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Evaluation of Low-Dose Aspirin use among Critically Ill Patients with COVID-19: A Multicenter Propensity Score Matched Study

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Abstract

Background: Aspirin is widely used as a cardioprotective agent due to its antiplatelet and anti-inflammatory properties. The literature has assessed and evaluated its role in hospitalized COVID-19 patients. However, no data are available regarding its role in COVID-19 critically ill patients. This study aimed to evaluate the use of low-dose aspirin (81-100 mg) and its impact on outcomes in critically ill patients with COVID-19.

Method: A multicenter, retrospective cohort study of all critically ill adult patients with confirmed COVID-19 admitted to intensive care units (ICUs) between March 1, 2020, and March 31, 2021. Eligible patients were classified into two groups based on aspirin use during ICU stay. The primary outcome was in-hospital mortality, and other outcomes were considered secondary. Propensity score matching was used (1:1 ratio) based on the selected criteria.

Results: A total of 1033 patients were eligible, and 352 patients were included after propensity score matching. The in-hospital mortality (HR 0.73 [0.56, 0.97], p = 0.03) was lower in patients who received aspirin during stay. Conversely, patients who received aspirin had a higher odds of major bleeding than those in the control group (OR 2.92 [0.91, 9.36], p = 0.07); however, this was not statistically significant. Additionally, subgroup analysis showed a possible mortality benefit for patients who used

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aspirin therapy prior to hospitalization and continued during ICU stay (HR 0.72 [0.52, 1.01], p = 0.05), but not with the new initiation of aspirin (HR 1.22 [0.68, 2.20], p = 0.50).

Conclusion: Continuation of aspirin therapy during ICU stay in critically ill patients with COVID-19 who were receiving it prior to ICU admission may have a mortality benefit; nevertheless, it may be associated with an increased risk of significant bleeding. Appropriate evaluation for safety versus benefits of utilizing aspirin therapy during ICU stay in COVID19 critically ill patients is highly recommended.

Keywords

COVID-19, SARS-coV-2, aspirin, critically ill, intensive care units (ICUs), 30-day mortality, in-hospital mortality

Introduction

Coronavirus disease 2019 (COVID-19) patients are usually present with mild symptoms.[1] However, severe critical illness has been reported in 6%–19% of patients with COVID-19.(1) Worsening of clinical symptoms can be related to various degrees of endothelial dysfunction, coagulopathy, platelet dysfunction, and hypercytokinemia.[2] Therefore, complications can occur in situ, such as acute respiratory distress syndrome, septic shock, thromboembolism, and multiple organ failure.[3]

The prothrombotic state described in COVID-19 patients does not seem to stem from the classic pathophysiology associated with venous thromboembolism (VTE).[4,5] Anticoagulation has been extensively studied.[6–8] Nevertheless, the optimal thromboprophylaxis strategy to combat the immune thrombotic response in critically ill patients with COVID-19 remains unknown. Despite thromboprophylaxis administration, patients with COVID-19 have been developing venous or arterial clots. Thus, the optimal way to avoid arterial and venous occlusion from developing is to prevent the immune-thrombosis response before it begins. In this regard, targeting multiple pathways in thrombus formation may play a potential role.

It has been suggested that in COVID-19 patients, platelet production is reduced along with a dysregulation in its functional role.[9,10] Platelets are also thought to have a lower threshold for activation, thus stimulating platelet aggregation and adherence.[9,10] Besides aspirin's mechanism of action on platelet aggregation and inhibition, it is proposed that aspirin might play a role in viral replication and anti-lung injury by inhibition of prostaglandin E2 (PGE2) in macrophages and upregulation of type I interferon production. Therefore, aspirin treatment could potentially benefit patients with COVID-19.

Several studies have reported that early use of aspirin prior to COVID-19 diagnosis is associated with milder disease, less intensive care unit (ICU) admission, and lower mortality rates. Additionally, in-hospital mortality was reduced in patients who were hospitalized for COVID-19 management and were on aspirin.[11–13] Since aspirin is commonly available and cheap and has a potential benefit, we aimed to evaluate the efficacy and safety of aspirin use during the ICU stay in critically ill patients with COVID-19.

Methods

Study Design

This is a multicenter, retrospective cohort study that included adult critically ill patients with confirmed COVID-19 who were hospitalized in the intensive care units (ICUs) at four hospitals between March 1, 2020, and March 31, 2021. This study was approved by King Abdullah International Medical Research Center

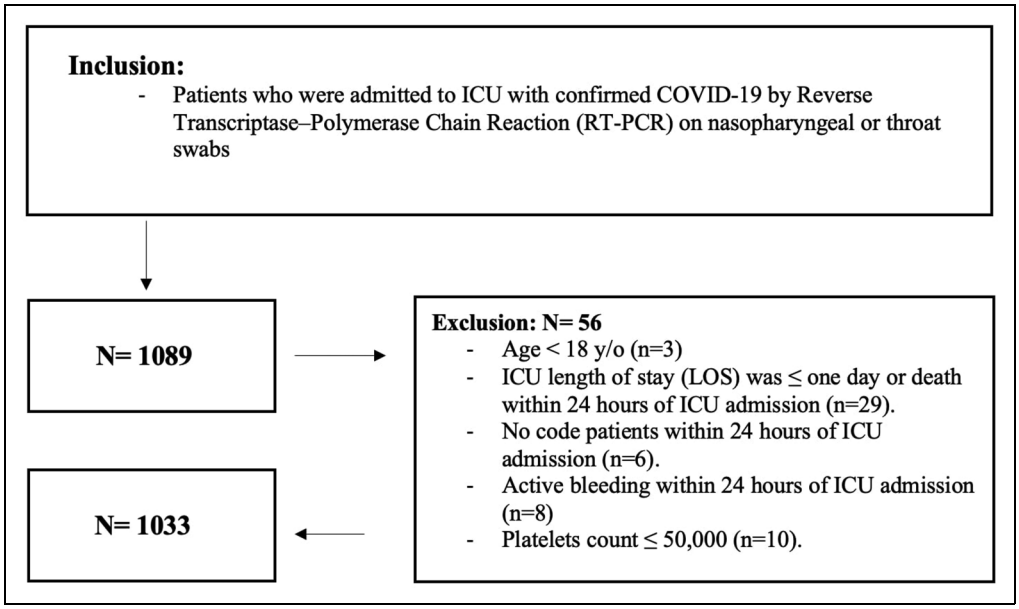

Figure 1. Eligibility criteria flowchart.

Table 1. Baseline Characteristics Before and After Propensity score matching.

	Before propensity score (PS) matching				After propensity score (PS) matching			
	Overall (N = 1033)	**Control (N = 838)**	**Aspirin (N = 195)**	**P-value**	**Overall (N = 352)**	**Control (N = 176)**	**Aspirin (N = 176)**	**P-value**
Age (Years), Mean (SD)	61.7 (14.77)	60.4 (15.08)	67.3 (11.89)	<.0001*	67.6 (12.86)	67.8 (13.68)	67.4 (12.02)	0.9281^
Gender – Male, n (%)	689 (69.1)	550 (68.2)	139 (72.8)	0.2224^^	238 (68.4)	113 (64.9)	125 (71.8)	0.1665^^
Weight (kg), Mean (SD)	81.4 (18.72)	81.1 (18.77)	82.7 (18.54)	0.2214^	79.4 (17.35)	76.8 (15.48)	82.1 (18.72)	0.0058^
APACHE II score, Median (Q1,Q3)	14.0 (9.00, 22.00)	14.0 (9.00, 23.00)	14.0 (10.00, 21.00)	0.4018^	15.0 (10.00, 22.00)	15.0 (10.00, 25.00)	14.5 (10.00, 21.00)	0.3867^
SOFA score, Median (Q1, Q3)	5.0 (3.00, 8.00)	5.0 (3.00, 7.00)	5.0 (3.00, 9.00)	0.0226^	5.0 (3.00, 8.00)	5.0 (3.00, 7.00)	5.0 (3.00, 9.00)	0.2092^
Systemic Corticosteroids use, n (%)	886 (89.9)	716 (89.7)	170 (90.9)	0.6277^^	315 (91.3)	159 (91.4)	156 (91.2)	0.9602^^
Tocilizumab use, n (%)	358 (36.2)	295 (36.9)	63 (33.3)	0.3561^^	111 (31.8)	53 (30.3)	58 (33.3)	0.5410^^
Estimated glomerular filtration rate (eGFR) Baseline, Median (Q1,Q3)	76.0 (45.00, 97.00)	77.0 (48.00, 98.00)	68.0 (38.00, 93.00)	0.0341^	66.0 (38.00, 92.00)	64.0 (38.00, 92.00)	68.0 (38.00, 92.00)	0.8786^
Acute Kidney Injury (AKI) within 24 hours of ICU admission, n (%)	244 (25.0)	191 (24.2)	53 (28.5)	0.2212^^	113 (32.4)	62 (35.4)	51 (29.3)	0.2220^^
Mechanical Ventilation within 24 hours of ICU admission, n (%)	702 (70.0)	558 (68.6)	144 (75.8)	0.0527^^	260 (74.5)	128 (73.1)	132 (75.9)	0.5601^^
Oxygenation Index (OI)	15.9 (8.40, 24.50)	15.5 (8.40, 24.54)	18.5 (7.64, 24.28)	0.6466^	18.7 (7.64, 29.95)	18.2 (7.10, 35.27)	19.2 (7.64, 24.28)	0.5484^
Lactic acid Baseline (mmol/L), Median (Q1, Q3)	1.7 (1.25, 2.31)	1.6 (1.24, 2.30)	1.7 (1.26, 2.42)	0.5358^	1.7 (1.30, 2.49)	1.7 (1.30, 2.46)	1.7 (1.26, 2.56)	0.8720^
Platelets count Baseline (10^9/L), Median (Q1, Q3)	242.0 (185.00, 310.00)	243.5 (188.00, 308.00)	234.0 (175.00, 319.00)	0.4117^	244.0 (179.00, 313.00)	255.0 (192.00, 312.00)	231.0 (173.50, 318.00)	0.1688^
Total WBC Baseline (10^9/L), Median (Q1, Q3)	9.6 (6.73, 12.90)	9.6 (6.59, 12.80)	9.6 (6.95, 13.00)	0.4859^	9.7 (7.15, 13.60)	9.9 (7.36, 14.00)	9.5 (7.01, 13.03)	0.3676^
International normalized ratio (INR), Median (Q1, Q3)	1.1 (1.03, 1.20)	1.1 (1.03, 1.21)	1.1 (1.02, 1.19)	0.0893^	1.1 (1.03, 1.23)	1.1 (1.04, 1.26)	1.1 (1.02, 1.19)	0.0182^
Activated partial thromboplastin time (aPTT) Baseline (Seconds), Median (Q1, Q3)	30.3 (27.00, 33.90)	30.5 (27.00, 34.00)	29.9 (26.70, 33.30)	0.3951^	30.5 (27.00, 34.40)	30.6 (27.10, 35.60)	30.0 (26.70, 33.30)	0.2143^
Total bilirubin (μmol/L), Median (Q1, Q3)	9.8 (6.80, 14.00)	9.8 (6.80, 14.00)	9.7 (6.50, 15.20)	0.8539^	9.8 (6.60, 14.80)	10.0 (6.60, 14.40)	9.6 (6.60, 15.20)	0.9610^
Albumin Baseline (gm/L), Median (Q1, Q3)	32.5 (28.00, 36.00)	33.0 (28.00, 36.30)	32.0 (29.00, 35.00)	0.3546^	32.0 (28.00, 35.90)	33.0 (28.00, 36.00)	32.0 (29.00, 35.00)	0.7768^
Creatine phosphokinase (CPK) baseline (U/l), Median (Q1,Q3)	172.0 (76.00, 421.00)	170.5 (77.00, 403.00)	190.0 (72.00, 508.00)	0.5002^	153.0 (67.00, 399.00)	124.0 (59.00, 267.00)	200.0 (76.00, 508.00)	0.0127^
C-reactive protein (CRP) baseline (mg/l)m Median (Q1,Q3)	129.0 (64.37, 196.20)	127.0 (63.80, 193.00)	134.5 (73.00, 220.00)	0.1943^	132.0 (66.00, 199.00)	129.0 (55.40, 199.00)	134.0 (69.00, 199.00)	0.5324^
Procalcitonin (ng/ml), Median (Q1,Q3)	0.4 (0.14, 1.08)	0.3 (0.14, 1.05)	0.4 (0.13, 1.24)	0.8457^	0.4 (0.14, 1.46)	0.4 (0.16, 1.66)	0.4 (0.13, 1.24)	0.4061^
Fibrinogen Level baseline (gm/l), Median (Q1,Q3)	5.4 (3.77, 7.18)	5.5 (3.77, 7.18)	5.3 (3.80, 7.38)	0.9787^	5.2 (3.60, 7.23)	5.1 (3.77, 6.80)	5.3 (3.10, 7.51)	0.4437^
				0.6422^				0.3255^

(continued)

Table 1. (continued)

	Before propensity score (PS) matching				After propensity score (PS) matching			
	Overall (N = 1033)	**Control (N = 838)**	**Aspirin (N = 195)**	**P-value**	**Overall (N = 352)**	**Control (N = 176)**	**Aspirin (N = 176)**	**P-value**
D-dimer Level baseline (mg/l), Median (Q1,Q3)	1.3 (0.71, 3.27)	1.3 (0.71, 3.40)	1.3 (0.70, 2.51)		1.4 (0.74, 3.48)	1.4 (0.77, 3.83)	1.3 (0.70, 2.51)	
DVT prophylaxis - Low, n (%)	84 (9.3)	62 (8.6)	22 (12.1)	0.3613^^	39 (12.1)	17 (10.8)	22 (13.3)	0.6994^^
DVT prophylaxis - Standard, n (%)	466 (51.8)	375 (52.3)	91 (50.0)	0.3613^^	164 (50.8)	83 (52.9)	81 (48.8)	0.6994^^
DVT prophylaxis - High, n (%)	349 (38.8)	280 (39.1)	69 (37.9)	0.3613^^	120 (37.2)	57 (36.3)	63 (38.0)	0.6994^^
Ferritin (ug/l), Median (Q1, Q3)	782.5 (383.95, 1621.50)	822.3 (400.10, 1650.00)	635.6 (296.00, 1301.00)	0.0140^	659.3 (338.40, 1500.00)	687.5 (386.50, 1650.00)	602.3 (300.90, 1212.00)	0.1259^
Blood sugar level (mmol/L) Baseline, Median (Q1, Q3)	11.2 (7.60, 15.60)	10.8 (7.50, 15.00)	12.6 (8.50, 17.40)	0.0026^	12.5 (8.20, 17.00)	12.3 (7.90, 16.80)	12.6 (8.40, 17.30)	0.7654^
PaO2/FiO2 ratio within 24 hours of admission, Median (Q1,Q3)	83.3 (60.20, 135.80)	85.0 (60.00, 140.20)	81.4 (63.50, 124.00)	0.5872^	80.0 (58.60, 126.40)	78.6 (55.33, 142.50)	81.6 (63.50, 121.40)	0.5284^
Respiratory Rate (RR/minute) Baseline, Median (Q1,Q3)	28.0 (23.00, 33.00)	28.0 (23.00, 33.00)	27.0 (23.00, 32.00)	0.4461^	27.0 (22.00, 33.00)	28.0 (22.00, 33.50)	26.5 (23.00, 32.00)	0.8407^
Maximum temperature Baseline (C°), Median (Q1, Q3)	37.4 (37.00, 38.10)	37.4 (37.00, 38.10)	37.3 (37.00, 38.10)	0.4209^	37.3 (37.00, 38.00)	37.3 (37.00, 38.00)	37.4 (37.00, 38.10)	0.3917^
Prone position status, n (%)	296 (30.4)	254 (32.1)	42 (23.1)	0.0174^^	74 (21.2)	34 (19.4)	40 (23.0)	0.4159^^
Patient received nephrotoxic drugs/material during ICU stay, n (%)	808 (81.4)	641 (79.5)	167 (89.3)	0.0020^^	292 (84.6)	140 (80.5)	152 (88.9)	0.0299^^
Comorbidity								
Atrial fibrillation (A Fib), **n (%)**	27 (2.7)	25 (3.1)	2 (1.0)	0.1195^^	15 (4.3)	13 (7.4)	2 (1.1)	0.0038^^
Heart Failure, **n (%)**	84 (8.4)	60 (7.4)	24 (12.6)	0.0196^^	44 (12.6)	21 (12.0)	23 (13.2)	0.7317^^
Hypertension, **n (%)**	558 (55.5)	406 (49.9)	152 (79.6)	<.0001^^	246 (70.5)	103 (58.9)	143 (82.2)	<.0001^^
Diabetes mellitus, **n (%)**	595 (59.2)	458 (56.3)	137 (71.7)	<.0001^^	241 (69.1)	113 (64.6)	128 (73.6)	0.0692^^
Dyslipidemia, **n (%)**	196 (19.5)	120 (14.7)	76 (39.8)	<.0001^^	88 (25.2)	20 (11.4)	68 (39.1)	<.0001^^
Ischemic heart disease (IHD), **n (%)**	85 (8.5)	56 (6.9)	29 (15.2)	0.0002^^	46 (13.2)	23 (13.1)	23 (13.2)	0.9834^^
Chronic kidney disease (CKD), **n (%)**	111 (11.0)	78 (9.6)	33 (17.3)	0.0023^^	47 (13.5)	16 (9.1)	31 (17.8)	0.0176^^
Cancer, **n (%)**	23 (2.3)	18 (2.2)	5 (2.6)	0.7353**	9 (2.6)	4 (2.3)	5 (2.9)	0.7290**
Acute Coronary Syndrome (ACS), **n (%)**	14 (1.4)	8 (1.0)	6 (3.1)	0.0220**	9 (2.6)	3 (1.7)	6 (3.4)	0.3068**
Deep vein thrombosis, **n (%)**	5 (0.5)	5 (0.6)	0 (0.0)	0.2775**	0 (0.0)	0 (0.0)	0 (0.0)	NA
Pulmonary embolism, **n (%)**	6 (0.6)	5 (0.6)	1 (0.5)	0.8836**	2 (0.6)	1 (0.6)	1 (0.6)	0.9968**
Liver disease (any type), **n (%)**	19 (1.9)	14 (1.7)	5 (2.6)	0.4122**	8 (2.3)	3 (1.7)	5 (2.9)	0.4693**
Stroke, **n (%)**	54 (5.4)	34 (4.2)	20 (10.5)	0.0005^^	37 (10.6)	19 (10.9)	18 (10.3)	0.8765^^

*T Test / ^ Wilcoxon rank sum test is used to calculate the P-value.
^^ Chi square/ ** Fisher's Exact teat is used to calculate P-value.

(KAIMRC) (Ref.# NRC21R/058/02). No informed consent was obtained from the patients due to the retrospective observational nature of the study.

Study Participants

Critically ill adult patients aged 18 years and above who were admitted to the ICU with confirmed COVID-19 were included in the study. COVID-19 was identified in patients utilizing nasopharyngeal and/or throat swabs and reverse transcriptase-polymerase chain reaction. Patients were excluded if their ICU LOS was one day, died within 24 hours of ICU admission, had a "Do-Not-Resuscitate" code status, had active bleeding, or had a platelet count of 50,000 or less within 24 h of ICU admission (Figure 1). Eligible patients were subsequently categorized into two groups depending on their use of aspirin therapy during their ICU stay. Patients who received aspirin as a new initiation during the ICU stay or as a continuation if prescribed in the pre-ICU period were included in the active group. The decision on continuing or initiating aspirin for patients admitted to the ICU was left to the clinical judgment of the managing team.

Table 2. Regression Analysis for the Outcomes After PS Adjustment.

Outcomes	number of outcomes/Total no-of patients		P-value^^	Hazard Ratio (HR) (95%CI)	P-value$
	Control	Aspirin			
30-day mortality, n (%)Δ	97/175 (55.4)	95/176 (54.0)	0.78	0.86 (0.65, 1.14)	0.30
In-hospital mortality, n (%)Δ	107/173 (61.9)	98/176 (55.7)	0.24	0.73 (0.56, 0.97)	0.03
			P-value^	**beta coefficient (Estimates) (95%CI)**	**P-value$***
Ventilator free days, Mean (SD)Δ	8.8 (±12.1)	9.5 (±12.3)	0.67	0.11 (−0.47, 0.69)	0.71
ICU Length of Stay (Days), Median (Q1, Q3)&	9.5 (6.0, 17.0)	9.0 (5.0, 16.0)	0.54	−0.06 (−0.30, 0.18)	0.63
Hospital Length of Stay (Days), Median (Q1,Q3)&	16.5 (11.0, 28.0)	20.0 (12.0, 28.0)	0.46	0.09 (−0.17, 0.35)	0.51

Δ Denominator of the percentage is the total number of patients.
& Denominator is patients who survived.
^ Wilcoxon rank sum test is used to calculate the P-value.
^^ Chi-square test is used to calculate the P-value.
$ Cox proportional hazards regression is used to calculate hazard ratio (HR) and p-value.
$* Negative binomial regression is used to calculate estimates and p-value.

Study Setting

The research was conducted in four hospitals in Saudi Arabia: King Abdulaziz Medical City in Riyadh, King Abdulaziz University Hospital in Jeddah, King Abdullah bin Abdulaziz University Hospital in Riyadh, and King Salman Specialist Hospital in Hail. The primary center for this multicenter retrospective study was the King Abdulaziz Medical City (Riyadh).

Data Collection

Data for each patient were collected and handled using the Research Electronic Data Capture (REDCap®) software. Electronic medical records were reviewed to ascertain their demographic information, past medical history, and vital signs from patient profiles. Moreover, laboratory tests within 24 h of ICU admissions, such as renal profile, liver function tests, coagulation profile (i.e., International Normalized Ratio, Activated partial thromboplastin time (aPTT), fibrinogen, D-dimer), and inflammatory markers (i.e., ferritin, procalcitonin, and creatine phosphokinase [CPK]) were collected. In addition, tocilizumab, corticosteroids, and pharmacological deep vein thrombosis (DVT) prophylaxis during ICU stay were recorded and administered for eligible patients based on the Ministry of Health (MOH) protocol for COVID-19 management.[14]

Severity scores (i.e., Acute Physiology and Chronic Health Evaluation II [APACHE II], Sequential Organ Failure Assessment [SOFA], and Nutrition Risk in Critically Ill [NUTRIC]), Glasgow Coma Score, acute kidney injury, prone status, mechanical ventilation (MV) needs, and MV parameters (e.g., PaO2/FiO2 ratio, FiO2 requirement) within 24 h of ICU admission were collected. Furthermore, minor bleeding, major bleeding, RBC/platelet transfusion, and other complications during ICU stay (i.e., acute kidney injury [AKI], liver injury, thrombosis, and respiratory failure requiring MV) were documented. All patients were followed either until they were discharged from the hospital or died while in the hospital.

Outcomes

The main outcome was the in-hospital mortality in COVID-19 critically ill patients who received aspirin treatment throughout their ICU stay. The secondary outcomes were 30-day mortality, hospital LOS, ICU LOS, Ventilator-free days (VFDs), and ICU-related complication (s) during ICU stay (ie, major/minor bleeding, RBCs transfusion requirement, respiratory failure necessitating MV, AKI, and liver injury).

Outcome Definition (s)

- The 30-day mortality was defined as in-hospital death occurring for any cause within 30 days of the admission date during the hospital stay.
- Major bleeding was defined as clinically overt bleeding with at least one of the following: fatal, symptomatic intracranial hemorrhage, retroperitoneal hemorrhage, and intraocular hemorrhage leading to significant vision loss, a decrease in hemoglobin of >3.0 g/dL (with each blood transfusion unit counting for 1.0 g/dL of HB) and requiring transfusion of two or more units of red blood cells or the equivalent of whole blood.
- Minor bleeding was defined as clinically significant bleeding not meeting the definition of major bleeding and leading to interruption of study drug, surgical intervention, or transfusion of 1 unit of blood.[15]
- Ventilator-free days (VFDs) at 30 days were computed as follows: if the patient died within 30 days

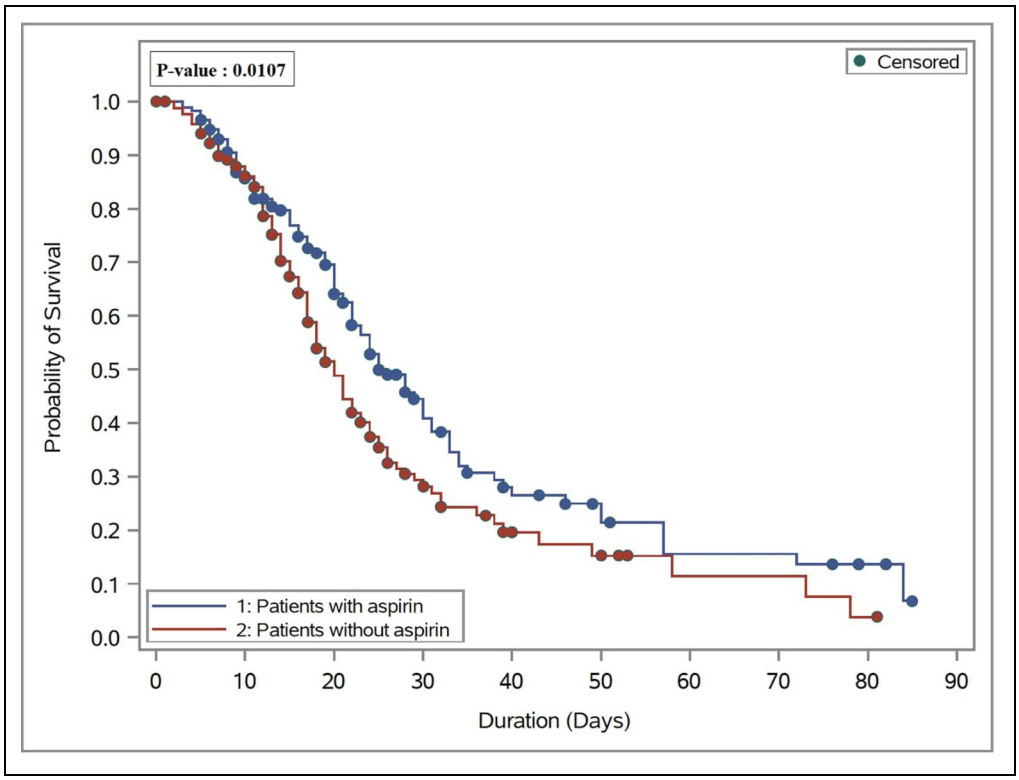

Figure 2. Overall survival plot during the hospital stay after PS matching comparing patients who received aspirin therapy (176 patients) versus the control group (176 patients).

of MV or remained on MV for more than 30 days, then the VFDs = 0, while if the patient survived and was successfully liberated from MV, then the VFDs = 30 - MV duration.

- Acute kidney injury (AKI) was defined as a sudden decrease of renal function within 48 hours, as an increase in absolute serum creatinine (SCr) of at least 26.5 μmol/L (0.3 mg/dL) or by a percentage increase in SCr ≥ 50% (1.5 × baseline value) during the ICU stay.[16]
- Acute liver injury was defined as alanine aminotransferase (ALT) exceeding three times the upper limit of normal or double in patients with elevated baseline ALT levels during the ICU stay.
- Respiratory failure was defined as either low arterial carbon dioxide tension ($PaCO_2$) or hypoxemic respiratory failure (PaO_2 < 60 mm Hg with a normal or hypercapnic respiratory failure ($PaCO_2$ > 50 mm Hg) that required MV.[17]

Statistical Analysis

As applicable, we reported continuous variables as mean and standard deviation (SD), or median with lower and upper quartile (Q1, Q3), and categorical variables as number (percentage). The normality assumptions for all numerical variables were evaluated using a statistical test (Shapiro–Wilk test) and graphical representation (ie, histograms and Q-Q plots). We assessed the model fit using the Hosmer–Lemeshow goodness-of-fit test.

We used the chi-square or Fisher exact test to compare categorical variables, the Student t-test to compare normally distributed continuous data, and the Mann–Whitney U test to compare non-normally distributed continuous variables. Baseline characteristics, baseline severity, and outcome variables were compared between the two groups. For the 30-day and in-hospital mortality, multivariable Cox proportional hazards regression analyses were performed. Kaplan–Meier (KM) graphs were generated for these outcomes. Multivariable logistic and negative binomial regression analysis were used for the other outcomes included in this study. Regression analysis was performed by considering PS score as one of the covariates in the model. The odds ratios (ORs), hazard ratios (HRs), or estimates with 95% confidence intervals (CIs) were reported as appropriate.

Propensity score matching (Proc PS match) (SAS, Cary, NC) was used to match patients (1:1 ratio) who received aspirin therapy (active group) to patients who did not (control group) based on the patient's age, SOFA score, MV status, prone position status, ischemic heart disease (IHD), and stroke as co-existing illnesses. A greedy nearest neighbor matching approach was utilized, with one patient from the active group paired with one from the control group, resulting in the lowest within-pair difference among all possible pairings with treated patients. The difference in the logits of the propensity

Table 3. Regression Analysis for ICU Complication (s) and Follow-up Markers During ICU Stay.

Outcomes	number of outcomes/Total no-of patients		P-value^^	Odds Ratio (OR) (95%CI)	P-value[$]
	Control	Aspirin			
Respiratory Failure Required MV, n (%)[$*]	25/47 (53.2)	23/42 (54.8)	0.88	1.14 (0.49, 2.69)	0.75
Acute kidney injury, n(%)[Δ]	87/176 (49.4)	79/176 (44.9)	0.40	0.79 (0.51, 1.20)	0.27
Liver injury, n(%)[Δ]	18/176 (10.2)	21/176 (11.9)	0.61	1.20 (0.61, 2.40)	0.59
All thrombosis cases, n(%)[Δ]	10/175 (5.7)	20/174 (11.5)	0.05	1.99 (0.95, 4.18)	0.06
Venous Thromboembolism, n(%)[Δ]	3/176 (1.7)	10/176 (5.7)	0.05	3.14 (0.83, 11.81)	0.09
Major bleeding, n(%)[Δ]	5/176 (2.8)	11/175 (6.3)	0.12	2.92 (0.91, 9.36)	0.07
Minor bleeding, n(%)[Δ]	8/176 (4.6)	13/176 (7.4)	0.26	1.70 (0.68, 4.20)	0.26
Follow-up markers (Highest during ICU stay)			**P-value^**	**beta coefficient (Estimates) (95%CI)**	**P-value[$]**
Ferritin levels, Median (Q1,Q3)[Δ]	1001.2 (564.6, 2112.9)	855.6 (332.0, 2199.1)	0.11	−0.15 (−0.41, 0.12)	0.30
Procalcitonin levels, Median (Q1,Q3)[Δ]	0.58 (0.16, 2.83)	0.58 (0.13, 1.72)	0.48	−0.73 (−1.23, −0.23)	0.004
C-reactive protein (CRP) levels, Median (Q1, Q3)[Δ]	128.0 (35.1, 241.0)	157.8 (91.0, 248.0)	0.04	0.19 (−0.05, 0.43)	0.11
D-dimer levels, Median (Q1,Q3)[Δ]	5.13 (1,9, 13.9)	3.0 (1.18, 10.70)	0.02	−2.84 (−3.32, −2.37)	<0.0001
Fibrinogen levels, Median (Q1,Q3)[Δ]	5.01 (3.4, 7.6)	5.41 (4.17, 7.28)	0.70	0.62 (0.25, 0.99)	0.001
Creatine phosphokinase (CPK) levels, Median (Q1,Q3)[Δ]	251.0 (76.0, 773.0)	276.5 (87.0, 679.0)	0.78	0.005 (−0.32, 0.33)	0.98
RBCs transfusion (Units), Mean (SD)[Δ]	2.4 (±1.5)	2.1 (±1.3)	0.33	−0.14 (−0.50, 0.22)	0.45

$* Denominator of the percentage is non-mechanically ventilated patients with 24 hours of ICU admission.
Δ Denominator of the percentage is the total number of patients.
^^ Chi-square test is used to calculate the P-value.
^ Wilcoxon rank sum test is used to calculate the P-value.
$ Propensity score matched used based on patient's age, SOFA score, Mechanical Ventilation status, Proning position status, ischemic heart disease (IHD) and stroke as co-existing illness.

scores for pairs of patients from the two groups was matched only if it was less than or equal to 0.5, the pooled estimate of the SD.

Subgroup analysis was done for those newly initiated on aspirin during ICU stay and those who used aspirin prior to hospitalization and continued during ICU stay. No imputation was made for missing data, as the cohort of patients in our study was not derived from random selection. Statistical significance was set at $P < 0.05$, and SAS version 9.4 for all statistical analyses was used.

Results

A total of 1033 patients were included in our analysis based on eligibility criteria. Among them, 195 (18.8%) patients received aspirin. After propensity score matching (1:1 ratio), 352 patients were included based on predefined criteria. Most of the patients who received aspirin (69.2%) were using it for chronic conditions (e.g., stroke, IHD). Only 21 patients (12.2%) required discontinuation of aspirin during ICU stay secondary to thrombocytopenia (7 patients), bleeding (3 patients), and other reasons (11 patients).

Demographic and Clinical Characteristics

The majority of the patients included in both arms (69.1%) were male, with a mean age of 61.7 (SD ± 14.77). Diabetes mellitus (59.2%), hypertension (55.4%), and dyslipidemia (19.5%) were the most prevalent underlying comorbidities in our patients. There was a notable difference before propensity score matching: patients who did not take aspirin throughout their ICU stay were younger, had a higher eGFR, and higher ferritin levels at baseline. In contrast, patients who received aspirin had considerably higher SOFA scores and blood glucose levels at baseline. Most of these differences were comparable between the two groups after propensity score matching (Table 1).

30-day and in-Hospital Mortality

In the crude analysis, patients who received aspirin showed lower in-hospital mortality (55.7% vs. 61.9%, p = 0.24) and 30-day mortality (54.0% vs. 55.4%, p = 0.78) than patients who did not receive aspirin; however, the difference was not statistically significant. The multivariable Cox proportional hazards regression analyses showed a statistically significantly lower in-hospital mortality in patients who received aspirin (HR 0.73; 95% CI 0.56-0.97; $P = 0.03$), but not the 30-day mortality (HR 0.86; 95% CI 0.65-1.14; $P = 0.30$) (Table 2). Additionally, the overall survival probabilities were higher during hospital stay among patients who received aspirin after propensity score matching, as shown in the survival curve (Figure 2).

In the prespecified subgroup analysis of patients who newly initiated on aspirin (N = 46), both 30-day mortality and in-hospital mortality were higher in aspirin patients; (HR

Table 4. Subgroup Analysis - Regression Analysis for the Outcomes After PS Adjustment (New Initiation of Aspirin).

Outcomes	number of outcomes/Total no-of patients				
	Control	Aspirin	P-value^^	Hazard Ratio (OR) (95%CI)	P-value[$]
30-day mortality, n (%)[Δ]	18 (40.9)	24 (54.5)	0.20	1.46 (0.78, 2.74)	0.24
In-hospital mortality, n (%)[Δ]	20 (45.5)	26 (59.1)	0.20	1.22 (0.68, 2.20)	0.50
Clinical Outcomes			**P-value^**	**beta coefficient (Estimates) (95%CI)**	**P-value[$*]**
Ventilator free days, Mean (SD)[Δ]	11.9 (12.66)	9.7 (12.48)	0.35^	−0.21 (−1.18, 0.76)	0.67
ICU Length of Stay (Days), Median (Q1,Q3)[&]	10.5 (6.0, 21.5)	8.5 (4.0, 14.0)	0.21	−0.41(−0.82, 0.005)	0.05
Hospital Length of Stay (Days), Median (Q1,Q3)[&]	19.5 (11.0, 40.5)	21.0 (14.0, 29.0)	0.82	−0.05 (−0.55, 0.43)	0.83
Complication (s) during ICU stay				**Odds Ratio (OR) (95%CI)**	**P-value[$]**
Respiratory Failure Required MV, n (%)[$*]	4/8 (50.0)	6/13 (46.2)	0.86^^	0.49 (0.07, 3.49)	0.49
Acute kidney injury, n(%)[Δ]	21 (47.7)	19 (43.2)	0.67^^	0.76 (0.32, 1.81)	0.53
Liver injury, n(%)[Δ]	6 (13.6)	7 (15.9)	0.76^^	1.14 (0.35, 3.75)	0.83
Venous Thromboembolism, n(%)[Δ]	3 (6.8)	1 (2.3)	0.30**	0.46 (0.04, 5.38)	0.54
Major bleeding, n(%)[Δ]	5 (11.4)	2 (4.5)	0.24**	0.35 (0.06, 1.93)	0.23
Minor bleeding, n(%)[Δ]	3 (6.8)	2 (4.5)	0.64**	0.60 (0.09, 3.95)	0.59

Δ Denominator of the percentage is the total number of patients.
& Denominator is patients who survived.
^ Wilcoxon rank sum test is used to calculate the P-value.
^^ Chi-square test is used to calculate the P-value.
$ Propensity score matched used based on patient's age, SOFA score, MV status, Proning position status, ischemic heart disease (IHD) and stroke as co-existing illness.
$* Negative binomial regression is used to calculate estimates and p-value.

Table 5. Subgroup Analysis - Regression Analysis for the Outcomes After PS Adjustment (Chronic use of Aspirin Only).

Outcomes	number of outcomes/Total no-of patients				
	Control	Aspirin	P-value	Hazard Ratio (OR) (95%CI)	P-value[$]
30-day mortality, n (%)[Δ]	71 (56.3)	68 (54.0)	0.70^^	0.77 (0.55, 1.08)	0.13
In-hospital mortality, n (%)[Δ]	75 (59.5)	68 (54.0)	0.37^^	0.72 (0.52, 1.01)	0.05
Clinical Outcomes				**beta coefficient (Estimates) (95% CI)**	**P-value[$*]**
Ventilator free days, Mean (SD)[Δ]	8.8 (12.25)	9.9 (12.46)	0.63^	0.11 (−0.57, 0.79)	0.76
ICU Length of Stay (Days), Median (Q1,Q3)[&]	10.0 (6.0, 18.0)	9.5 (6.0, 18.0)	0.34^	−0.07 (−0.36, 0.22)	0.62
Hospital Length of Stay (Days), Median (Q1, Q3)[&]	17.0 (11.0, 32.0)	20.0 (12.0, 27.0)	0.49^	−0.04 (−0.34, 0.26)	0.78
Complication (s) during ICU stay				**Odds Ratio (OR) (95%CI)**	**P-value[$]**
Respiratory Failure Required MV, n (%)[$*]	15/29 (51.7)	17/28 (60.7)	0.49^^	1.49 (0.52, 4.34)	0.45
Acute kidney injury, n(%)[Δ]	69 (54.8)	57 (45.2)	0.13^^	0.65 (0.39, 1.08)	0.09
Liver injury, n(%)[Δ]	17 (13.5)	14 (11.1)	0.57^^	0.79 (0.37, 1.70)	0.55
All Thrombosis cases, n(%)[Δ]	4 (3.2)	12 (9.5)	0.04^^	2.50 (0.93, 6.74)	0.07
Venous Thromboembolism, n(%)[Δ]	3 (2.4)	9 (7.1)	0.07^^	2.78 (0.72, 10.77)	0.14
Major bleeding, n(%)[Δ]	5 (4.0)	9 (7.2)	0.26^^	2.37 (0.71, 7.91)	0.16
Minor bleeding, n(%)[Δ]	6 (4.8)	11 (8.7)	0.21^^	1.91 (0.68, 5.36)	0.22

Δ Denominator of the percentage is the total number of patients.
& Denominator is patients who survived.
$* Denominator of the percentage is non-mechanically ventilated patients with 24 hours of ICU admission.
^ Wilcoxon rank sum test is used to calculate the P-value.
^^ Chi-square test is used to calculate the P-value.
$ Propensity score matched used based on patient's age, SOFA score, MV status, Proning position status, ischemic heart disease (IHD) and stroke as co-existing illness.
$* Negative binomial regression is used to calculate estimates and p-value.

1.46; 95% CI 0.78, 2.74; P = 0.24); and (HR 1.22; 95% CI 0.68, 2.20; P = 0.50), respectively (Table 4).

Conversely, aspirin showed possible mortality benefit for the in-hospital mortality in for patients who used aspirin therapy prior to hospitalization and continued during ICU stay ((HR 0.72; 95% CI 0.52, 1.01; P = 0.05) (Table 5).

Ventilator Free Days and LOS

Ventilator free days (VFD) during ICU stay were 9.5 days (±12.3) for patients who received aspirin compared to 8.8 days (±12.1) in the control group. However, a statistical difference was not reached between the two groups with a beta coefficient (95%CI): 0.11 (−0.47, 0.69), p-value of 0.71. Moreover, both ICU and hospital LOS were not statistically significant between the two groups with a beta coefficient (95%CI): −0.06 (−0.30, 0.18), p-value of 0.63, and beta coefficient (95%CI): 0.09 (−0.17, 0.35), p = 0.51, respectively (Table 2).Additionally, subgroup analysis showed similar outcomes in terms of VFD and LOS. (Table 4, 5).

Complications During ICU Stay

In the crude analysis, major bleeding events were not statistically significantly higher in patients who received aspirin than those who did not (6.3% vs. 2.8%; p = 0.12). Results from the multivariable logistic regression analysis; demonstrated a higher odds of major bleeding by three-fold; however, the difference did not reach the statistically significant (OR [95%CI]: 2.92 [0.91, 9.36], p = 0.07). Moreover, patients who received aspirin were shown to have a non-statistically significantly higher odds of minor bleeding (OR [95%CI]: 1.70 [0.68, 4.20], p = 0.26). Furthermore, the RBCs transfusion requirement was similar between the two groups (Table 3).

Interestingly, all thrombosis cases were twofold higher in patients who received aspirin (OR [95%CI]: 1.99 [0.95, 4.18], p = 0.06); however, this difference was not statistically significant. In terms of other secondary outcomes, such as respiratory failure requiring MV (OR:1.14, p = 0.75), acute kidney injury (OR:0.79, p = 0.27), and liver injury (OR:1.20, p = 0.59) did not differ substantially between the two groups (Table 3). Subgroup analysis showed that all thrombosis cases were three-fold higher in patients who received aspirin as a chronic medication (OR [95%CI]: 2.50 [0.93, 6.74], p = 0.07); however, it was not statistically significant (Table 5).

Follow-up Inflammatory Markers During ICU Stay

Most of the follow-up inflammatory markers during stay (eg, ferritin, CRP, and CPK) were the same between the two groups, except that D-dimer was significantly lower and the fibrinogen level was higher in patients who received aspirin in comparison to those who did not with a beta coefficient (95%CI): −2.84 (−3.32, −2.37), p-value <0.0001, and beta coefficient (95%CI): 0.62 (0.25, 0.99, p <0.001, respectively (Table 3).

Discussion

In this multicenter cohort study of 352 critically ill patients with COVID-19, we investigated the effect of aspirin on both mortality and in-hospital ICU complications. When examining mortality as an outcome, the in-hospital mortality was statistically significantly lower in aspirin users, but the 30-day mortality was similar between aspirin and non-aspirin recipients. Most of our patients (69.2%) were already taking aspirin prior to hospital admission and had a clear indication for aspirin continuation during the hospital stay. It is important to highlight that in our study, patients who received aspirin had more comorbidities (hypertension, dyslipidemia, CKD) at baseline. However, this difference didn't translate into higher mortality among that group.

The ideal thromboprophylaxis strategy to prevent the prothrombotic and hypercoagulable state induced by COVID-19 during critical illness remains unclear.[6–8] Currently, no guidelines endorse the use of aspirin to treat or prevent COVID-19 thromboembolism. Aspirin utilization is usually continued in patients with COVID-19 for other underlying conditions, such as microvascular thrombotic disease or post-Acute Coronary Syndrome (ACS). Several studies have investigated the mortality benefits of aspirin use in patients with COVID-19.[11,12,18–21] Nonetheless, the mortality benefit of aspirin was inconsistent among these studies. The Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial evaluated 14892 COVID-19 who were initiated on aspirin upon admission and were not receiving invasive MV. Aspirin did not reduce 28 days mortality among those patients however, it has been observed that aspirin recipients patients did have an increase in the rate of being discharged alive within 28 days, this observed effect was small (1% absolute difference). It is of highly importance to note not only did these patients differ from our patient population in terms of disease severity but they also differed in baseline comorbidities at baseline. For instance, heart disease and diabetes were prevalent in 11% and 22% respectively. In contrary, about 60% of our patients had diabetes at baseline and about 55% of our patients had hypertension. These are some of the risk factors that increases mortality with COVID-19 patients. Probably, that small benefit of patients being discharged alive could have been seen if those patients had higher risk factors for disease progression and severity.

An observational study conducted by Sahai et al found no mortality benefit when aspirin was used. However, this study included all hospitalized patients, and only 16.9% and 16.5% in the aspirin group were hemodynamically unstable and on vasopressors/inotropes, respectively.[19] Another small retrospective study investigated the use of aspirin in hospitalized patients with COVID-19. This study included patients who started aspirin within 24 hours of admission or 7 days before admission. After adjusting for confounders, aspirin use was

associated with a significantly lower risk of MV, ICU admission, and in-hospital mortality.[12] However, further conclusions remain difficult to draw. It is important to note that these studies, in addition to the retrospective observational nature, differed in their methodological approach. In addition, the inclusion criteria, illness severity, and pre-hospital aspirin use were varied in the existing literature.

It was postulated that combating thrombus formation through different pathways, such as antiplatelet or direct thrombin inhibitors, could potentially help overcome the cytokine storm associated with COVID-19 patients.[22] Interestingly, we observed a twofold increase in the all thrombosis cases in aspirin recipients. This observation could potentially be explained by the fact that these patients, due to their underlying risk, may require an additional new therapeutic approach or higher doses of aspirin may be warranted. However, this requires further investigation.

In this study, the mean VFDs and ICU LOS in patients who received aspirin were not statistically different from those in the control group. The mean ICU LOS was shorter in patients using aspirin, but the difference was not statistically significant. In contrast, a retrospective, observational cohort study of adult patients admitted to the hospital with COVID-19 in the United States reported longer hospital and ICU LOS with aspirin use.[12] A previous study also found that patients on aspirin had significantly lower rates of MV (35.7% aspirin vs. 48.4%, $P = .03$) and ICU admission (38.8% vs. 51.0%). Conversely, we found that the number of patients who developed respiratory failure requiring MV was not significantly different between the aspirin and control groups (54.8% vs. 53.2%, $P = .88$).

In two large studies evaluating aspirin use for the primary prevention of cardiovascular disease, aspirin use has shown an increase in bleeding risk.[23,24] It is important to note that these patients were not critically ill, as opposed to our study. In our analysis, patients who received aspirin had a higher odd of major and minor bleeding than those in the control group; however, this difference did not reach statistical significance ($P = 0.07$). It is worth mentioning that we excluded patients with thrombocytopenia (platelet count 50,000 or lower) and those with active bleeding within 24 hours of ICU admission from our study. In addition, the use of pharmacological DVT prophylaxis with different intensities was not statistically significant between the two groups before and after PS matching.

Aspirin use by itself is known to be a risk factor for bleeding, especially if concomitantly used with other anticoagulants.[23–25] The risk of bleeding is cumulative, and critically ill patients may be at a higher risk for bleeding due to several risk factors, including but not limited to respiratory failure requiring MV, coagulopathy, pharmacological DVT prophylaxis, disseminated intravascular coagulation, renal replacement therapy, and other invasive procedures.[26–28] Therefore, bleeding risk evaluation and benefit-risk assessment should be tailored to each patient. Larger studies are generally warranted to better assess bleeding risk in patients with COVID-19 treated with aspirin.

Despite using propensity score matching to minimize bias and adjust for confounders, this study has several limitations. First, the retrospective cohort nature of the study had some bias. Second, the pre-existing use of aspirin before hospital admission may preclude the accuracy of the potential benefit of aspirin and the appropriate time for initiation in naive COVID-19 critically ill patients. Third, the safety results may be confounded by the type of anticoagulation agents used and dosing intensity, which may augment the bleeding risk and mitigate the thrombosis risk. Due to these limitations, our results need to be confirmed in well-conducted randomized controlled trials. We are awaiting the release of the randomized controlled trial (PEAC) results investigating the benefit of aspirin use specifically in critically ill patients with COVID-19.[29]

Conclusion

The use of aspirin in critically ill patients with COVID-19 has been associated with a significant reduction in mortality during hospital stay. The risk of bleeding was also higher in these patients; however, the difference was not statistically significant. Thus, clinicians should assess the benefit of aspirin continuation or initiation during the ICU stay based on each patient's risk.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The study was approved in March 2021 by King Abdullah International Medical Research Center Institutional Review Board, Riyadh, Saudi Arabia (Ref.# NRC21R/058/02).

Consent to Participate

Participants' confidentiality was strictly observed throughout the study by using 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.

Consent for Publication

Not applicable.

Availability of Data and Material

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

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