. Favipiravir was the most common medication used for COVID-19 treatment (65%), followed by remdesivir (15%) and molnupiravir (10%). The authors observed the following during SARS-CoV-2 infection: Firstly, patients' warfarin dosage decreased by an average of 0.91 mg/day, which represents a 28.30% reduction compared with before the infection. Secondly, the warfarin dosage continued to decrease, with an average reduction of 0.39 mg/day or 11.54% after following-up with patients for 180 days after hospital discharge. When the authors analyzed the dosage over periods of 1 to 60, 61 to 120, and 121 to 180 days after infection, we noticed a slight increase over time, but it did not reach the pre-infection levels. Lastly, despite the decrease in warfarin dosage after infection, the average INR and TTR did not show a statistically significant before and after infection. These results suggest that infection with SARS-CoV-2 may result in a decreased need for warfarin to maintain therapeutic levels, both during and after infection for at least 180 days. However, the duration of this effect remains unclear and might require further data collection for future investigations.

The average D-dimer level was elevated upon admission, which aligns with previous reports indicating that proinflammatory states could reduce the need for warfarin dosage[12,13]. In a systematic review and meta-analysis, all studies indicated significantly higher D-dimer concentrations in patients with more severe SARS-CoV-2[14]. However, in our study, we did not find a correlation between D-dimer levels on the first day of admission and the WDD changes during infection or after hospital discharge as compared with before SARS-CoV-2 infection. The limitation of our cohort did not have sufficient power to demonstrate such an association, as only four out of 20 patients had D-dimer levels greater than 0.5 ng/ml. According to the findings of a systematic review, meta-analysis, and meta-regression study, obesity is significantly linked to increased severity and higher mortality among patients with SARS-CoV-2[15]. In a retrospective study of 301 adult patients who used

warfarin for more than 3 months, the researchers noted that obese patients (BMI >30 kg/m^2) required a 20% higher dose of warfarin compared with those with normal BMI (BMI 18.5 to 24.9 kg/m^2) and overweight patients (BMI 25 to 29.9 kg/m^2)[16]. In addition, another previous study found that morbidly obese patients may need a higher total warfarin weekly dose to achieve and maintain an INR[17]. In our study, we found that as compared with patients with a BMI <25 kg/m^2, a BMI ≥25 kg/m^2 was significantly associated with a lower WDD during SARS-CoV-2 infection. This result may explain why infection with SARS-CoV-2 could result in a decreased need for warfarin to maintain therapeutic levels during hospitalization. However, there was no significant difference between before SARS-CoV-2 infection and after discharge from the hospital. In our cohort, 13 out of 20 patients were on favipiravir, mainly metabolized in the liver by aldehyde oxidase. Favipiravir also inhibits cytochrome P450 (CYP) 2C8, so when taken with warfarin, which is metabolized by CYP2C8, INR levels should be closely monitored[18]. This real-world study found a significant increase in INR levels among patients using favipiravir in combination with warfarin[19].

In Thailand, the popularity of green chiretta (Andrographis paniculata), also known as "Fah Talai Jone," increased during the SARS-CoV-2 crisis. Two studies conducted in Thailand on the use of green chiretta in treating SARS-CoV-2 infection indicated that A. paniculata extract from green chiretta treatment regimens was potentially effective and safe for adults with mild SARS-CoV-2[20,21]. In our study, we observed that patients with SARS-CoV-2 who received green chiretta treatment tended to require lower WDD after discharge from the hospital compared with those who did not receive green chiretta treatment during hospitalization. There is supportive evidence from a literature review showing green chiretta inhibited the activity of the CYP450 enzyme and its isoforms, including the CYP1A2 enzyme, which warfarin is involved with. Thus, concurrent use of green chiretta with warfarin could contribute to warfarin toxicity[22]. As a result, warfarin dose reduction is required during hospitalization for SARS-CoV-2 infection, which is also observed in our patients. These study results could raise clinicians' awareness of drug-drug interaction by closely monitoring INR levels during in-hospital SARS-CoV-2 infection. Also, after hospitalization, the INR level should be followed in these patients earlier and more frequently than in the general population.

Limitation

The present study had several limitations. First, the small population size might have contributed to a lack of significant differences in the factors affecting warfarin dosage. Most patients had mild symptoms of SARS-CoV-2 infection. The study had limitations in analyzing the effect of WDD on the severity of SARS-CoV-2 infection. Second, the adjustment of warfarin dosage is influenced by various factors that might not have been controlled for, such as concurrent medications, illness severity, nutrition status, dietary intake, drug compliance, and treatment decisions made by physicians. Lastly, this was a retrospective study that relied on electronic medical records, which could have led to missing or incomplete data.

Conclusion

SARS-CoV-2 infection with mild symptoms and its treatment can potentially influence warfarin levels in hospitalized patients. Our study revealed that adults hospitalized with SARS-CoV-2 infection, as well as during post-hospital follow-up, exhibited significantly reduced average warfarin daily doses. The green chiretta (Andrographis paniculata) has the potential to interact with warfarin during treatment for SARS-CoV-2 infection. This highlights the importance of considering adjustments to warfarin dosage to ensure the safety and effectiveness of treatment in this patient population.

What is already known on this topic?

SARS-CoV-2 infection may affect warfarin levels during hospitalization. The duration of this effect remains unclear.

What this study adds?

SARS-CoV-2 infection and its treatment can influence warfarin levels, resulting in a substantial decrease of approximately 30% in average warfarin daily doses among hospitalized patients with the infection. This effect appears to persist for at least 6 months. Green chiretta (A. paniculata) has the potential to interact with warfarin during treatment for SARS-CoV-2 infection. These findings highlight the importance of considering adjustments to warfarin dosage to enhance the safety and effectiveness during treatment for SARS-CoV-2.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Vinding NE, Kristensen SL, Rørth R, Butt JH, Østergaard L, Olesen JB, et al. Ischemic stroke severity and mortality in patients with and without atrial fibrillation. J Am Heart Assoc 2022;11:e022638.
2. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS):

The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:373-498.
3. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: A report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. Circulation 2024;149:e1-156.
4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67.
5. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, et al. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. Thromb Haemost 2013;110:1087-107.
6. Smith DR. Review a brief history of coronaviruses in Thailand. J Virol Methods 2021;289:114034. doi: 10.1016/j.jviromet.2020.114034.
7. Kollias A, Kyriakoulis KG, Lagou S, Kontopantelis E, Stergiou GS, Syrigos K. Venous thromboembolism in COVID-19: A systematic review and meta-analysis. Vasc Med 2021;26:415-25.
8. Conway EM, Mackman N, Warren RQ, Wolberg AS, Mosnier LO, Campbell RA, et al. Understanding COVID-19-associated coagulopathy. Nat Rev Immunol 2022;22:639-49.
9. Zinellu A, Paliogiannis P, Carru C, Mangoni AA. INR and COVID-19 severity and mortality: A systematic review with meta-analysis and meta-regression. Adv Med Sci 2021;66:372-80.
10. Irwin MN, Adie S, Sandison K, Alsomairy SA, Brancaccio A. Warfarin dose requirements in adults hospitalized with COVID-19 infection: A retrospective case series. J Pharm Pract 2022;35:654-60.
11. Holbrook AM, Pereira JA, Labiris R, McDonald H, Douketis JD, Crowther M, et al. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med 2005;165:1095-106.
12. Abdel-Aziz MI, Ali MA, Hassan AK, Elfaham TH. Factors influencing warfarin response in hospitalized patients. Saudi Pharm J 2015;23:642-9.
13. Yoon IK, Choi YJ, Chang BC, Lee KE, Rhie JY, Lee BK, et al. Effects of inflammatory cytokine gene polymorphisms on warfarin maintenance doses in Korean patients with mechanical cardiac valves. Arch Pharm Res 2014;37:752-9.
14. Düz ME, Balcı A, Menekşe E. D-dimer levels and COVID-19 severity: Systematic Review and Meta-Analysis. Tuberk Toraks 2020;68:353-60.
15. Singh R, Rathore SS, Khan H, Karale S, Chawla Y, Iqbal K, et al. Association of obesity with COVID-19 severity and mortality: An updated systemic review, meta-analysis, and meta-regression. Front Endocrinol (Lausanne) 2022;13:780872. doi: 10.3389/fendo.2022.780872.
16. Alshammari A, Altuwayjiri A, Alshaharani Z, Bustami R, Almodaimegh HS. Warfarin dosing requirement according to body mass index. Cureus 2020;12:e11047.
17. Tellor KB, Nguyen SN, Bultas AC, Armbruster AL, Greenwald NA, Yancey AM. Evaluation of the impact of body mass index on warfarin requirements in hospitalized patients. Ther Adv Cardiovasc Dis 2018;12:207-16.
18. Wadelius M, Chen LY, Eriksson N, Bumpstead S, Ghori J, Wadelius C, et al. Association of warfarin dose with genes involved in its action and metabolism. Hum Genet 2007;121:23-34.
19. Wattana K, Uitrakul S, Leesakulpisut N, Khunkit P. Potential drug interaction between favipiravir and warfarin in patients with COVID-19: A real-world observational study. J Clin Pharmacol 2023;63:338-44.
20. Wanaratna K, Leethong P, Inchai N, Chueawiang W, Sriraksa P, Tabmee A, et al. Efficacy and safety of andrographis paniculata extract in patients with mild COVID-19: A randomized controlled trial. Arch Intern Med Res 2022;5:423-7.
21. Sa-Ngiamsuntorn K, Suksatu A, Pewkliang Y, Thongsri P, Kanjanasirirat P, Manopwisedjaroen S, et al. Anti-SARS-CoV-2 activity of Andrographis paniculata extract and its major component andrographolide in human lung epithelial cells and cytotoxicity evaluation in major organ cell representatives. J Nat Prod 2021;84:1261-70.
22. Intharuksa A, Arunotayanun W, Yooin W, Sirisa-Ard P. A comprehensive review of Andrographis paniculata (Burm. f.) nees and its constituents as potential lead compounds for COVID-19 drug discovery. Molecules 2022;27:4479. doi: 10.3390/molecules27144479.