

Evaluation of low-dose aspirin use among COVID-19 critically ill patients: A Multicenter Propensity Score Matched Study

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Abstract

Background

Multiple medications with anti-inflammatory effects have been used to manage the hyper-inflammatory response associated with COVID-19. Aspirin is used widely as a cardioprotective agent due to its antiplatelet and anti-inflammatory properties. Its role in hospitalized COVID-19 patients has been assessed and evaluated in the literature. However, no data regards its role in COVID-19 critically ill patients. Therefore, this study aims to evaluate the use of low-dose aspirin (81-100 mg) and its impact on outcomes in COVID-19 critically ill patients.

Method

This is a multicenter, retrospective cohort study for all adult critically ill 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 is the in-hospital mortality; other outcomes were considered secondary. Propensity score-matched used based on patient's age, SOFA score, MV status within 24 hours of ICU admission, prone position status, ischemic heart disease (IHD), and stroke as co-existing illness. We considered a P value of < 0.05 statistically significant.

Results

A total of 1033 patients were eligible; 352 patients were included after propensity score matching (1:1 ratio). The in-hospital mortality (HR (95%CI): 0.73 (0.56, 0.97), p-value=0.03) were lower in patients who received aspirin during hospital stay. On the other hand, patients who received aspirin have a higher risk of major bleeding compared to the control group (OR (95%CI): 2.92 (0.91, 9.36), p-value=0.07); but was not statistically significant.

Conclusion

Aspirin use in COVID-19 critically ill patients may have a mortality benefit; nevertheless, it may be linked with an increased risk of significant bleeding. The benefit-risk evaluation for aspirin usage during an ICU stay should be tailored to each patient.

Introduction

Coronavirus disease 2019 (COVID-19) cases are usually mild.(1) However, severe critical illness has been reported in 6–19% of patients.(1) Worsening of clinical symptoms can be related to variable degrees of endothelial dysfunction, coagulopathy, platelet dysfunction and hyper-cytokemia.(2) As a result, complications can in situ, such as acute respiratory distress syndrome (ARDS), septic shock, thromboembolism, and multiple organ failure (MOF).(3)

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

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

Several studies 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, the in hospital mortality was also reduced in patients who were hospitalized for COVID-19 management and were on aspirin. (11–13) Since aspirin is broadly available, cheap, and due to its potential benefit, we aimed to evaluate the efficacy and safety of aspirin use during ICU stay in critically ill patients with COVID-19.

Methods

Study design

Adult critically ill patients with confirmed COVID-19 who were hospitalized to the ICU at four hospitals between March 1, 2020, and March 31, 2021, were included in this multicenter, retrospective cohort research. The King Abdullah International Medical Research Center (KAIMRC) gave its approval to the study in March 2021 (Ref.# NRC21R/058/02). No informed consent was needed from the patients due to the retrospective observational nature of the study.

Study participants

Adults critically ill patients aged 18 and above 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 (RT-PCR). We intended to recruit all patients who matched the inclusion criteria. Patients were excluded if the ICU length of stay (LOS) was one day or death occurred within 24 hours of ICU admission, if they were identified as "Do-Not-Resuscitate" code status within 24 hours of ICU admission, if they had active bleeding and/or platelets counted 50,000 or less (Fig. 1). The eligible patients were subsequently categorized into two groups depending on their

usage of aspirin therapy during their ICU stay. Patients who received aspirin as a new initiation during ICU stay or as a continuation if prescribed in the pre-ICU period were included in the active group.

Study setting

The research was conducted in four Saudi hospitals: 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 King Abdulaziz Medical City (Riyadh).

Data collection

Each patient's data was collected and handled using Research Electronic Data Capture (REDCap®) software. Electronic medical record was reviewed to ascertain their demographic information, past medical history, and vital signs from patients' profiles. Moreover, laboratory tests within 24 hours of ICU admission, such as renal profile, liver function tests (LFTs), coagulation profile (i.e., INR, aPTT, fibrinogen, D-dimer), and inflammatory markers (i.e. Ferritin, procalcitonin, and creatine phosphokinase (CPK)) were collected. Also, tocilizumab, corticosteroids and pharmacological DVT prophylaxis use during ICU stay were recorded for eligible patients.

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 (GCS), acute kidney injury, prone status, mechanical ventilation (MV) needs, and MV parameters (e.g., PaO₂/FiO₂ ratio, FiO₂ requirement) within 24 hours of ICU admission were collected.

Furthermore, the eligible patients' minor bleeding, major bleeding, RBCs/platelet's transfusion, and other complications during ICU stay (i.e., AKI, liver injury, thrombosis, and respiratory failure required MV) were documented. All patients were tracked 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, and ICU-related complication (s) during ICU stay (i.e., major/minor bleeding, RBCs transfusion requirement, respiratory failure necessitating MV, AKI, and liver injury).

Outcome definition (s)

- The 30-day mortality was defined as the in-hospital death occurring for any cause within 30 days of the admission date during hospital stay.
- Major Bleeding defined as clinically overt bleeding with at least one of the following: Fatal, Symptomatic intracranial hemorrhage, retroperitoneal hemorrhage, 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 defined clinically significant bleeding not meeting the definition of major and leading to interruption of study drug surgical intervention or transfusion of 1 unit of blood.(14)
- Ventilator-free days (VFDs) at 30 days were calculated as the following: if the patients die within 30 days of MV, the VFDs = 0, VFDs = 30 – days after MV initiation (if patient survived and was successfully liberated from MV), and VFDs = 0 if the patient is on MV for > 30 days.
- Acute kidney injury (AKI) was defined as a sudden decrease of renal function within 48 hours, defined by an increase in absolute SCr of at least 26.5 $\mu\text{mol/L}$ (0.3 mg/dL) or by a percentage increase in SCr $\geq 50\%$ (1.5 \times baseline value) during ICU stay.(15)
- 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 during the ICU stay.
- Respiratory failure was defined as either low arterial carbon dioxide tension (PaCO_2) or hypoxemic respiratory failure ($\text{PaO}_2 < 60$ mm Hg with a normal or hypercapnic respiratory failure ($\text{PaCO}_2 > 50$ mm Hg) that requires mechanical ventilation.(16)

Statistical analysis

As applicable, we reported numerical variables (continuous variables) as mean and standard deviation (SD), or median with lower quartile (Q1) and upper quartile (Q3), and categorical variables as number (percentage). The normality assumptions for all numerical variables were evaluated using a statistical test (the Shapiro–Wilk test) and graphical representation (i.e., histograms and Q-Q plots). We assessed 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. The two groups' baseline characteristics, baseline severity, and outcome variables were compared. For 30-day and in-hospital mortality, multivariable Cox proportional hazards regression analyses were performed. Kaplan-Meier (KM) graphs were also generated for these outcomes. For the other outcomes included in this study, multivariable regression analysis and negative binomial regression were utilized. Regression analysis was done by consider PS score as one of the covariates in the model. The odds ratios (OR), hazard ratio (HR), or estimates with the 95% confidence intervals (CI) were reported as appropriate.

Propensity score matching (Proc PS match) (SAS, Cary, NC) was used to match patients who received aspirin therapy (active group) to patients who did not (control group) based on 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 scores for pairs of patients from the two groups was matched only if it was less than or equal to 0.5 times the pooled estimate of the standard deviation.

No imputation was made for missing data as the cohort of patients in our study was not derived from random selection. We considered a *P* value of < 0.05 statistically significant and used SAS version 9.4 for all statistical analyses.

Results

A total of 1033 patients were included in our analysis based on the eligibility criteria. Among them, 195 (18.8%) of those patients were receiving 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 higher eGFR, and higher ferritin levels at baseline. On the other hand, 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 using propensity score matching (Table 1, Additional file 1).

30-day and in-hospital mortality

In crude analysis, patients who received aspirin showed lower in-hospital mortality (55.7 % vs. 61.9 %, *p* = 0.24) and 30-days mortality (54.0 % vs. 55.4 %, *p* = 0.78) as compared with patient who didn't received aspirin, respectively. 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 matched as presented in the survival curve (Figure 2).

Ventilator free days and Length of stay

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, did not reach to a statistical difference between the two groups with a beta coefficient (95%CI): 0.11 (-0.47, 0.69), p-value 0.71. Moreover, both ICU and hospital length of stay were not statistically significant between the two groups with a beta coefficient (95%CI): -0.06 (-0.30, 0.18), p-value 0.63, and beta coefficient (95%CI): 0.09 (-0.17, 0.35), p-value 0.51; respectively (Table 2).

ICU Complications during ICU stay

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

Interestingly, venous thromboembolism was 3-fold higher in patients who received aspirin (OR (95%CI): 3.14 (0.83, 11.81), p-value=0.09); but this difference did not reach a statistical significance. In terms of other secondary outcomes such as respiratory failure required MV (OR:1.14, p-value=0.75), acute kidney injury (OR:0.79, p-value=0.27) and liver injury (OR:1.20, p-value=0.59) did not differ substantially between the two groups (Table 3).

Follow-up inflammatory markers during ICU stay and RBC transfusion

Most of the follow-up inflammatory markers during stay (e.g. Ferritin, CRP, and CPK) were the same between the two groups, except that D-dimer was significantly lower and 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-value <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 significant lower in aspirin users, but the 30-day mortality were similar between aspirin and non-aspirin recipients. The majority of our patients were already taking aspirin prior to hospital admission and had a clear indication for aspirin continuation during the hospital stay.

The ideal thromboprophylaxis strategy to prevent the prothrombotic and hypercoagulable state induced by COVID-19 during critical illness remains unclear.(6–8) Currently, no guideline endorses using aspirin to

treat or prevent COVID-19 thromboembolism. Aspirin utilization is usually continued in patients with COVID-19 for another underlying conditions such as microvascular thrombotic disease or post-acute coronary syndrome. Several studies have investigated the mortality benefit of aspirin use in patients with COVID-19.(11, 12, 17–20) Nonetheless, the mortality benefit of aspirin was inconsistent among these studies. While some studies observed no significant mortality reduction such as the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial. However, the study is not yet published, only the preliminary results were released.(19) Furthermore, patients' severity of illness and the condition at which aspirin was started or continued are unknown.

An observational study conducted by Sahai et al. found no mortality benefit with using aspirin. However, this study included all hospitalized patients and only 16.9% and 16.5% in aspirin group were hemodynamically unstable and on vasopressors/inotropes respectively.(18) Another small retrospective study investigated using aspirin for hospitalized patients with COVID-19. This study included patients started aspirin within 24 hours of admission or 7 days before admission. After adjusting for confounders, aspirin use was associated with statistically significant lower risk of mechanical ventilation, ICU admission and in-hospital mortality.(12) Yet, a further conclusion remains hard to draw. It is important to note that these studies in addition to the retrospective observational nature differed in their methodological approach. Also, inclusion criteria, illness severity, and pre-hospital aspirin use all were varied in the existing research literature.

It was postulated that combating the thrombus formation throughout different pathways such antiplatelet or direct thrombin inhibitor could potentially help overcoming the cytokine storm associated with COVID-19 patients.(21) Interestingly, we observed a threefold increase in VTE rate in aspirin recipients. Potentially this observation could 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 future investigation.

In this study, the mean VFDs and ICU LOS in patients who received aspirin were not statically different than the control group. The mean ICU LOS was shorter in patient's using aspirin but was not statistically significant. Contrary to that, 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) The previously mentioned study also found patient's on aspirin had significantly lower rates of MV (35.7% aspirin versus 48.4%, $P = .03$) and ICU admission (38.8% versus 51.0%). Conversely, we found that the number of patients who developed respiratory failure requiring MV was not statistically significant between the aspirin and control groups, respectively (54.8% versus 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.(22, 23) It is important to note that these patients were not critically ill, as opposed to our study. In our analysis, patients who received aspirin have a higher odd of major and minor bleeding compared to control; however, it did not reach statistical significance (P -value:0.07). It worth to mention, that we have excluded patients with thrombocytopenia (platelets count

50,000 or lower) and who have 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 anticoagulation.(22–24) 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.(25–27) 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 the bias and adjust for cofounders, this study remains to have several limitations. First, the retrospective cohort nature of the study leaves 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.(28)

Conclusion

The use of aspirin in critically ill patients with COVID-19 was associated with a significant reduction in mortality during hospital stay. The risk of bleeding was also higher in these patients however it wasn't statistically significant. Thus, the clinician should assess the benefit of aspirin continuation or new initiation during ICU stay to its risk for each patient individually.

Declarations

Acknowledgments

Not applicable.

Author contributions

All authors contributed to data collections, analysis, drafted, revised, and approved the final version of the manuscript.

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Availability of data and material

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

Ethics approval and consent to participate

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

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.

Competing interests

No author has a conflict of interest in this study.

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Table 1

Table 1 has been provided in the Supplementary Files section.

Tables 2-3

Table 2: Regression analysis for the outcomes after PS adjustment

Outcomes	n of outcomes/Total no-of patients			Hazard Ratio (OR) (95%CI)	P-value \$
	Control	Aspirin	P-value		
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
				beta coefficient (Estimates) (95%CI)	P-value \$*
Ventilator free days, Mean (SD)	8.8 (\pm 12.1)	9.5 (\pm 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
<p>Δ Denominator of the percentage is the total number of patients</p> <p>& Denominator is patients who survived.</p> <p>\wedge Wilcoxon rank sum test is used to calculate the P-value.</p> <p>$\wedge\wedge$ Chi-square test is used to calculate the P-value.</p> <p>\S Propensity score matched used based on patient's age, SOFA score, MV status, Prone position status, ischemic heart disease (IHD) and stroke as co-existing illness.</p> <p>\S^* Negative binomial regression is used to calculate estimates and p-value.</p>					

Table 3: Regression analysis for ICU complication (s) during ICU stay

Outcomes	n 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
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
				beta coefficient (Estimates) (95%CI)	P-value [§]
Ferritin level follow-up (Highest during ICU stay), 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
C-reactive protein (CRP) level follow-up (Highest during ICU stay), 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 level follow-up (Highest during ICU stay), 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 level follow-up (Highest during ICU stay), 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) level follow-up (Highest during ICU stay) , 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
<p>^{§*} Denominator of the percentage is non-mechanically ventilated patients with 24 hours of ICU admission.</p> <p>^Δ Denominator of the percentage is the total number of patients</p> <p>^{^^} Chi-square test is used to calculate the P-value.</p> <p>[^] Wilcoxon rank sum test is used to calculate the P-value.</p>					

\$ 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.

Figures

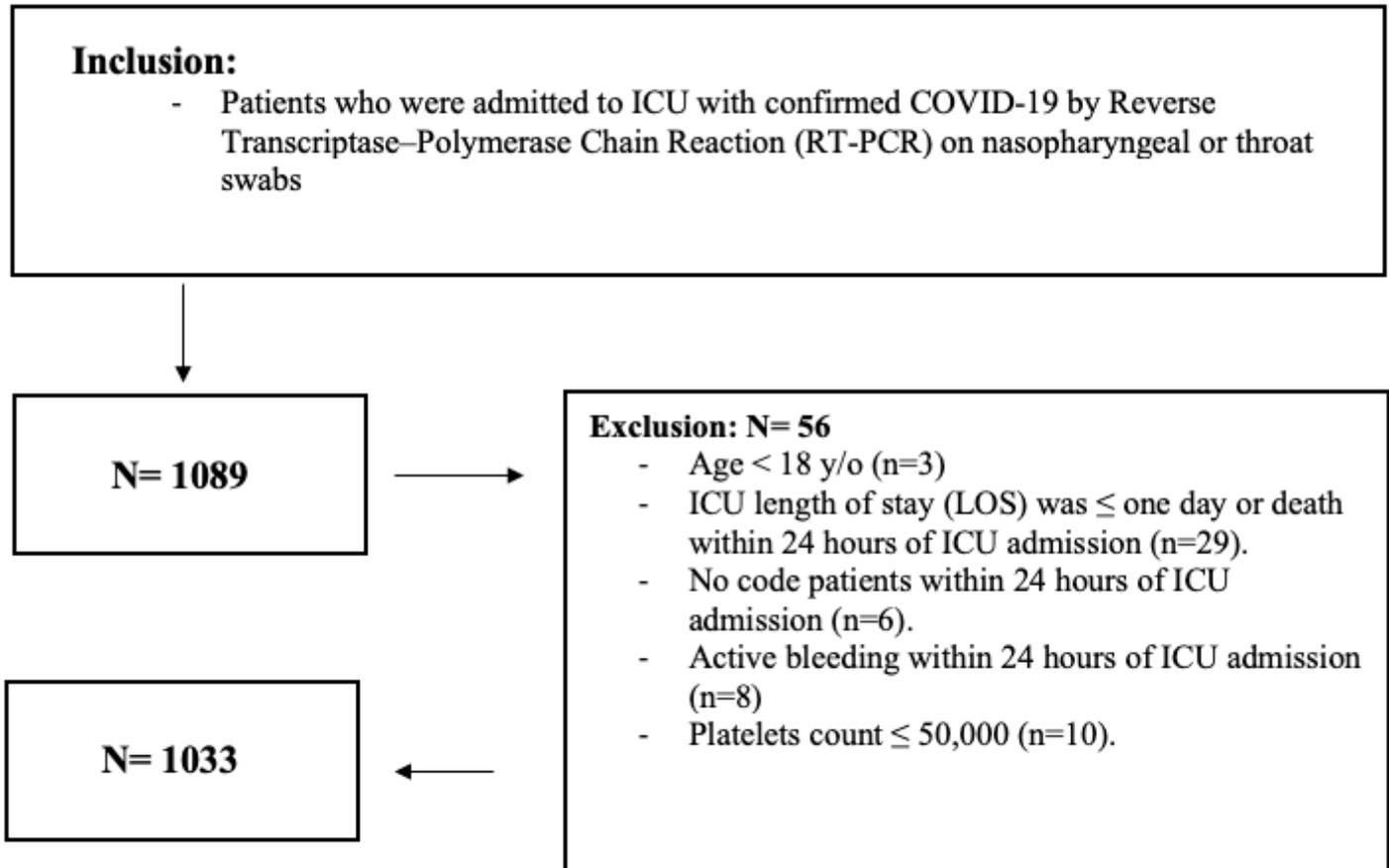


Figure 1

Flowchart

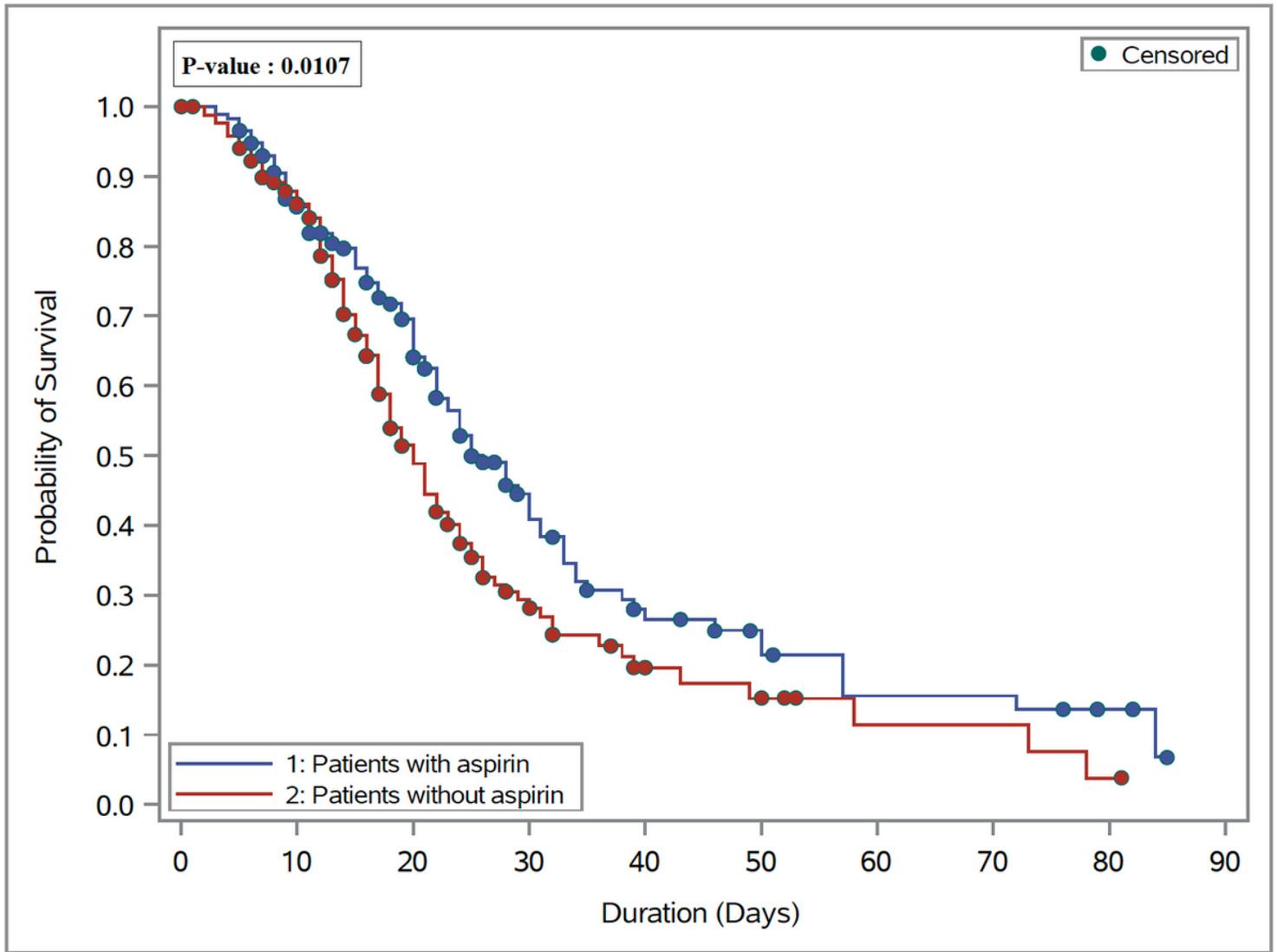


Figure 2

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

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile1Table1.docx](#)