ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

The Clinical Outcomes of COVID-19 in Patients on Warfarin: A Propensity Score Matching Study

COVID-19 Hastalarında Varfarin Kullanımının Klinik Sonuçları: Bir Propensity Skor Eşleştirme Çalışması

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

ABSTRACT

Background: COVID-19 is associated with vascular thrombosis in critical patients. However, warfarin has not been adequately studied in patients with COVID-19. This study aimed to evaluate whether the use of warfarin, a potent oral anticoagulant, was of clinical benefit in patients with COVID-19.

Methods: This was a retrospective cohort study of COVID-19 patients diagnosed at 3 different centers in Turkey between April 2020 and April 2021. Patients were grouped by whether they were taking warfarin or not. Propensity score matching analysis was used to compare the differences between the groups in mortality, hospitalization, and admission to the intensive care unit.

Results: A propensity score analysis was performed on 128 patients in the warfarin group and 372 patients in the control group. After matching, 84 pairs of patients were compared. The patients in the control group were more likely to be admitted to the intensive care unit (33.3% vs. 14.3%, respectively; $P=.007$) and had longer hospital stays than the warfarin group (7.1 vs. 14.1 days; $P=.005$). The warfarin group had a lower death rate compared to the control group (7.1% vs. 27.4%, respectively; $P=.001$), and surviving patients were significantly more likely to be in the warfarin group than the control group (56.1% vs. 20.7%, respectively; $P=.001$). In patients on warfarin, there was a lower incidence of in-hospital death (log-rank test $P=.005$).

Conclusions: Warfarin therapy could provide clinical benefits in patients with COVID-19. The current data highlight the importance of potent anticoagulation in the treatment of COVID-19.

Keywords: Clinical benefits, COVID-19, warfarin

ÖZET

Amaç: COVID-19, kritik hastalarda vasküler tromboz ile ilişkilidir. Ancak COVID-19 hastalarında varfarin kullanımının klinik etkileri yeterince değerlendirilmemiştir. Bu çalışmada, COVID-19 hastalarında güçlü bir antikoagülan olan varfarinin klinik etkilerinin değerlendirilmesi amaçlandı.

Yöntemler: Çalışma retrospektif olarak planlandı. Türkiye'de 3 farklı pandemi merkezinde Nisan 2020 ile Nisan 2021 tarihleri arasında COVID-19 tanısı almış hastalar tarandı. Hastalar COVID-19 hastalığı sürecinde varfarin kullanmakta olan ve kullanmayan olarak gruplandırıldı. Gruplar arasında mortalite, hastaneye yatış ve yoğun bakım ünitesine yatış açısından farklılıkları karşılaştırmak için *propensity* skor eşleştirme analizi kullanıldı.

Bulgular: Varfarin grubunda 128 hasta ve kontrol grubunda 372 hastada propensity skor analizi yapıldı. Eşleştirme sonrası 84 hasta çifti karşılaştırıldı. Kontrol grubundaki hastaların yoğun bakım ünitesine alınma oranları daha yüksekti (%33,3'e karşı %14,3; $P=$,007) ve varfarin grubuna göre daha uzun hastanede kalış süreleri vardı (7,1'e karşı 14,1 gün; $P=$,005). Varfarin grubu, kontrol grubuna kıyasla daha düşük bir ölüm oranına sahipti (%7,1'e karşı %27,4; $P=$,001) ve hayatta kalan hastaların, kontrol grubuna göre varfarin grubunda olma olasılığı önemli ölçüde daha yüksekti (%56,1'e karşı %20,7; $P=$,001). Varfarin kullanan hastalarda, hastane içi ölüm insidansı daha düşüktü (log-rank testi $P=$,005).

Sonuç: Varfarin kullanımı, COVID-19 hastalarında klinik faydalar sağlayabilir. Mevcut veriler, COVID-19 tedavisinde güçlü antikoagülasyonun önemini vurgulamaktadır.

Anahtar Kelimeler: COVID-19, klinik faydalar, varfarin

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Received: January 31, 2022
Accepted: August 16, 2022

Cite this article as: Oğuz M, Akbulut T, Saylık F, Sipal A, Demirci M, Erdal E. The clinical outcomes of COVID-19 in patients on warfarin: A propensity score matching study. *Turk Kardiyol Dern Ars.* 2022;50(8):576-582.

DOI:10.5543/tkda.2022.22344

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic continues to be a global cause of mortality. In early studies, death in COVID-19 patients was mostly attributed to progression to respiratory failure.[1] However, recent studies have shown that it is associated with coagulopathy and a prothrombotic state with high D-dimer and fibrinogen levels.[2,3] Despite pharmacological thromboprophylaxis, a very high cumulative incidence of thrombotic complications has been reported in 25%-42% of patients, and this is associated with increased mortality in critically ill patients with COVID-19.[4,5] Although vascular thrombosis is seen in many extrapulmonary organs, findings of pulmonary vascular thrombosis were observed more frequently in autopsy studies.[6,7] Alveolar capillary microthrombi were 9 times more prevalent in patients with COVID-19 compared to patients with influenza.[8] Due to the frequent monitoring of common thrombotic vascular complications, several studies with anticoagulant therapy have been conducted. Paranjpe et al[9] showed that systemic anticoagulation confers a survival benefit in hospitalized patients with COVID-19. Another study concluded that patients with severe SARS-CoV-2 pneumonia had higher platelet counts than those with pneumonia of other causes. The study also demonstrated that patients with markedly elevated D-dimer may benefit from anticoagulant therapy, mainly with low-molecular-weight heparin (LMWH).[10] Also, direct oral anticoagulant use was associated with a lower risk of mortality from all causes in patients with COVID-19.[11] Few studies have evaluated the clinical benefit of warfarin use in COVID-19.[12]

Methods

Study Population

This study was performed according to the guidelines of the Declaration of Helsinki of 1975, as it was revised in 2008. The study was approved by the Van Training and Research Hospital (No: 2021/004). The study was conducted at 3 research hospitals of the University of Health Sciences, which were all designated pandemic hospitals. Patients admitted between April 15, 2020, and January 15, 2021, with polymerase chain reaction-proven SARS-CoV-2 were identified from electronic medical records. All patients were unvaccinated as the study was conducted prior to the public COVID-19 vaccination program.

In this retrospective study, we evaluated 131 COVID-19 patients (aged 18 years or older) with a diagnosis of atrial fibrillation and/or prosthetic valve disease using warfarin in the warfarin group and 372 COVID-19 patients in the control group. Two patients had not achieved a time in the therapeutic range >60% and 1 patient who had discontinued warfarin and switched to LMWH after the COVID-19 diagnosis was excluded. After propensity score matching analysis, 84 pairs of patients were compared.

Clinical Data

The data were acquired from the electronic health records and confirmed with patients and/or patients' families by telephone. The parameters included were demographics, laboratory measurements, prior diagnoses, comorbidities, history of invasive procedures and outcomes, that is, death, hospital admission, intensive care unit (ICU) admission, and hospital stay. Pneumonia was confirmed by computed tomography in all hospitalized patients in both groups. Patients with moderate to severe diseases were hospitalized according to current guidelines.

Major bleeding was defined as bleeding that necessitated a blood transfusion or surgical intervention; nasopharyngeal bleeding necessitated intervention; and ocular, intracranial, or gastrointestinal bleeding that required a blood transfusion.

Definition of Warfarin Use

Warfarin use was defined as being treated with warfarin for at least 15 days before the COVID-19 diagnosis. This period was accepted as the minimum SARS-CoV-2 incubation period. If a mechanical prosthetic valve was the indication for warfarin therapy, only patients who were on warfarin for at least 155 days before the COVID-19 diagnosis were included. This was necessary for the ability to calculate time in the therapeutic range. During admission, LMWH was the most commonly used anticoagulant as a prophylactic dose to prevent thrombotic complications in patients with COVID-19. Warfarin was not switched to LMWH in patients who were already on warfarin before being hospitalized for COVID-19. In this group, daily international normalized ratio controls were performed, and warfarin doses were adjusted accordingly. Prophylactic-dose LMWH was given to patients who were not on warfarin during hospitalization. The hospitalized patients not on warfarin with elevated D-dimer levels were initiated on therapeutic LMWH.

Statistical Analysis

Statistical Package for the Social Sciences software was used for all analyses (version 22.0, IBM Corp.; Armonk, NY, USA). The Kolmogorov–Smirnov test was used to determine the data's normality. For quantitative variables with a normal distribution, arithmetic means (standard deviation) were presented, whereas median values (interquartile ranges [IQR]) were presented for those with a non-normal distribution. Numbers and percentages were used to express categorical variables. An unpaired Student's *t*-test was used to compare normally distributed variables, and the Mann–Whitney *U* test was used to compare non-normally distributed variables. Where appropriate, the chi-square test or Fisher's exact test was used to compare categorical variables. To determine the independent predictors of the in-hospital mortality of the COVID-19 patients, univariable logistic regression analysis was used; those that exhibited significant association in univariable logistic regression analysis with a relevant clinical situation were included in the multivariable logistic regression analysis. Comparable warfarin and control group cohorts were created by propensity score matching techniques. After matching, dependent *t*-tests were performed. A logistic regression model calculated propensity scores for each patient with COVID-19 based on the independent variables of demographic

ABBREVIATIONS

ACEi	Angiotensin receptor enzime
ARDS	Acute respiratory distress syndrome
COVID-19	Coronavirus disease 2019
DOAC	Direct oral anticoagulant
ICU	Intensive care unit
INR	International normalized ratio
LMWH	Low molecular weight heparin
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
TTR	Time in the therapeutic range

Table 1. Demographics Before and After Propensity Score Matching

	Unmatched Comparisons				Matched Comparisons			
	Warfarin Positive	Warfarin Negative	*P*	Standard Difference	Warfarin Positive	Warfarin Negative	*P*	Standard Difference
	(n=128)	(n=372)			(n=84)	(n=84)		
Age, years	55.3(14.5)	53.4(18.2)	.269	0.1287	52.6(14.9)	55.1(17.3)	.244	–0.2009
Gender, male	63(49.2)	212(57)	.155	–0.1548	42(50)	43(51.2)	1.000	–0.0237
DM	16(12.5)	56(15.1)	.573	–0.0772	10(11.9)	18(21.4)	.147	–0.2880
Hypertension	60(46.9)	123(33.1)	**.007**	0.2768	29(34.5)	34(40.5)	.524	–0.1193
Thyroid dysfunction	5(3.9)	17(4.6)	.947	–0.0343	4(4.8)	4(4.8)	1.000	0.0000
Hyperlipidemia	12(9.4)	30(8.1)	.782	0.0450	9(10.7)	7(8.3)	.793	0.0817
Chronic kidney disease	4(3.1)	20(5.4)	.431	–0.1294	4(4.8)	3(3.6)	1.000	0.0684
COPD	21(16.4)	43(11.6)	.207	0.1309	15(17.9)	13(15.5)	.836	0.0643
Coronary artery disease	17(13.3)	58(15.6)	.626	–0.0681	15(17.9)	12(14.3)	.674	0.1052
Congestive heart failure	54(42.2)	21(5.6)	**<.0001**	0.7399	10(11.9)	11(13.1)	1.000	–0.0241
Cigarette smoking	29(22.7)	53(14.2)	**.037**	0.2009	17(20.2)	12(14.3)	.414	0.1422
Atrial fibrillation	6(4.6)	-	-	-	5(5.9)	-	-	-
Atrial fibrillation and prosthetic valve disease	24(18.7)	-	**-**	-	15(17.9)	-	-	-
Prosthetic valve disease	97(75.7)	-	**-**	-	64(76.2)	-	-	-

DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease.

and baseline characteristics and a dependent variable of whether the patient was on warfarin or not. A Kaplan–Meier curve was used to estimate the difference between the mortality rates of patients on warfarin treatment and the controls. A *P*-value less than .05 was considered significant.

Results

The demographic and baseline characteristics of the warfarin group and the control group before propensity score matching are summarized in Table 1. In the warfarin group, the mean age was 55.3 ± 14.5, and 49.2% were men, whereas, in the control group, the mean age was 53.4 ± 18.2, and 57% were men. Congestive heart failure (CHF) was seen more frequently in the warfarin group than in the control group ($P < .0001$), and the warfarin group had more HT ($P = .007$). There were no differences between groups among the other comorbidities. After propensity score matching, 84 matched pairs of warfarin and control group patients were compared (Table 2). Neutrophil, lymphocyte, and monocyte counts were lower in the warfarin group compared to the control group ($P < .001$). Only beta-blocker use was higher in the warfarin group compared to the control group in terms of drugs ($P < .001$). There were no differences in hospitalization rates or ICU stays between groups. The control group had longer hospital stays than the warfarin group ($P = .005$) and were more likely to be admitted to an ICU (33.3% vs. 14.3%, respectively; $P = .007$). The warfarin group had a lower death rate compared to the control group (7.1% vs. 27.4%, respectively; $P = .003$).

A comparison of the demographic, clinical, laboratory, and hospital records of the patients who died (n=29) and the patients who survived (n=139) with COVID-19 in this study is presented in Table 3. In the survivor group, the median age was 50.9, and 50.4% were men. Among the patients who died, the medium age was 69.3 years, and 51.7% were men. The patients who died were older than the survivor group ($P < .001$). The patients who died had more comorbidities. Diabetes mellitus, HT, CHF, chronic kidney disease (CKD), coronary artery disease, and chronic obstructive pulmonary disease were statistically significantly higher in the deceased patients than in the survivor patients. The use of warfarin was statistically significantly higher in the survivor patients than in the patients who died (56.1% vs. 20.7%, respectively; $P = .001$). The patients who died tended to have higher levels of white blood cells, C-reactive protein (CRP), and D-dimer. There were no differences between the groups in the use of other drugs.

Because of the small sample size, we designed the multivariable logistic regression analysis using 2 different models (Table 4). Model 1 was conducted using age, CRP, D-dimer, and the use of warfarin, and all other variables were demonstrated as independent predictors of COVID-19 mortality. In model 2, age, CKD, D-dimer, and the use of warfarin were calculated, and again, 4 variables were found to be independent predictors of mortality. The Kaplan–Meier curve analysis showed that patients using warfarin had a lower incidence of in-hospital death than those who were not (log-rank test $P = .004$) (Figure 1).

Discussion

In this study, warfarin use was associated with clinical benefits in patients with COVID-19. The patients on warfarin had lower in-hospital mortality and fewer ICU admissions and non-intensive care hospital stays.

Table 2. Comparison of Laboratory, Drugs Use, and Hospital Records of Warfarin Used and Warfarin Non-used Groups

Variables	Warfarin Used (n=84)	Warfarin Non-used (n=84)	*P*
WBC, 10^9/L	7.48(6.02-9.65)	8.04(6.12-10.3)	.467
Hemoglobin, g/dL	14.7(13.2-16.3)	14.5(13.7-15.7)	.596
Platelet, 10^3/L	236.5(71.3)	219.7(86)	.169
Neutrophil, 10^9/L	5.4(4.3-7.2)	6.3(5.4-8.1)	**.032**
Lymphocyte, 10^9/L	1.9(1.3-3.2)	3.4(2.1-4.4)	**<.0001**
Monocyte, 10^9/L	0.7(0.5-4.6)	3.6(0.6-6.9)	**<.001**
RDW, %	44.9(43.1-49.4)	43.6(41.8-48.9)	.109
Creatinine, mg/dL	0.91(0.75-1.07)	0.84(0.72-0.99)	.237
Albumin, g/dL	3.5(0.8)	3.5(0.9)	.936
Ferritin, ng/dL	159(62-285)	192(81-299)	.362
D-dimer, ng/mL	244(117-654)	245(98-584)	.329
Fibrinogen, mg/dL	283.9(114.3)	262.4(82.2)	.162
CRP, mg/L	12.1(5.5-59.5)	16.9(5.9-68.5)	.513
INR	2.9(1.6-4.6)	-	-
Use of drugs			
Aspirin, n (%)	7(8.3)	9(10.7)	.793
P2Y12 inhibitors, n (%)	4(4.8)	4(4.8)	1.000
Ca blocker, n (%)	16(19)	8(9.5)	.123
Beta blocker, n (%)	49(58.3)	27(32.1)	**.001**
ACEinh/ARBs, n (%)	26(31)	22(26.2)	.608
Insulin, n (%)	1(1.2)	2(2.4)	1.000
OAD, n (%)	9(10.7)	15(17.9)	.270
Statin, n (%)	12(14.3)	6(7.1)	.212
Diuretics, n (%)	13(15.5)	13(15.5)	1.000
Hospitalization rate, n (%)	24(28.6)	37(44)	.054
Hospital stay in total, days	7.1 ± 4.5	14.1 ± 10.5	**.005**
Admission to ICU, n (%)	12(14.3)	28(33.3)	**.007**
ICU stay, days	2.6(2-7)	8.1(3-11)	.125
In-hospital death, n (%)	6(7.1)	23(27.4)	**.001**

ACEinh, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; CRP, C-reactive protein; ICU, intensive care unit; INR, international normalized ratio; OAD, oral anti-diabetics; WBC, white blood cell; RDW, red blood cell distribution width.

Table 3. Comparison of Demographic, Clinical, Laboratory, and Hospital Records of Survived and Non-survived Patients with COVID-19

Variables	Survivor (n=139)	Non-survivor (n=29)	*P*
Age, years	50.9(15)	69.3(12.5)	**<.0001**
Male gender	70(50.4)	15(51.7)	1.000
DM	15(10.8)	13(44)	**<.0001**
Hypertension	44(31.7)	19(65.5)	**.002**
CAH	17(12.2)	10(34.5)	**.009**
CHF	10(7.2)	11(37.9)	**<.0001**
CKD	2(1.4)	5(17.2)	**.002**
COPD	17(12.2)	11(37.9)	**.001**
Cigarette smoking	25(18)	4(13.8)	.785
WBC	7.56(5.86-9.8)	8.81(7.31-11.7)	**.019**
Neutrophil	5.7(4.5-7.3)	6.4(4.7-8.6)	.362
Lymphocyte	2.3(1.5-3.8)	3.3(2.1-4.4)	.272
Monocyte	1.4(0.5-6.4)	2.2(0.5-3.3)	.475
RDW	44(42-49.3)	45.3(43-49.9)	.472
Creatinine	0.9(0.7-1)	0.9(0.8-1)	.796
Albumin	3.5(0.9)	3.5(0.7)	.731
CRP	11.2(4.7-60)	62.3(16.5-78.1)	**.001**
D-dimer	204(99-589)	345(200-705)	**.012**
Fibrinogen	271(98)	280(109)	.684
Ferritin	171(72-276)	265(85-425)	.051
Use of drugs			
Aspirin	12(8.6)	4(13.8)	.483
Clopidogrel	6(4.3)	2(6.9)	.628
Ca blocker	21(15.1)	3(10.3)	.770
Beta blocker	62(44.6)	14(48.3)	.876
ACEinh/ARBs	40(28.8)	8(27.6)	1.000
Insulin	2(1.4)	1(3.4)	.436
OAD	17(12.2)	7(24.1)	.139
Statin	15(10.8)	3(10.3)	1.000
Diuretics	21(15.1)	5(17.2)	.779
Use of warfarin	78(56.1)	6(20.7)	**.001**

ACEinh, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; CRP: C-reactive protein; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; INR, international normalized ratio; OAD, oral anti-diabetics; WBC, white blood cell; RDW, red blood cell distribution width.

According to initial studies, COVID-19-related deaths were mostly attributed to acute respiratory distress syndrome (ARDS) after respiratory system involvement.[13] It was later found that the symptoms of COVID-19 were not limited to the respiratory system: the virus could trigger multiple systemic inflammatory responses and coagulopathy.[14] Now, it is obvious that COVID-19 is associated with hypercoagulation and pulmonary micro-thrombosis.[15,16] The mechanisms of coagulopathy are not fully elucidated; however, high levels of Von Willebrand factor (vWF) and factor VIII (FVIII) in infectious lung diseases, including pneumonia and sepsis, indicate endothelial inflammation.[17] Immune

Table 4. Univariable and Multivariable Logistic Regression Analysis for Predicting In-hospital Mortality with COVID-19 Patients

	Univariate OR (95% CI)	*P*	Multivariate OR (95% CI)	*P*
Age	1.100 (1.058,1.144)	**<.0001**	1.098 (1.051,1.147)	**<.001**
DM	6.717 (2.712,16.636)	**<.0001**	-	-
HT	4.102 (1.762,9.549)	**.001**	-	-
CAD	3.777 (1.507,9.464)	**.004**	-	-
CHF	7.883 (2.935,21.178)	**<.0001**	-	-
CKD	14.271 (2.617,77.822)	**.002**	17.138 (2.168,135.501)	**.004**
COPD	4.386 (1.773,10.847)	**.001**	-	-
WBC	1.082 (1.004,1.166)	**.04**	-	-
CRP	1.006 (1.001,1.012)	**.03**	-	-
D-dimer	1.001 (1.000,1.001)	**.03**	1.001 (1.000,1.001)	**.004**
Use of warfarin	0.204 (0.078,0.532)	**.001**	0.127 (0.036,0.449)	**<.001**

CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HT, hypertension; WBC, white blood cell; CRP, C-reactive proteins; OR, odds ratio.

response dysregulation is thought to massively increase inflammatory cytokines.[18] Lymphocyte cell death and hypoxic damage to endothelial cells in the pulmonary capillaries may result in vasoconstriction, which in turn reduces blood flow and promotes vascular thrombosis.[17] The transmembrane ACE-2 receptor is a gateway for the cellular entry of SARS-CoV-2, which makes organs with this receptor expression vulnerable to SARS-CoV-2 infection. Tropism toward vascular ACE2 receptors may lead to an inflammatory cascade causing generalized pulmonary thrombosis.[19] These pathophysiological mechanisms generate a hypercoagulable state and increase the potential risk of thrombosis in patients with COVID-19. Unfortunately, thrombotic complications are common in these patients despite adequate prophylactic or therapeutic anticoagulation. In studies of the post-mortem findings of patients with COVID-19, multiple thrombi were frequently observed in the vasculature, despite the use of prophylactic anticoagulation, particularly in segmental and subsegmental pulmonary arterial vessels.[15,16] Although many treatment protocols have been applied since the beginning of the pandemic, anticoagulant prophylaxis and treatment still play a key role in clinical management.[20] Nadkarni et al[21] showed that therapeutic anticoagulation was associated with lower mortality and intubation compared to prophylactic anticoagulation with LMWH, although the difference was not statistically significant. According to the results of our study, the length of hospital stay

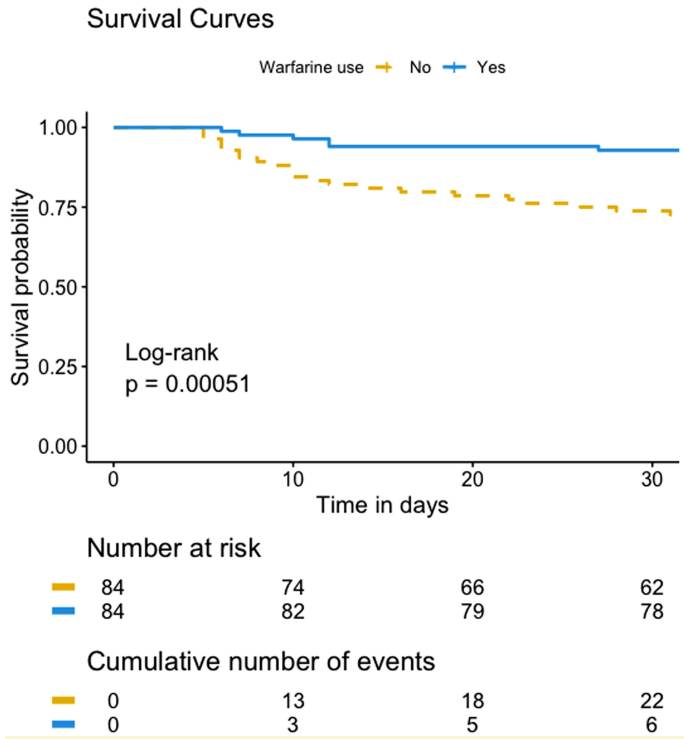

Figure 1. Kaplan-Meier plot of the two groups' survival data.

and ICU admission rates were significantly lower in the warfarin group. We thought that warfarin may have had a better clinical impact due to its potent anticoagulant effect.

Although anticoagulation has been extensively studied, we found limited data on warfarin use in patients with COVID-19. Warfarin is a potent oral anticoagulant that reduces coagulation factors II, VII, IX, and X and provides anticoagulation by vitamin K antagonism. It is widely used in thrombolysis and for preventing thrombosis. Many drugs and foods interact with warfarin, so it has a narrow therapeutic range and needs clinical follow-up for the maintenance of its effect. Warfarin use is associated with a risk of major bleeding.[22] However, we did not observe increased major bleeding associated with warfarin use in the warfarin group in our study. Many trials related to COVID-19 have been published on the benefits of anticoagulant therapy on morbidity and mortality. Tang et al[10] showed that anticoagulant and antiaggregant therapy, mainly with LMWH, appeared to be associated with a better prognosis in severe COVID-19 patients. Chow et al[23] observed that aspirin use was associated with lower mechanical ventilation, ICU admission, and in-hospital mortality in COVID-19 hospitalized patients. In our study, we identified lower in-hospital mortality (warfarin group vs. control group: 7.1% vs. 27.4%, respectively; $P = .001$). We also identified lower rates of ICU admission and shorter lengths of hospital stay in the warfarin group. This indicates that effective anticoagulant therapy with warfarin provides clinical benefit.

Warfarin is a potent coagulation factor inhibitor, so it can dissolve COVID-19-associated thrombosis burden more easily than other anticoagulants, and ongoing use of anticoagulation may prevent COVID-19-associated thrombosis. Microvascular analyses of COVID-19 patients' autopsies demonstrated that SARS-CoV-2

infects endothelial cells in many organs, causing endothelitis, inflammation, microthrombosis, and impaired microcirculation.[8] Alveolar microthrombi have been discovered 9 times more frequently than in influenza patients.[8] Prevention or lysis of microthrombi with warfarin could be vital for not only the pulmonary vasculature but also many other organ functions during the course of COVID-19. Patients on warfarin have co-morbidities which increase their thrombosis risk. It could be thought that COVID-19 might pose an additional risk of thromboembolism and worse outcomes in patients with high thrombogenicity due to mechanical valve replacement and/or AF. However, it could be theorized that warfarin use may lead to better outcomes in patients with COVID-19. Similar to Wong et al's study,[12] in our study, the clinical benefits of warfarin were demonstrated in COVID-19 patients with a high risk of thromboembolism.

In contrast to other studies that enrolled all patients at high risk for ARDS, we enrolled COVID-19 cases both in-hospital and outpatient. Even when the hospitalization rate was similar in both groups, warfarin use was associated with significantly lower in-hospital mortality, ICU admissions, and shorter non-intensive care length of hospital stay in our study.

Our data demonstrated that warfarin use was associated with statistically significantly lower in-hospital mortality, ICU admissions, and length of hospital stay but not less hospitalization. Alleviating the progression of macro and microthrombi with a potent anticoagulant in the early stages may provide better outcomes for COVID-19. This study shows that COVID-19 is associated with coagulopathy and potent anticoagulant treatment is associated with better outcomes.

The limitations of our study include its nature as an observational retrospective study and its small sample size, which may have created confounding factors and led to differences in the outcomes for both groups. The power of the statistical method could have been greater with larger sample size. For endpoints of bleeding, we chose to include only clinically significant bleeding that required hospital admission, a blood transfusion, or surgical intervention. Minor and occult bleeding events may have been missed. However, compared to the control group recruited for similar baseline characteristics, the warfarin group had more comorbid diseases, which represents a reverse bias. We know that warfarin users smoke less, use less alcohol, and are more likely to have influenza and pneumococcus vaccinations than the control group. Moreover, patients on warfarin may seek medical attention and may be hospitalized in the early stages of COVID-19. These may have conferred clinical benefits to patients on warfarin and may have introduced bias favoring warfarin. Patients with milder COVID-19 may have been hospitalized in the early pandemic. Therefore, a lack of objective data on the stage of disease may have affected our interpretations of some outcomes. All patients were unvaccinated against COVID-19 as the study was conducted prior to the public COVID-19 vaccination program. Influenza and pneumococcus vaccine status has not been evaluated.

Conclusion

This investigation aimed to assess the clinical outcomes of COVID-19 in patients on warfarin. The results showed that warfarin can provide clinical benefits in patients with COVID-19. Warfarin use was associated with a statistically significant reduction in in-hospital mortality, ICU admissions, and length of hospital stay but not with a reduction in the rate of hospitalization and ICU stays. The current data highlight the importance of effective anticoagulation for COVID-19 treatment. Further research could also be conducted to determine the clinical benefits of warfarin for patients with COVID-19. Visual summary of the article can be seen in Figure 2.

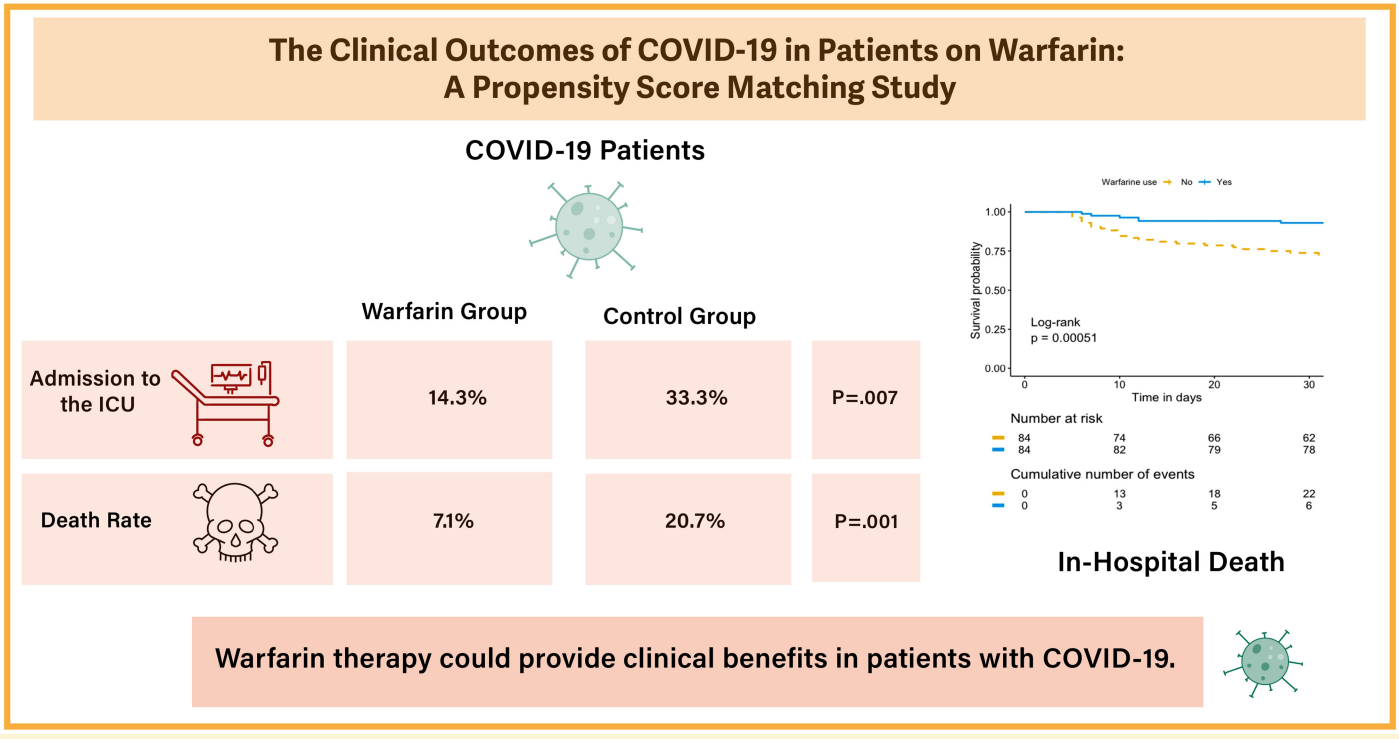

Figure 2. A visual summary of the article.

Ethics Committee Approval: The study was approved by the medical ethics committee of Van Training and Research Hospital (No: 2021/004).

Informed Consent: Verbal informed consent was obtained from all subjects or their relatives.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.O., T.A.; Design – M.O., T.A.; Data Collection and/or Processing – M.O., T.A., F.S., A.S., M.D., E.E.; Analysis and/or Interpretation – F.S., M.E.A.; Writing Manuscript – M.O.; Critical Review – M.O., T.A., F.S., A.S., M.D., E.E.

Declaration of Interests: The authors declare that they have no conflicts of interest.

Funding: This study received no funding.

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