




## ORIGINAL PAPER

Cardiovascular medicine

# The effect of chronic DOAC treatment on clinical outcomes of hospitalized patients with COVID-19

Burhan Aslan<sup>1</sup>  | Abdurrahman Akyüz<sup>1</sup> | Ferhat Işık<sup>1</sup> | Murat Çap<sup>1</sup>  | Ümit İnci<sup>1</sup> | İlyas Kaya<sup>1</sup> | Mehmet Zülküf Karahan<sup>1</sup>  | Adem Aktan<sup>2</sup> | Önder Bilge<sup>1</sup> | Mehmet Özbek<sup>3</sup> | Bernas Altıntaş<sup>1</sup> | Bedrettin Boyraz<sup>4</sup>

<sup>1</sup>Department of Cardiology, Diyarbakır Gazi Yaşargil Education and Research Hospital, Health and Science University, Diyarbakır, Turkey

<sup>2</sup>Department of Cardiology, Mardin State Hospital, Mardin, Turkey

<sup>3</sup>Department of Cardiology, Diyarbakır Dicle University, Diyarbakır, Turkey

<sup>4</sup>Department of Cardiology, Tatvan State Hospital, Tatvan, Turkey

**Correspondence**

Burhan Aslan, Department of Cardiology, Diyarbakır Gazi Yaşargil Education and Research Hospital, Health and Science University, Diyarbakır, Turkey.  
Email: burhanaslnr@gmail.com

**Abstract**

**Background:** Recent findings indicate that thrombosis is one of the underlying pathophysiology and complication of COVID-19 infection. Therefore, the prognosis of the disease may be more favourable in people who were under oral anticoagulant treatment before the COVID-19 diagnosis. This study aims to evaluate the effects of chronic DOAC use on ICU admission and mortality in hospitalized patients due to COVID-19 infection.

**Method:** Between 1 September and 30 November 2020, 2760 patients hospitalized in our hospital due to COVID-19 were screened. A total of 1710 patients who met the inclusion criteria were included in the study. The patients were divided into two groups as those who use DOAC due to any cardiovascular disease before the COVID-19 infection and those who do not.

**Results:** Seventy-nine patients were enrolled in the DOAC group and 1631 patients in the non-DOAC group. Median age of all study patient was 62 (52-71 IQR) and 860 (50.5%) of them were female. The need for intensive care, in-hospital stay, and mechanical ventilation were observed at higher rates in the DOAC group. Mortality was observed in 23 patients (29%) in the DOAC group, and it was statistically higher in the DOAC group ( $P = .002$ ). In the multivariable analysis, age (OR: 1.047, CI: 1.02-1.06,  $P < .001$ ), male gender (OR: 1.8, CI: 1.3-2.7,  $P = .02$ ), lymphocyte count (OR: 0.45, CI: 0.30-0.69,  $P < .001$ ), procalcitonin (OR: 1.12, CI: 1.02-1.23,  $P = .015$ ), SaO<sub>2</sub> (OR: 0.8, CI: 0.77-0.82,  $P < .001$ ) and creatinine (OR: 2.59, CI: 1.3-5.1,  $P = .006$ ) were found to be associated with in-hospital mortality. DOAC treatment was not found to be associated with lower in-hospital mortality in multivariable analysis (OR:1.17, CI: 0.20-6.60,  $P = .850$ ).

**Conclusion:** Our study showed that the use of DOAC prior to hospitalization had no protective effect on in-hospital mortality and intensive care need in hospitalized COVID-19 patients.

## 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) remains the most important problem affecting public health around the world. While the most patients present with mild symptoms or asymptomatic, some may have a fatal course due to severe pneumonia, systemic inflammatory response syndrome, and disseminated intravascular coagulopathy.<sup>1</sup> The different effect of COVID-19 on individuals makes it difficult to understand the pathophysiology and find an effective treatment. Recent findings show that arterial and venous thrombosis is one of the underlying pathophysiology and complication of COVID-19 infection.<sup>2-4</sup> Studies have shown that venous and arterial thrombosis is common in hospitalized patients and especially in intensive care units, and this incidence is between 25% and 13%-31% in studies.<sup>5,6</sup> Also, macro and microemboli were observed in autopsy studies.<sup>7</sup> D-dimer is a coagulation parameter, and it has been emphasized that high D-dimer levels are associated with poor outcomes in COVID-19 patients, and this finding may indicate increased thrombogenicity.<sup>8</sup> As a result of these findings, anticoagulant agents have taken place in the treatment, especially in hospitalized COVID-19 patients, but the effect of this treatment on the prognosis is still unknown. The results of studies on this subject are still controversial and insufficient.<sup>9-13</sup>

Direct oral anticoagulant (DOAC) treatment is used in atrial fibrillation (AF) to prevent ischemic stroke and for the treatment and prophylaxis of venous thromboembolism. In recent years, DOAC therapy has been preferred to warfarin in patients with nonvalvular AF and venous thrombosis due to its ease of use. DOAC therapy is at least as effective as warfarin in preventing thrombosis, and superior to warfarin in major and minor bleeding.<sup>27</sup> In the early stages of COVID-19, the transition from the asymptomatic process to the symptomatic process and the development of respiratory failure may be sudden, and the effect of the treatments started after the advanced stage of COVID-19 may be insufficient. Therefore, the prognosis of the disease may be more favourable in people who were under oral anticoagulant treatment before the COVID-19 infection. This study aims to evaluate the effects of chronic DOAC use on intensive care unit (ICU) admission and mortality in hospitalized patients due to COVID-19 infection.

## 2 | MATERIAL AND METHODS

Between 1 September and 30 November 2020, 2760 patients hospitalized in our hospital due to COVID-19 were screened. Patients with positive PCR tests with combined oral and nasopharyngeal swab samples were included in the study. 850 patients with two negative PCR tests were excluded from the study. Additionally, patients who used warfarin, had creatinine clearance <30 mL/min (due to limitation of using DOAC), and had incomplete data were excluded from the study. A total of 1710 patients who met these criteria were included in the study. The patients were divided into two groups as those who use DOAC due to any cardiovascular disease prior to COVID-19 infection and those who do not. Also, the patients

### What's known

- Due to the frequent occurrence of arterial and venous thrombosis, anticoagulant agents have been included in the treatment of COVID-19 infection. The effect of chronic DOAC treatment on the prognosis is still unknown.

### What's new

- Chronic DOAC treatment had no protective effect on mortality and intensive care unit need. Patients on DOAC therapy are more vulnerable and have more comorbid diseases, so they should be hospitalized and followed up more closely after the diagnosis of COVID-19 infection.

were divided into two groups according to presence and absence of in-hospital mortality.

The information about the drugs used by the patients was obtained from the Ministry of Health database. Demographic characteristics, laboratory findings, physical examination, and follow-up data of the patients were obtained from the hospital database. The treatment and follow-up of patients diagnosed with COVID-19 infection were carried out according to the recommendations of the COVID-19 guidance of the Ministry of Health of the Republic of Turkey.<sup>14</sup> The diagnosis of ARDS was based on the WHO interim guideline.<sup>15</sup> DOAC treatment was continued in patients using DOAC as long as no clinical condition developed that would limit its use. Unless contraindicated, parenteral anticoagulant treatment was given to all hospitalized patients who did not receive DOAC. The primary outcome was in-hospital mortality. Our study was approved by the Ministry of Health academic board and our hospital's ethics committee.

## 2.1 | Statistical analysis

IBM SPSS version 24.0 package programme was used for the analysis. For the study, type 1 error was determined as 5%, type 2 error was determined as 20%. A minimum of 96 patients was needed to estimate the intercept in logistic regression. There must be ideally 10 to 20 participants having the primary outcome per candidate predictor variables.<sup>16</sup> Other patients included in the study were enrolled according to this rule. The continuous variables were presented as a median interquartile range (IQR) (25%-75%) owing to their non-normal distribution. The histogram and Shapiro-Wilks test were used to verify the normal distribution of data. The categorical variables were expressed as percentages. Chi-square test was used to compare categorical variables between groups. Continuous variables were compared by Mann Whitney *U* tests. The univariable and multivariable logistic regression analyses were performed to determine the predictors of in-hospital

mortality. Variables with a *P* value of <0.2 in the univariable analysis were added to the multivariable analysis. When included in the regression model, logarithmic transformation was applied for log-normal continuous variables such as D-dimer and ferritin. Values of *P* < .05 were considered to be statistically significant.

### 3 | RESULTS

The patients were divided into two groups as those who used DOAC before diagnosis and those who did not, and 79 patients were enrolled in the DOAC group and 1631 patients in the non-DOAC group. Median age of all study patient was 62 (52-71 IQR) and 860 (50.5%) of them were female. The median age was 74 (67-81 IQR) in the DOAC group and 61 (51-70 IQR) in the other group, and it was statistically higher in the DOAC group. Seventy-four (93.7%) of the patients were using DOAC due to AF and five patients due to venous thrombosis. The frequency of DOAC agents in the study was

as follows: 41 (51.8%) rivaroxaban, 14 (17.7%) apixaban, 13 (16.4%) edoxaban, and 11 (14%) dabigatran. The mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score of patients using DOAC for AF was calculated as 3.96.

Glomerular filtration rate (GFR) and c-reactive protein (CRP) were lower in the DOAC group than the other group. Creatinine, procalcitonin, neutrophile count, and international normalized ratio (INR) were higher in the DOAC group. Laboratory findings of the groups were summarized in Table 1.

Hypertension (HT), heart failure (HF), coronary artery disease (CAD), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and cerebrovascular disease (CVD) were statistically higher in DOAC group. The need for intensive care, in-hospital stay, mechanical ventilation, and high flow oxygen therapy were observed at higher rates in the DOAC group. Mortality was observed in 23 patients (29%) in the DOAC group and in 244 patients (15%) in the non-DOAC group, and it was statistically higher in the DOAC group (*P* = .002). Demographic characteristics and follow-up data are shown in Table 2.

**TABLE 1** Laboratory parameters of groups

Variables	Overall	DOAC	Non-DOAC	P value
	n = 1710	n = 79	n = 1631	
GFR, mL/min	80 (62-90)	53 (40-68)	81 (65-90)	<.001
Creatinine, mg/dL	0.89 (0.76-1.10)	1.16 (0.99-1.40)	0.88 (0.76-1.08)	<.001
Sodium, meq/L	137 (134-139)	137 (135-140)	137 (134-139)	.100
Potassium, meq/L	4.10 (3.80-4.40)	4.20 (3.90-4.70)	4.1 (3.80-4.46)	.070
Calcium, meq/L	8.30 (7.90-8.70)	8.30 (7.90-8.90)	8.30 (7.90-8.70)	.190
AST, U/L	32 (24-46)	26 (22-36)	33 (24-47)	.004
ALT, U/L	26 (18-40)	21 (15-29)	26 (18-40)	.001
LDH, U/L	318 (255-416)	287 (231-359)	320 (256-417)	.035
Ferritin, ng/mL	393 (199-758)	305 (157-532)	396 (201-770)	.070
CRP, mg/dL	68 (30-116)	45.9 (13-99.7)	68 (31-117)	.008
Procalcitonin, ng/mL	0.09 (0.05-0.18)	0.27 (0.09-0.70)	0.09 (0.05-0.17)	<.001
D-dimer, ng/mL	244 (165-395)	249 (153-442)	244 (165-392)	.970
Troponin, ng/mL	0.10 (0.10-0.10)	0.10 (0.10-0.10)	0.10 (0.10-0.10)	.140
INR	1.19 (1.10-1.28)	1.32 (1.20-1.40)	1.18 (1.10-1.27)	<.001
PT	12.8 (12-13.9)	15 (13.4-18.2)	12.8 (12-13.7)	<.001
WBC, 10 <sup>3</sup> /μL	6.80 (5.10-9.20)	8.7 (6.34-12.9)	6.70 (5.10-9.10)	<.001
Hemoglobin, g/dL	13.6 (12.4-14.6)	13.2 (12-14.5)	13.6 (12.40-14.60)	.210
Neutrophile, 10 <sup>9</sup> /L	5.1 (3.50-7.50)	6.48 (4.30-10.8)	4.98 (3.50-7.39)	<.001
Lymphocyte, 10 <sup>9</sup> /L	1.1 (0.80-1.50)	1.05 (0.70-1.69)	1.10 (0.79-1.49)	.900
Platelet, 10 <sup>3</sup> /μL	208 (166-261)	199 (160-286)	208 (166-260)	.940
Admission SaO <sub>2</sub> , %	90 (85-93)	88 (82-92)	90 (85-93)	.057
SBP, mm Hg	120 (110-120)	120 (110-130)	120 (110-120)	.530
DBP, mm Hg	70 (65-80)	70 (60-80)	70 (65-80)	.500

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; DBP, diastolic blood pressure. DOAC, direct oral anticoagulant; GFR, glomerular filtration rate; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time; SaO<sub>2</sub>, oxygen saturation; SBP, systolic blood pressure; WBC, white blood cell.

We observed that the use of angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), calcium channel blockers, beta-blockers and diuretics was more in the DOAC group. The information about the cardiovascular drugs used by the patients at admission is given in Table 3.

The study patients were divided into two groups according to the presence or absence of in-hospital mortality. Age, in-hospital stay, CRP, ferritin, D-dimer, prothrombin time (PT), procalcitonin, neutrophile count were found to be higher in presence of in-hospital mortality group. ICU, HT, DM, AF, DOAC, MV, COPD, CAD, and ARDS rate were found to

Parameters	Overall	DOAC	Non-DOAC	P value
	n = 1710	n = 79	n = 1631	
Age, years	62 (52-71)	74 (67-81)	61 (51-70)	<.001
In-hospital stay, day	7 (6-11)	9 (6-14)	7 (6-10)	.010
Need for ICU, n (%)	397 (23)	34 (43)	363 (22.3)	<.001
Gender, female, n (%)	860 (50.5)	43 (54.4)	817 (50)	.490
HT, n (%)	726 (42)	76 (96.2)	650 (39.9)	<.001
CAD, n (%)	258 (15)	32 (40)	226 (13.9)	<.001
HF, n (%)	54 (3)	16 (20)	38 (2.3)	<.001
DM, n (%)	467 (27)	25 (31.6)	442 (27)	.300
COPD, n (%)	109 (6)	18 (22.8)	91 (5.6)	<.001
CVD, n (%)	71 (4)	7 (8.9)	64 (3.9)	.040
AF, n (%)	87 (5)	74 (93.7)	13 (0.8)	<.001
Unilateral lesions, n (%)	102 (5.9)	10 (12)	92 (5.6)	.100
Bilateral lesions, n (%)	1608 (94)	71 (89.9)	1537 (94.3)	.130
ARDS, n (%)	252 (14.7)	16 (20.5)	236 (14.5)	.190
Nasal O <sub>2</sub> , n (%)	1077 (62)	56 (71)	1021 (62.6)	.150
MV, n (%)	235 (13.7)	22 (27.8)	213 (13.1)	.001
HFNC, n (%)	128 (7.4)	19 (24.1)	109 (6.7)	<.001
Mortality, n (%)	267 (15.6)	23 (29)	244 (15)	.002

Note: Data are expressed as median interquartile range and percentage.

Abbreviations: AF, atrial fibrillation; ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DM, diabetes mellitus; HF, heart failure; HFNC, high flow nasal cannula; HT, hypertension; ICU, intensive care unit; MV, mechanical ventilation.

**TABLE 2** Demographic and clinical characteristics of groups

Drugs	Overall	DOAC	NON-DOAC	P value
	n = 1710	n = 79	n = 1631	
ACEI, n (%)	268 (15.6)	46 (58.2)	222 (13.6)	<.001
ARB, n (%)	341 (20)	25 (31.6)	316 (19.4)	.013
CCB, n (%)	345 (20.1)	26 (33)	319 (19.6)	.006
Beta-blocker, n (%)	343 (20)	56 (70)	287 (17.6)	<.001
Statin, n (%)	165 (9.6)	7 (8.9)	158 (9.7)	.900
Thiazide diuretic, n (%)	373 (21.8)	39 (43)	334 (21)	<.001
Spironolactone, n (%)	25 (1.4)	14 (17.7)	11 (0.7)	<.001
Loop diuretic, n (%)	41 (2.3)	23 (29.1)	18 (1.1)	<.001
Antiplatelet, n (%)	412 (24)	12 (15)	400 (24.5)	.060
Insulin, n (%)	116 (6.7)	7 (8.9)	109 (6.7)	.480
Oral antidiabetic, n (%)	389 (22.7)	20 (25.6)	369 (22.6)	.500

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DOAC, direct oral anticoagulant.

**TABLE 3** The data about the cardiovascular drugs used by the patients at hospital admission

**TABLE 4** Laboratory findings of patients with and without in-hospital mortality

Variables	In-hospital mortality	In-hospital mortality	P value
	Present	Absent	
	n = 267	n = 1443	
Creatinine, mg/dL	e.03 (0.82-1.30)	0.86 (0.75-1.06)	<.001
Ferritin, ng/mL	530 (286-1098)	369 (184-711)	<.001
CRP, mg/dL	114.7 (65.5-165.7)	60 (26-107)	<.001
Procalcitonin, ng/mL	0.24 (0.11-0.74)	0.08 (0.05-0.14)	<.001
D-dimer, ng/mL	366 (215-704)	229 (160-364)	<.001
Troponin, ng/mL	0.10 (0.10-0.10)	0.10 (0.10-0.10)	.140
PT, seconds	13 (12-14.6)	12.8 (12-13.8)	<.001
Hemoglobin, g/dL	41.5 (38.5-41.5)	42.4 (39.1-45.3)	.060
Neutrophile, 10 <sup>9</sup> /L	7 (4.66-10.4)	4.79 (3.45-6.85)	<.001
Lymphocyte, 10 <sup>9</sup> /L	0.79 (0.59-1.16)	1.17 (0.85-1.56)	<.001
Admission SaO <sub>2</sub> , %	79 (70-84)	90 (88-94)	<.001
SBP, mm Hg	120 (110-130)	118 (110-120)	.08
DBP, mm Hg	70 (60-80)	70 (65-80)	.052

Note.: Data are expressed as median interquartile.

Abbreviations: CRP, C-reactive protein; DBP, diastolic blood pressure; PT, protrombin time; SaO<sub>2</sub>, oxygen saturation; SBP, systolic blood pressure.

be higher in presence of in-hospital mortality group than the absence group. Also, lymphocyte count and oxygen saturation(SaO<sub>2</sub>) found to be lower in presence of in-hospital mortality group than the absence group ( $P < .001$ ,  $P < .001$ , respectively). Laboratory, demographic, and clinical follow-up data of the groups are shown in Tables 4 and 5.

To identify the predictors of in-hospital mortality, multivariable logistic regression analysis was performed using variables with a  $P$  value  $<0.2$  such as age, male gender, diabetes mellitus, ferritin, D-dimer, neutrophile, lymphocyte, creatinine, CRP, SaO<sub>2</sub>, procalcitonin, DOAC, HT, HF, AF, CAD, COPD, systolic BP and hematocrit in univariable logistic regression analysis. Age (OR: 1.047, 95% confidence interval CI: 1.02-1.06,  $P < .001$ ), male gender (OR: 1.8, CI: 1.3-2.7,  $P = .02$ ), lymphocyte count (OR: 0.45, CI: 0.30-0.69,  $P < .001$ ), procalcitonin (OR: 1.12, CI: 1.02-1.23,  $P = .015$ ), arrival SaO<sub>2</sub> (OR: 0.8, CI: 0.77-0.82,  $P < .001$ ) and creatinine (OR: 2.59, CI: 1.3-5.1,  $P = .006$ ) were found to be associated with in-hospital mortality in multivariable logistic regression analysis (Table 6). Using DOAC and the presence of AF were not found to be associated with in-hospital mortality. (OR: 1.17, CI: 0.20-6.60,  $P = .850$ , OR:0.71, CI: 0.15-3.68,  $P = .682$ , respectively).

## 4 | DISCUSSION

In this study, our main finding was that the use of DOAC prior to hospitalization had no positive effect on mortality and intensive care need in hospitalized COVID-19 patients. In the DOAC group, in-hospital mortality, need for intensive care and in-hospital stay were observed higher than the non-DOAC group. Age, male gender, lymphocyte count, creatinine, procalcitonin, and SaO<sub>2</sub> were determined as independent factors associated with in-hospital mortality.

**TABLE 5** Demographic and clinical findings of patients with and without in-hospital mortality

Parameters	In-hospital mortality	In-hospital mortality	P value
	Present	Absent	
	n = 267	n = 1443	
Age, years	71 (64-77)	60 (49-69)	<.001
In-hospital stay, day	10 (7-14)	7 (6-10)	<.001
Need for ICU, n (%)	262 (98.1)	135 (9.4)	<.001
Gender, female, n (%)	105 (39.3)	755 (52.3)	<.001
DOAC, n (%)	23 (8.6)	56 (3.9)	<.001
HT, n (%)	137 (51.3)	589 (40.8)	.001
CAD, n (%)	67 (25.1)	191 (13.2)	<.001
HF, n (%)	13 (4.9)	41 (2.8)	.082
DM, n (%)	93 (34.8)	374 (26)	.003
COPD, n (%)	29 (10.9)	80 (5.5)	.001
CVD, n (%)	13 (4.9)	58 (4)	.520
AF, n (%)	28 (10.5)	59 (4.1)	<.001
Bilateral lesions on CT, n (%)	1343 (93.1)	265 (99.6)	<.001
ARDS, n (%)	212 (79.7)	40 (2.8)	<.001
Nasal O <sub>2</sub> , n (%)	190 (73.8)	880 (61)	<.001
MV, n (%)	232 (86.8)	3 (0.2)	<.001
HFNC, n (%)	83 (31)	45 (3.1)	<.001

Note: Data are expressed as median interquartile range and percentage. Abbreviations: AF, atrial fibrillation; ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CT, computed tomography; CVD, cerebrovascular disease; DM, diabetes mellitus; HF, heart failure; HFNC, high flow nasal cannula; HT, hypertension; ICU, intensive care unit; MV, mechanical ventilation.

Parameters	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Procalcitonin	1.10 (1.00-1.20)	<.001	1.12 (1.02-1.23)	.015
DOAC	2.33 (1.41-3.86)	.001	1.17 (0.20-6.60)	.850
Creatinin	2.50 (1.23-4.92)	.007	2.59 (1.30-5.10)	.006
Age	1.04 (1.02-1.06)	.001	1.05 (1.03-1.07)	<.001
SaO <sub>2</sub>	0.80 (0.77-0.82)	.001	0.80 (0.77-0.82)	<.001
Lymphocyte	0.52 (0.33-0.81)	.004	0.45 (0.30-0.69)	<.001
Neutrophile	1.04 (1.00-1.08)	.015	1.02 (0.98-1.06)	.262
Hematocrit	0.98 (0.96-1.00)	.144	0.97 (0.94-1.01)	.255
Gender, male	1.80 (1.20-2.60)	.002	1.80 (1.30-2.70)	.020
HF	1.70 (0.90-3.30)	.086	1.41 (0.48-4.17)	.525
AF	2.74 (1.71-4.39)	<.001	0.71 (0.15-3.68)	.682
CVD	1.22 (0.62-2.20)	.520		
CRF	0.52 (0.01-4.50)	.800		
HT	1.53 (1.17-1.98)	.002	1.11 (0.71-1.72)	.637
COPD	2.23 (1.30-3.21)	.001	0.94 (0.47-1.88)	.870
DM	1.53 (1.10-2.30)	.003	0.83 (0.54-1.28)	.418
CAD	2.10 (1.60-3.20)	.003	0.84 (0.50-1.40)	.506
Systolic BP	1.02 (1.01-1.03)	<.001	0.99 (0.98-1.00)	.438
CRP	1.01 (1.00-1.01)	<.001	1.00 (0.99-1.00)	.780
D-dimer	4.40 (3.20-6.20)	<.001	1.15 (0.67-1.98)	.590
Ferritin	2.98 (2.10-4.10)	<.001	0.95 (0.56-1.63)	.873

**TABLE 6** Univariable and multivariable regression analysis for determine predictor of in-hospital mortality

Abbreviations: AF, atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CRP, C-reactive protein; CVD, cerebrovascular disease; DM, diabetes mellitus; DOAC, direct oral anticoagulant; HF, heart failure; HT, hypertension; SaO<sub>2</sub>, oxygen saturation.

COVID-19 has complex pathophysiology and according to the latest informations, it causes morbidity and mortality in hospitalized patients by creating a hypercoagulant state.<sup>3</sup> In autopsy studies of COVID-19 patients, extensive endothelial damage, macrothrombi and microthrombi in the pulmonary capillary area were detected.<sup>4,17</sup> In addition, widespread inflammation, platelet activation, and excessive cytokine release have been shown as other underlying causes of COVID-19 coagulopathy.<sup>18,19</sup> It is aimed to reduce these complications with anticoagulant therapy, but the effectiveness of anticoagulant therapy is different in studies. While anticoagulant therapy was shown to reduce mortality in the study by Tang et al, mortality was high in patients despite anticoagulant therapy in other study.<sup>20,21</sup>

Cardiovascular diseases are common in COVID-19 patients and increase morbidity and mortality.<sup>21,22</sup> As a result of different studies, the most common concomitant diseases were stated as HT, DM, and CAD, respectively.<sup>23</sup> In our study, cardiovascular diseases were observed with a similar frequency to other studies in both groups, but all concomitant diseases were observed with a statistically higher rate in the DOAC group. HT, CAD, and DM which have inflammation

and endothelial dysfunction in their pathogenesis and complications were observed at a higher rate in the DOAC group. The addition of COVID-19 coagulopathy to the basal endothelial damage and widespread inflammation due to cardiovascular diseases may cause thrombo-inflammatory complications to be observed more frequently or severely in these patients. These changes may explain the higher rates of mortality in the DOAC group.

Previous studies have shown that advanced age is the most influential factor on mortality in COVID-19 patients.<sup>24-26</sup> In the elderly population, an increase in the number of concomitant chronic diseases, a decrease in the immune system response, more drug interactions, decreased renal functions, and inactivity make this special patient group more susceptible. All these factors may lead to increased morbidity and mortality by predisposing to thrombogenicity, especially in patients who are in ICU. Patients in the DOAC group were older than the other group and may have a significant effect on increased mortality.

The prevalence of AF increases with age, and in our study, 93.7% (74) of the patients in the DOAC group were using DOAC due to AF and the rate of AF in the other group was 0.8% (13).

The CHA<sub>2</sub>DS<sub>2</sub>-VASC score estimates the annual risk of stroke in patients with AF, and higher values are associated with higher stroke risk.<sup>27</sup> When the CHA<sub>2</sub>DS<sub>2</sub>-VASC score is one (without gender criteria) and above, oral anticoagulant therapy is recommended, especially DOAC therapy.<sup>26</sup> In our study, the mean CHA<sub>2</sub>DS<sub>2</sub>-VASC score of 74 AF patients was found to be 3.96. This value suggests an average of 4% risk of stroke per year.<sup>27</sup> As seen, AF creates a procoagulant state, and the addition of COVID-19 coagulopathy to this procoagulant state, make the patients more susceptible to thrombotic complications.

Similar to our study, patients using chronic OAC were included in the study conducted by Rivera-Caravaca et al. Most of the patients were using OAC due to AF. However, in this study, 75% of the patients received vitamin K antagonists, 25% received DOAC treatment, and the mortality in the OAC group (68.2%) was higher than the other group (26.1%).<sup>13</sup> Cardiovascular diseases were observed with a higher rate in these patients, and the median age was higher. In our study, patients using vitamin K antagonists were not included, only patients on DOAC therapy were included. Similarly, the mortality rate (29%) and concomitant diseases were observed with a higher rate in the DOAC group. In another study, there was no effect of chronic DOAC use on hospitalization and prognosis of COVID-19 infection.<sup>28</sup> On the contrary, in the study conducted by Rossi et al. it was observed that chronic DOAC use in elderly patients was associated with lower mortality rates, but only 70 patients over the age of 70 were included in this study, and only 26 patients were on DOAC treatment.<sup>10</sup>

The different effects of anticoagulant therapy on COVID-19 patients or not showing the expected effect may be due to additional pathophysiological conditions other than thrombosis. With the direct invasion of the virus into endothelial cells, the inflammatory process begins and diffuse vascular inflammation develops as a result of extensive endothelitis, immune complex accumulation, and type 3 hypersensitivity reaction.<sup>33</sup> Studies have shown that pulmonary capillary angiopathy and vasculitis caused by COVID-19 may occur as a result of these mechanisms.<sup>29-31</sup> This may explain why anticoagulant therapy alone is not effective in treating vascular complications caused by COVID-19 infection.

Gremese et al. have shown the hypoperfusion in affected areas by the early COVID-19 pneumonia, and they asserted this situation may be due to microvascular thrombosis rather than classical pulmonary embolism.<sup>32</sup> Another study demonstrated that hyperinflammation and leukotrombosis were the main underlying causes of ARDS patients and high D-dimer levels with high CRP and ferritin are laboratory findings of this situation.<sup>33,34</sup> Although high D-dimer levels, lung hypoperfusion (due to leukotrombosis) can be detected without pulmonary embolism.<sup>34</sup> Gremese and colleagues suggested that DOAC therapy may be ineffective in leukocyte-related thrombosis and insufficient to prevent severe COVID-19 infection.<sup>35</sup> Similarly to these studies, we did not observe a positive effect of using DOAC before the hospital admission in hospitalized COVID-19 patients. We found a higher rate of ICU admission and higher mortality in the DOAC group. This finding may be explained by the fact that patients

using DOAC are older and have more comorbid diseases rather than the use of DOAC. Elderly patients are more fragile and susceptible to COVID-19 complications, and we also know that comorbid diseases and advanced age are associated with morbidity and mortality in COVID-19 infection.

#### 4.1 | Study limitations

This is an observational study and, like all similar studies, there may be some limitations. The single-centre nature of our study may reduce the effect of different patient populations on outcomes. Interpretation of the findings might be limited due to the small number of patients on DOAC treatment and selection bias. Missing even a single dose of DOAC drugs will cause a decrease in effective plasma concentrations. Due to its retrospective nature, it is not known that patients on DOAC therapy using their drugs regularly and in effective doses, so effective anticoagulation may not be achieved in these patients and these factors may have an impact on the results. Therefore, randomized, controlled studies with more patients are needed on this subject.

## 5 | CONCLUSION

In the present study, we observed that using DOAC prior to hospitalization had no protective effect on mortality and intensive care need in hospitalized COVID-19 patients. Also, since patients who are on DOAC treatment are older and have more comorbid diseases, they should be hospitalized and followed up more closely after the diagnosis of COVID-19 infection.

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#### DISCLOSURES

The authors declared no conflicts of interest.

#### DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

#### ORCID

Burhan Aslan  <https://orcid.org/0000-0002-8994-7414>

Murat Çap  <https://orcid.org/0000-0003-1164-2124>

Mehmet Zülküf Karahan  <https://orcid.org/0000-0001-8145-9574>

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