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A Multicenter Study Assessing the Optimal Anticoagulation Strategies in COVID-19 Critically Ill Patients with New-Onset Atrial Fibrillation: Balancing Effectiveness and Safety

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Purpose: To evaluate the effectiveness and safety of anticoagulation regimens in COVID-19 critically ill patients with new-onset Atrial fibrillation (Afib) during their intensive care unit (ICU) stays.

Methods: A multicenter, retrospective cohort study included critically ill patients with COVID-19 admitted to the ICUs. Patients with new-onset Afib were categorized into two groups based on anticoagulation doses (Prophylaxis vs Treatment). The primary outcome was the bleeding rate; other outcomes were considered secondary. Logistic, negative binomial regression, and Cox proportional hazards regression analyses were applied as appropriate after PS matching.

Results: A total of 107 patients were eligible. After PS matching (1:1 ratio), 56 patients were included in the final analysis. A higher odd for major and minor bleeding were observed in the patients who received treatment doses of anticoagulation; however, it did not reach the statistically significant (OR 1.46; 95% CI 0.29, 7.42; *P*=0.65 and OR 2.04; 95% CI 0.17, 24.3; *P*=0.57, respectively). The hospital length of stay and in-hospital mortality showed no differences between the two groups (beta coefficient −0.00; CI −0.38, 0.37; *P*=0.99 and HR 1.12, 95% CI 0.58–2.14; p = 0.74, respectively). On the other hand, patients in the treatment group had a statistically significant higher requirement of RBCs transfusion than patients who received a prophylaxis dose (beta coefficient 1.17; 95% CI 0.11, 2.22, *P*=0.03).

Conclusion: The use of treatment anticoagulation doses in COVID-19 critically ill patients with new-onset Afib did not show better effectiveness over prophylactic anticoagulation doses; however, patients who received treatment anticoagulation doses had higher RBCs transfusion requirements. Our results must be cautious; thus, larger randomized interventional studies with a larger sample size are required to confirm our findings.

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Keywords: COVID-19, anticoagulation, prophylaxis, treatment dose, thrombosis, bleeding, atrial fibrillation, critically ill, mortality

Introduction

Coronavirus disease 2019 (COVID-19) is a substantial public health concern that led to significant morbidity and mortality globally.[1,2] Respiratory failure and acute respiratory distress syndrome (ARDS) were the leading causes of clinical deterioration in patients with COVID-19.[1] In addition, cardiovascular complications such as heart failure, cardiac arrest, thromboembolic events, and arrhythmias were reported in critically ill patients with COVID-19.[3] As commonly seen in critically ill patients, new-onset atrial fibrillation (Afib) was also observed in critically ill patients with COVID-19.[3,4] The prevalence of new-onset Afib in patients with COVID-19 during hospitalization ranges from 5.4% to 11% among critically ill patients.[4–6]

Recent studies have found that patients with COVID-19 and new-onset Afib were associated with worsening patient outcomes, higher mortality rates, and increased need for mechanical ventilation (MV) compared to those with pre-existing Afib.[7–9] In a cohort including 9564 hospitalized patients with COVID-19, with propensity score matching of 1238 patients with and without Afib, in-hospital mortality was greater in patients with Afib (54% vs 37%; respectively).[10] In a propensity-score-matched analysis of 500 patients, those with new-onset Afib had less favorable outcomes than those with a history of Afib (55% vs 47%). Some of the proposed proarrhythmic factors affecting patients with COVID-19 include systemic inflammation, myocardial injury, and medications, all linked to cardiovascular side effects.[4] Another concern following new-onset Afib in COVID-19 is the high inflammatory load. Elevated levels of markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) are frequently associated with the presence and severity of Afib, where inflammation and Afib amplify and sustain each other, leading to a rapid clinical decline.[11–13] In addition, in critically ill patients, pressors and high angiotensin-converting enzyme 2 (ACE2) levels may predispose them to develop new-onset Afib.[4,14]

Afib is associated with an increased risk of cardioembolic stroke.[15] Thus, it is recommended to use anticoagulation for stroke prevention in all patients with Afib who have a high risk of developing stroke.[16] Also, Afib was found to contribute to morbidity and mortality in those with coexistent Coronary Artery Diseases (CAD) in COVID-19 cohort.[17] The presence of COVID-19 and Afib puts the patient at increased risk of thrombosis.[16] COVID-19 activates the thrombo-inflammatory, which subsequently aggravates the coagulation cascade, increasing the risk of thromboembolic complications in those patients.[18,19] At the same time, critically ill patients with Afib are at increased risk of bleeding and urgent need for invasive procedures.[20,21] Especially in patients who were on antiplatelet medications for any indications.[22] Therefore, deciding to start anticoagulation for those patients is challenging due to balancing the risk of bleeding and thrombosis.

The use of parenteral anticoagulation in critically ill patients is always preferred due to the feasibility of adjusting the dose and easily reversing their action.[20,23] A cross-sectional survey distributed to 910 intensivists from 14 countries showed variation in the anticoagulation dosing in critically ill patients with acute Afib.[23] That study reported that 61% of the intensive care unit (ICU) physicians admitted giving anticoagulation in therapeutic doses, and 39% admitted giving prophylactic doses of anticoagulation.[23] However, the decision on the timing, the agent, and the dosing of anticoagulation in critically ill patients are affected by the patient's desired goals, hemodynamic status, renal function, bleeding, and stroke risk.[24] A previous retrospective study including 113,511 hospitalized patients with Afib and sepsis found that using higher than venous thromboembolism prophylaxis doses of parenteral anticoagulation was associated with a higher risk of bleeding than benefit.[25] However, that study did not include patients with COVID-19.

The optimal dosing of anticoagulation in critically ill patients with new-onset Afib remains undefined. Thus, inconsistent parental anticoagulation dosing regimens in critically ill patients with new onset Afib are commonly seen, especially in patients with COVID-19. A previous systemic review reported no significant difference in the incidence of thrombosis in critically ill patients with Afib who received anticoagulation; less than half received a therapeutic dose compared to those who did not. Still, the incidence of bleeding was higher in patients who received anticoagulation.[25] There is limited evidence about the safety and efficacy of the parental anticoagulation regimens (therapeutic vs prophylactic dose) in critically ill patients with Afib and COVID-19.[25–27] Therefore, our study aimed to compare the effectiveness and safety of prophylactic anticoagulation to therapeutic regimens in critically ill patients with COVID-19 patients who developed new-onset Afib.

Methods

Study Design

This study is part of the Saudi Critical Care Pharmacy Research (SCAPE) platform, which conducted several studies that evaluate the safety and effectiveness of multiple therapies in critically ill patients.[28] The design of this multi-center retrospective cohort study is similar to previously published studies.[29–33] This study included adult critically ill patients with confirmed COVID-19 who developed new-onset Afib and were admitted to ICUs at five centers in Saudi Arabia from March 01, 2020, until July 31, 2021. Reverse transcriptase-polymerase chain reaction (RT–PCR) from either nasopharyngeal or throat swabs was used for COVID-19 diagnosis. New-onset Afib was defined as a new onset or a first detectable episode of atrial fibrillation (any type), whether symptomatic or not.

The included patients were categorized into two groups based on the anticoagulation regimen (prophylaxis vs treatment anticoagulation dose). The control group was patients who received prophylaxis doses of Enoxaparin or Unfractionated Heparin (UFH) (eg Enoxaparin 40 mg q24h SubQ, UFH 5000 U q8h). While the treatment group was patients who received (enoxaparin 1mg/kg SQ twice daily, enoxaparin 1.5 mg/kg SQ once daily, IV continuous infusion UFH, orweight-based UFH) All patients were followed until they were discharged from the hospital or died during their stay. The King Abdullah International Medical Research Center (KAIMRC) approved the study in August 2022 (Ref.# RSS22R.004.07). The study was conducted following the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (adopted 1964; updated 2013), national ethical regulations, and local institutional guidance of study centers.

Study Population

We screened all adult patients (age ≥18 years) admitted to the ICUs with confirmed COVID-19 and developed new-onset atrial fibrillation. Patients were excluded if they had a history of venous thromboembolism (VTE)/myocardial infarction (MI), chronic atrial fibrillation, valve replacement, unknown medical history, platelets count ≤50 × 109/L, had bleeding at admission, not on pharmacological deep vein thrombosis (DVT) prophylaxis within 24 hours of admission, received anticoagulation treatment dose for other indications, died within the first 24 hours of ICU admission or were labeled "Do-Not-Resuscitate" (Figure 1).

Study Setting

The study was conducted at five medical facilities and cities in Saudi Arabia; details of participating hospitals and the leading centers can be found in supplementary file 1.

Data Collection

Variables and data were collected using the Research Electronic Data Capture (REDCap®) platform that included demographic data, comorbidities, laboratory, vital signs, and baseline severity; details of data collected can be found in Supplementary file 1.

Clinical Outcomes

This study aimed to evaluate the effectiveness and safety of anticoagulation treatment doses compared with prophylaxis doses in critically ill patients with COVID-19 who developed new-onset Afib during ICU stay. The primary endpoint was bleeding rate during the ICU stay. The secondary endpoints were RBCs transfusion, blood product transfusion, thrombosis, mortality, length of stay (LOS), and MV duration. Thrombosis was identified using radiology findings (eg, CT scan, US) or the patient's chart documentation.

Outcome's Definition

Major bleeding was defined according to the ISTH as clinically overt bleeding associated with a fall in hemoglobin by ≥20 g/L, transfusion of ≥2 U packed red blood cells (PRBCs) or whole blood, retroperitoneal or intracranial bleeding, or fatal bleeding. [34,35]

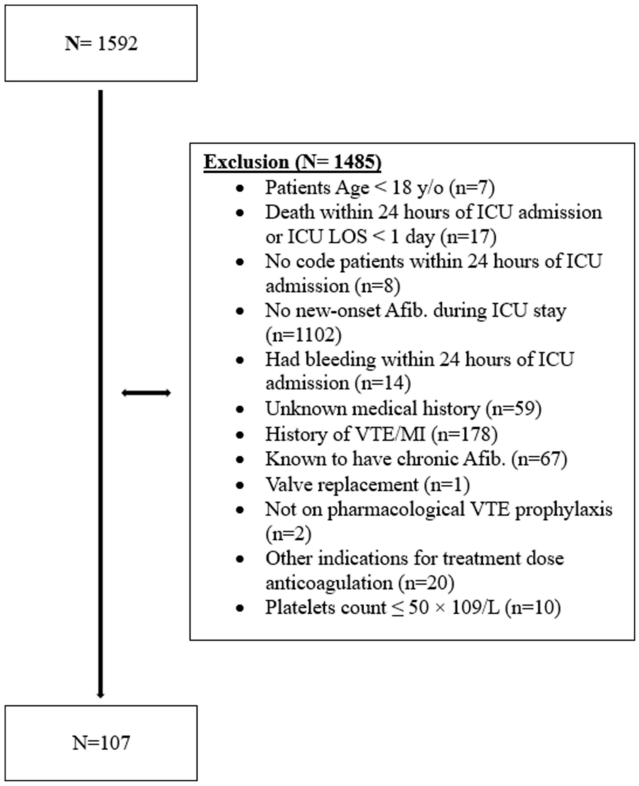

Figure 1 Patient flowchart.

Minor bleeding was defined according to the ISTH definition as any sign or symptom of bleeding that does not fit the criteria for the ISTH definition of major bleeding.

Sample Size Calculations

Group sample sizes of 56 patients in each arm would achieve 80% power to detect a meaningful difference of 12% between the two groups. Under the null hypothesis, the proportion of major bleeding in Group 1 is assumed to be 6%, while in Group 2 it is assumed to be 18%. A two-sided Z test with pooled variance was used, with a significance level of 5%.

Statistical Analysis

Baseline and outcome variables were compared between the two study groups. The Chi-square or Fisher exact test was used for categorical variables. Normally distributed continuous variables were compared using Student's *t*-test, and the Mann–Whitney *U*-test was used to compare non-normally distributed variables. Regression analysis was performed for the study outcomes after considering PS scores as covariates in the model. Cox proportional hazards regression analysis and negative binomial regression were utilized for 30-day, in-hospital mortality, and continuous outcomes (eg, RBCs transfusion, MV duration, and LOS), respectively. While multivariable logistic regression analysis was utilized for bleeding, thrombosis, and the need for blood product transfusion during ICU stay. The odds ratios (OR), estimates, and hazard ratio with the 95% confidence intervals (CI) were reported as appropriate.

The propensity score matching procedure was used to match patients who received anticoagulation treatment doses (active group) to patients who received prophylaxis doses (control group) using 1:1 ratio (Proc PS match) (SAS, Cary, NC, Version 9.4). These PS scores were generated through propensity score analysis (greedy nearest neighbor) after considering all relevant covariates, such as baseline SOFA score and gender. The standard deviations of the variables, pooled across the treated and control groups, are computed based on all observations. The pooled standard deviations are then used to compute standardized mean differences based on all observations, observations in the support region, and

matched observations. No imputation was made for missing data, as the cohort of patients in our study was not derived from random selection.

Results

Demographic and Clinical Characteristics

A total of 1592 patients were screened; one hundred seven were included in the study. Among the included patients, 72 received a prophylaxis dose, and the remaining 35 received a treatment dose of anticoagulation. In the whole cohort and before PS matching, the mean age of patients was 71.7 years (SD ± 11.44). Most patients were male (55.7%) with a mean BMI of 32.9 (SD ± 15.28). All patients' predominant baseline comorbidities were hypertension (76.6%) and diabetes (62.6%), which were statistically significantly higher in the prophylaxis group compared to the treatment group before PS matching. The median APACHE II score was comparable between the two groups before and after PS matching. After conducting the PS matching, there were no statistically significant differences between both groups in all baseline demographics and characteristics except baseline aPTT and platelet count, which were both significantly higher in the treatment group, and HF as the comorbid condition was higher in the prophylaxis group. (Table 1).

Bleeding and Thrombosis

In crude analysis, major bleeding events occurred in three (10.7%) patients in the prophylaxis group compared with four (14.3%) patients who developed atrial fibrillation and received a treatment dose of anticoagulation (OR 1.46; 95% CI 0.29, 7.42; *P*=0.65). In addition, patients who received treatment doses had higher odds of minor bleeding (OR 2.04; 95% CI 0.17, 24.36; *P*=0.57); however, this was not statistically significant. On the other hand, patients in the treatment group required higher odds of blood product transfusion during ICU stay (OR 2.73; CI 0.84, 8.84; *P*=0.09) as well as a higher mean of RBCs units transfused (1.1 vs 0.3; *P*=0.03) compared with prophylaxis dose group (beta coefficient 1.17; CI 0.11, 2.22; *P*=0.03) as shown in Table 2. Thrombosis occurred in two patients in each group (7.1%), which was not statistically significant between the two groups (OR 0.99; 95% CI 0.13, 7.61; *P*=0.99). Of importance, the use of either antiplatelet medications or Aspirin before admission was not statistically significant between the two groups. (Table 1)

Mortality, MV duration, and Length of Stay

The prophylaxis group had a higher 30-day mortality rate than patients who received treatment doses (HR 0.66; CI 0.31, 1.41; *P*=0.28). On the other hand, the in-hospital mortality rate was higher in the treatment group during hospital stay (HR 1.12; CI 0.58, 2.14; *P*=0.74); however, both 30-day and in-hospital mortality were not statistically significant between the two groups. In addition, MV duration, ICU length of stay, and hospital length of stay were not statistically significant between the two groups (Table 3).

Discussion

This multicenter, retrospective cohort study evaluated the effectiveness and safety of prophylactic and therapeutic dosing of parenteral anticoagulation in COVID-19 patients who developed Afib during their ICU stay. Our primary outcome, the incidence of major and minor bleeding, was not found to be statistically significant between the two groups. However, a significantly higher requirement for blood products and RBCs transfusion in the treatment group was reported compared to the prophylaxis regimen. On the other hand, thrombosis events, VFDs, LOS, and mortality were similar between the two groups.

Although our results describe higher events of major and minor bleeding with therapeutic anticoagulation in new-onset Afib COVID-19 patients, we did not identify a significant difference between prophylactic and therapeutic doses. Similar results were reported in a retrospective cohort study that compared the incidence of major bleeding among Afib COVID-19 patients.[36] Initially, they reported a significantly high incidence of bleeding among COVID-19 Afib patients receiving treatment doses of low molecular weight heparin (LMWH) compared to non-Afib patients.[36] However, in their subgroup analysis that compared Afib patients who developed bleeding vs non-bleeding, no differences were found regarding prophylactic and therapeutic doses of LMWH, with both groups having the same baseline D-dimer level.[36] In

Table 1 Baseline Characteristics of Critically Ill Patients with COVID and Afib Before and After Propensity Score Matching

	Before Propensity Score (PS)				After Propensity Score (PS)			
	Overall (N=107)	Prophylaxis (N=72)	Treatment (N=35)	P-value	Overall (N=56)	Prophylaxis (N=28)	Treatment (N=28)	P-value
Age (Years), Mean (SD)	71.7 (11.44)	72.3 (12.14)	70.5 (9.83)	0.4503*	72.7 (10.53)	74.4 (11.40)	70.9 (9.47)	0.2216*
Gender – Male, n (%)	59 (55.7)	37 (51.4)	22 (64.7)	0.1977^^	37 (66.1)	18 (64.3)	19 (67.9)	0.7778^^
Body Mass Index (BMI), Mean (SD)	32.9 (15.28)	32.0 (7.73)	34.5 (24.49)	0.2292^	30.3 (9.12)	30.6 (7.57)	30.1 (10.53)	0.3589^
APACHE II score, Median (Q1,Q3)	15.0 (12.00, 21.00)	15.0 (13.00, 21.00)	15.0 (12.00, 19.00)	0.4753^	15.0 (12.00, 20.00)	15.5 (13.00, 21.00)	15.0 (12.00, 19.00)	0.4548^
SOFA score, Median (Q1,Q3)	5.0 (3.00, 7.00)	5.0 (4.00, 7.00)	4.5 (2.00, 6.50)	0.2959^	4.5 (3.00, 6.50)	4.5 (3.00, 6.50)	4.5 (2.00, 6.50)	0.7343^
Multiple Organ Dysfunction Score at admission, Median (Q1,Q3)	6.0 (5.00, 7.00)	6.0 (5.00, 8.00)	6.0 (5.00, 7.00)	0.6605^	6.0 (5.00, 8.00)	6.0 (5.00, 8.00)	6.0 (4.00, 7.00)	0.4847^
Serum creatinine (umol/L) at admission, Median (Q1,Q3)	100.0 (71.00, 160.87)	102.0 (69.50, 173.50)	98.0 (71.00, 149.00)	0.5003^	91.0 (70.50, 143.50)	95.5 (68.50, 149.44)	90.5 (72.00, 140.00)	0.8827^
Blood Urea nitrogen (BUN) (mmol/L) at admission, Median (Q1,Q3)	9.8 (6.10, 13.50)	10.3 (6.20, 13.95)	8.5 (5.80, 13.00)	0.2231^	9.7 (5.70, 13.00)	9.2 (6.00, 12.86)	9.7 (5.61, 13.00)	0.6313^
Lowest PaO2/FiO2 ratio within 24 hours of admission, Median (Q1,Q3)	81.4 (58.59, 128.97)	85.3 (64.22, 131.50)	67.0 (52.62, 112.76)	0.1131^	80.7 (60.11, 127.20)	84.8 (62.63, 127.20)	80.6 (57.50, 142.57)	0.9503^
Inotropes/vasopressors use within 24 hours of admission), n(%)	33 (30.8)	21 (29.2)	12 (34.3)	0.5906^^	21 (37.5)	9 (32.1)	12 (42.9)	0.4076^^
Lactic acid Baseline (mmol/L), Median (Q1,Q3)	1.9 (1.28, 2.67)	2.0 (1.23, 2.68)	1.7 (1.40, 2.56)	0.6408^	1.9 (1.41, 2.63)	2.2 (1.27, 2.83)	1.7 (1.42, 2.31)	0.4087^
Platelets count Baseline (10^9/L), Median (Q1, Q3)	231.5 (192.00, 318.00)	222.0 (190.00, 300.00)	250.0 (193.00, 334.00)	0.3825^	221.5 (187.00, 304.00)	197.5 (178.50, 243.50)	250.0 (203.50, 334.00)	0.0130*
International normalized ratio (INR), Median (Q1,Q3)	1.1 (1.00, 1.15)	1.1 (1.01, 1.15)	1.1 (1.00, 1.11)	0.5932^	1.1 (1.00, 1.11)	1.1 (1.01, 1.11)	1.1 (1.00, 1.11)	0.7769^
activated partial thromboplastin time (aPTT) Baseline (seconds), Median (Q1,Q3)	29.2 (25.60, 33.00)	28.9 (25.30, 32.00)	30.6 (27.40, 34.00)	0.0795^	29.5 (25.60, 32.65)	27.9 (25.00, 30.50)	31.1 (28.30, 34.00)	0.0058*
Total bilirubin (umol/L), Median (Q1,Q3)	10.2 (6.10, 13.20)	10.2 (6.30, 14.10)	9.6 (5.70, 12.70)	0.6519^	10.3 (5.70, 13.20)	10.6 (4.60, 13.95)	10.1 (6.10, 13.20)	0.9173^
Alanine transaminase (ALT) at admission (U/L), Median (Q1,Q3)	33.0 (21.00, 58.00)	31.5 (20.00, 54.00)	36.0 (23.00, 58.00)	0.7327^	30.0 (21.00, 58.00)	27.5 (19.00, 50.50)	36.0 (23.00, 58.00)	0.3451^
Aspartate transaminase (AST) at admission (U/L), Median (Q1,Q3)	47.0 (32.00, 80.00)	50.0 (32.00, 84.00)	41.0 (32.00, 70.00)	0.4184^	56.2 (42.10)	55.0 (37.55)	57.2 (46.46)	0.7988^
Albumin Baseline (gm/L), Median (Q1,Q3)	32.5 (30.00, 36.00)	33.0 (30.00, 36.00)	32.0 (29.00, 38.00)	0.9222^	32.0 (29.00, 36.00)	32.0 (29.00, 34.00)	32.5 (29.00, 38.80)	0.5991^
Hematocrit at admission (L/L), Mean (SD)	0.4 (0.35, 0.43)	0.4 (0.34, 0.43)	0.4 (0.37, 0.44)	0.3266^	0.4 (0.35, 0.44)	0.4 (0.33, 0.43)	0.4 (0.37, 0.44)	0.2941^
Creatine phosphokinase (CPK) baseline (U/L), Median (Q1,Q3)	82.0 (48.00, 265.00)	85.5 (44.00, 250.00)	82.0 (66.00, 388.00)	0.6734^	85.5 (42.00, 265.00)	79.5 (30.00, 140.00)	113.5 (67.00, 475.00)	0.2482^
C-reactive protein (CRP) baseline (mg/l), Median (Q1,Q3)	86.0 (56.00, 148.00)	84.0 (52.50, 194.50)	88.0 (62.00, 142.00)	0.9008^	88.0 (63.00, 146.00)	77.0 (67.00, 146.00)	88.0 (62.00, 142.00)	0.9717^

Fibrinogen Level baseline (gm/l), Median (Q1,Q3)	4.2 (2.74, 6.85)	4.0 (2.65, 7.51)	4.9 (3.88, 5.18)	0.7180^	4.9 (3.06, 5.53)	4.1 (3.06, 7.51)	4.9 (3.88, 5.18)	0.9385^
D-dimer Level baseline (mg/L), Median (Q1,Q3)	1.6 (0.71, 3.22)	1.8 (0.73, 3.29)	1.6 (0.67, 3.04)	0.5554^	1.6 (0.95, 3.22)	1.5 (0.93, 3.29)	1.7 (0.98, 3.04)	0.9835^
Ferritin Level baseline (ug/L), Median (Q1,Q3)	710.0 (393.45, 1777.70)	757.0 (397.00, 2241.10)	600.8 (337.30, 1351.20)	0.3705^	600.8 (397.00, 1647.00)	561.8 (397.00, 2073.20)	645.9 (314.80, 1633.10)	0.8165^
Blood glucose level Baseline Within 24 hours of ICU admission (mmol/L), Median (Q1,Q3)	10.4 (7.20, 14.50)	10.6 (7.20, 15.10)	8.9 (6.65, 13.55)	0.3280^	10.6 (8.20, 14.75)	11.3 (9.20, 15.30)	9.1 (8.20, 13.00)	0.1782^
Patient received nephrotoxic drugs/material during ICU stay, n (%)*$	101 (95.3)	69 (97.2)	32 (91.4)	0.1888**	53 (94.6)	27 (96.4)	26 (92.9)	0.5529**
Comorbidity, n (%)								
Atrial fibrillation (A Fib)	0 (0)	0 (0)	0 (0)	NA	0 (0)	0 (0)	0 (0)	NA
Heart Failure	7 (6.5)	7 (9.7)	0 (0.0)	0.0564**	4 (7.1)	4 (14.3)	0 (0.0)	0.0379**
Hypertension (HTN)	82 (76.6)	60 (83.3)	22 (62.9)	0.0189^^	40 (71.4)	23 (82.1)	17 (60.7)	0.0759^^
Diabetes Mellitus	67 (62.6)	50 (69.4)	17 (48.6)	0.0363^^	33 (58.9)	19 (67.9)	14 (50.0)	0.1744^^
Dyslipidemia	29 (27.1)	23 (31.9)	6 (17.1)	0.1061^^	12 (21.4)	9 (32.1)	3 (10.7)	0.0507^^
Ischemic heart disease (IHD)	0 (0)	0 (0)	0 (0)	NA	0 (0)	0 (0)	0 (0)	NA
Chronic kidney disease (CKD)	19 (17.8)	12 (16.7)	7 (20.0)	0.6721^^	11 (19.6)	6 (21.4)	5 (17.9)	0.7366^^
Cancer	7 (6.5)	5 (6.9)	2 (5.7)	0.8092**	2 (3.6)	0 (0.0)	2 (7.1)	0.1498**
Deep Vein Thrombosis (DVT)	0 (0)	0 (0)	0 (0)	NA	0 (0)	0 (0)	0 (0)	NA
Pulmonary Embolism (PE)	0 (0)	0 (0)	0 (0)	NA	0 (0)	0 (0)	0 (0)	NA
Liver disease (any type)	2 (1.9)	2 (2.8)	0 (0.0)	0.3196**	1 (1.8)	1 (3.6)	0 (0.0)	0.3130**
Stroke	7 (6.5)	4 (5.6)	3 (8.6)	0.5539**	2 (3.6)	1 (3.6)	1 (3.6)	>0.9999**
Prior Antiplatelet use (Home medication)	31 (29)	24 (33.3)	7 (20)	0.1538 ^^	15 (26.8)	10 (35.7)	5 (17.9)	0.1314^^
Aspirin Use Before ICU admission	15 (14)	12 (16.7)	3 (8.6)	0.2578**	4 (7.1)	3 (10.7)	1 (3.6)	0.2994**
Aspirin Use During ICU stay	32 (29.9)	22 (30.6)	10 (28.6)	0.8334^^	14 (25.0)	7 (25.0)	7 (25.0)	>0.9999^^

Notes: *T Test / ^ Wilcoxon rank sum test is used to calculate the P-value. ^^Chi square/ **Fisher's Exact test is used to calculate P-value. *$ Nephrotoxic medications/ material included IV Vancomycin, Gentamicin, Amikacin, Contrast, Colistin, Furosemide, and/or Sulfamethoxazole/trimethoprim.

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Table 2 Complications During ICU Stay

Outcomes	Number of Outcomes/ Total Number of Patients		P-value	Odds Ratio (OR) (95% CI)	P-value $
	Prophylaxis	Treatment			
Thrombosis, n(%)Δ	2 (7.1)	2 (7.1)	>0.99**	0.99 (0.13,7.61)	0.99
Major bleeding, n(%)Δ	3 (10.7)	4 (14.3)	0.69**	1.46 (0.29,7.42)	0.65
Minor bleeding, n(%)Δ	1 (3.6)	2 (7.4)	0.53**	2.04 (0.17,24.36)	0.57
Requiring blood products transfusion during ICU stay, n(%)Δ	6 (21.4)	12 (42.9)	0.09^^	2.73 (0.84,8.84)	0.09
				Beta coefficient (Estimates) (95% CI)	**P-value $***
RBCs transfusion (U), Mean (SD)	0.3 (0.86)	1.1 (1.63)	0.03^	1.17 (0.11,2.22)	0.03

Notes: ΔDenominator of the percentage is the total number of patients. ^^Chi-square test/ **Exact test is used to calculate the P-value. ^Wilcoxon rank sum test is used to calculate the P-value. $Logistic regression is used to calculate the OR and p-value. $*Negative binomial regression is used to calculate estimates and p-value.

Table 3 Clinical Outcomes of Critically Ill Patients with COVID-19 After Regression Analysis

Outcomes	Number of Outcomes/Total Number of Patients			Hazard Ratio (HR) (95% CI)	P-value $
	Prophylaxis	Treatment	P-value		
30-day mortality, n (%)Δ	16 (66.7)	12 (57.1)	0.51^^	0.66 (0.31, 1.41)	0.28
In-hospital mortality, n (%)Δ	18 (75.0)	19 (86.4)	0.33**	1.12 (0.58, 2.14)	0.74
				Beta coefficient (Estimates) (95% CI)	**P-value $***
MV duration, Median (Q1, Q3) Δ	12.0 (7.50, 17.50)	13.0 (9.00, 28.00)	0.45^	0.06 (−0.41,0.53)	0.81
ICU Length of Stay (Days), Median (Q1, Q3) Δ	15.0 (11.00, 20.00)	20.5 (10.00, 29.00)	0.24^	0.05 (−0.31,0.40)	0.80
Hospital Length of Stay (Days), Median (Q1, Q3) Δ	20.0 (14.50, 33.50)	23.5 (17.50, 32.50)	0.49^	−0.00 (−0.38,0.37)	0.99

Notes: ΔThe denominator of the percentage is the total number of patients. ^^Chi-square test/ **Fisher's Exact test is used to calculate the P-value. ^Wilcoxon rank sum test is used to calculate the P-value. $Cox proportional hazards regression analysis used to calculate HR and p-value. $*Negative binomial regression is used to calculate estimates and p-value.

another retrospective analysis conducted by Sanz et al, they reported that the incidence of bleeding was significantly higher in new-onset Afib patients receiving prophylactic or therapeutic doses of anticoagulants compared to chronic ones in Afib patients (P = 0.005).[7] However, no differences were observed in the multivariable analysis (OR 1.82, 95% CI 0.21–15.66, P = 0.96).[7]

The RAPID trial reported a higher incidence of major bleeding with therapeutic doses of anticoagulants in COVID-19 patients.[37] On the other hand, another retrospective cohort study by Al Sulaiman et al compared the outcomes of prophylactic LMWH vs UFH, and reported no differences in bleeding risk, but a higher requirement for blood transfusion was associated with the UFH group.[32] Nonetheless, those results were reported with respect to all COVID-19 patients without Afib. subgroup analysis.[32,37] We recognize that the overall incidence of new-onset Afib is common among COVID-19 patients and was estimated earlier to be 10.7% in the same population.[38] Furthermore, this population is at risk for clinically significant bleeding that requires blood transfusion compared to non-Afib patients despite the anticoagulant or the dose used[4,7,36,38] In line with this information, this could justify the lack of differences in bleeding risk between the prophylactic and treatment group in our report.

Our study found that patients in the treatment group required significantly higher odds of blood product transfusion during their ICU stay as well as a higher mean of RBC units compared with the prophylaxis group. The RAPID trial, however, reported numerically higher RBCs transfusion (≥1 unit) in the treatment group compared to the prophylaxis group.[37] Despite this numerical difference, it did not reach statistical significance (3.8% vs 1.3%, P = 0.14).[36] It is important to note that RAPID trial was conducted to compare treatment and prophylactic anticoagulation in critically ill patients with COVID-19 without focusing on Afib patients. In addition to bleeding, our findings might be attributed to several factors related to critically ill patients such as hemodilution, frequent blood sampling, inflammation, pre-existing comorbidities (eg, CKD), nutritional deficiencies, hemolysis, and/or variations in blood transfusion protocols among the included centers.[39–44]

Our study reported a similar thrombosis rate in both groups but was not statistically significant. On the contrary, Sanz et al, the retrospective analysis found that new-onset Afib was associated with a significantly higher incidence of embolic events between the control and Afib groups; importantly, all five patients had embolic events in the new-onset Afib group in the Sanz study were on prophylactic heparin.[7] Even though the previously published studies evaluated the use of treatment versus prophylactic anticoagulation in critically ill patients with COVID-19, which included Afib, those patients either represented a minority in most studies or were investigated separately compared to non-Afib patients, which raises a need to further investigate the use of different anticoagulation dosing modalities in this population.[7]

Our results demonstrated no differences in terms of in-hospital mortality and 30-day mortality between both groups, although numerically prophylactic doses of anticoagulant were associated with lower in-hospital mortality but higher 30-day mortality. Both proper prophylactic and therapeutic anticoagulation are directly linked to lower in-hospital mortality in patients with COVID-19.[45] Subsequently, delaying anticoagulation in COVID-19 Afib patients is associated with higher in-hospital mortality.[36] Our analysis included only the patients who started anticoagulation during the first 24 hours of admission. Moreover, the lack of a difference in in-hospital and 30-day mortality between the groups may be explained by the absence of significant differences in major bleeding and thrombotic events, which could otherwise contribute to higher mortality in COVID-19 patients.

Furthermore, our study found no significant statistical difference between the treatment and prophylaxis groups in the mean VFDs. It is unclear if different dosings of anticoagulant in the subgroup of COVID-19 patients might have an impact on mechanical ventilation duration, as both groups are similar in terms of their P/F ratio at baseline. On contrary, an earlier study by Rosenblatt et al found that critically ill COVID-19 patients who developed new-onset Afib were more likely to require mechanical ventilation than non-Afib patients (47.6% vs 15.7%, P < 0.0001). However, there were no comparisons in anticoagulation modality, and patients who developed Afib were compared to those who did not.[4]

This study contributes to current evidence investigating the optimal anticoagulation dosing regimen for critically ill COVID-19 patients with new-onset Afib. Despite that, we acknowledge some limitations. First, the retrospective observational study design leaves a potential risk of unmeasured confounders despite using propensity score matching to adjust for confounders. Second, the decision to prescribe prophylaxis or treatment dose anticoagulation to critically ill COVID-19 patients with new onset Afib COVID-19 was guided by the institutional and the Ministry of Health (MOH) treatment protocols, which faced several changes as evidence kept emerging over time. Third, parenteral anticoagulation dose adjustment was made depending on the patient's characteristics. Fourth, the statistically significant differences found on our secondary outcomes were associated with a wide confidence interval, making the results less reliable. Lastly, it was very challenging to determine the exact cause of RBC transfusion as its multifactorial. Thus, well-conducted randomized controlled trials are needed to confirm our results.

Conclusion

The use of treatment anticoagulation doses in critically ill patients with new-onset Afib and COVID-19 did not show better effectiveness over prophylactic anticoagulation doses. Instead, patients who received treatment anticoagulation doses had higher RBCs transfusion requirements. Our results must be cautiously adapted as they may support prophylactic anticoagulation dosing in those patients after carefully considering the individualized clinical characteristics, including bleeding and thrombosis risks. Therefore, larger randomized interventional studies with a larger sample size are required to confirm our findings.

Declaration of Generative AI in Scientific Writing

The authors did not use AI and AI-assisted technologies in the writing of the manuscript.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Statement

The study was approved in August 2022 by the King Abdullah International Medical Research Center Institutional Review Board, Riyadh, Saudi Arabia (Ref.# RSS22R.004.07). Participants' confidentiality was strictly observed throughout the study by using an anonymous unique serial number for each subject and restricting data only to the investigators. Informed consent was not required due to the research's method as per the policy of the governmental and local research center.

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