

Statins' safety and impact on the clinical outcomes in COVID-19 critically ill patients: A Multicenter, Cohort Study

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Abstract

Purpose

The complications of Severe Corona Virus Disease 2019 (COVID-19) are attributed to the overproduction of early response proinflammatory cytokines, causing a systemic hyperinflammatory state. Statins are potentially a potent adjuvant therapy in COVID-19 infection due to their pleiotropic and anti-inflammatory effects, which are independent of their cholesterol-lowering activity. This study investigates the impact of statin use on the outcome of critically ill patients with COVID-19.

Methods

A multicenter, retrospective cohort study of 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 statin use during ICU stay and were matched with a propensity score which was based on patient's age and admission APACHE II and SOFA scores. The primary endpoint was in-hospital mortality. Other outcomes were considered secondary...

Results

A total of 1049 patients were eligible; 502 patients were included after propensity score matching (1:1 ratio). The 30-day (hazard ratio 0.75 (95% CI 0.58, 0.98), $P=0.03$) and in-hospital mortality (hazard ratio 0.69 (95% CI 0.54, 0.89), $P=0.004$) were significantly lower in patients who received statin therapy on multivariable cox proportional hazards regression analysis. Moreover, patients who received statin have a lower risk of hospital-acquired pneumonia (OR 0.48(95% CI 0.32, 0.69), $P<0.001$), lower levels of markers of inflammation on follow up and no increased risk of liver injury.

Conclusion

The use of statin during ICU stay in COVID-19 critically ill patients may have a beneficial role and survival benefits with a good safety profile.

Introduction

Since the spread of the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), leading to Corona Virus Infectious Disease 2019 (COVID-19) in 2019, over four million people have died worldwide[1]. Although the mortality of patients with COVID-19 is usually due to respiratory-related complications[2], growing evidence shows increased morbidity and mortality related to cardiac complications, including myocardial infarction, new or worsening heart failure, and new or worsening arrhythmia[3–5]. These complications are attributed to the overproduction of early response

proinflammatory cytokines, causing a systemic hyperinflammatory state in patients with severe COVID-19[6, 7].

The pre-existence of cardiovascular disease (CVD) or cardiovascular (CV) risk factors has been associated with poor prognosis and increased mortality of hospitalized patients with COVID-19[8, 9]. In critically ill patients with COVID-19, the risks of ICU and in-hospital mortality in patients with underlying heart failure were significantly higher, reaching 44.6% and 39%, respectively.[10] The use of statin therapy has been associated with reduced CV risk and CV death in non-COVID-19 patients[11]. Therefore, the international guidelines recommend using statin therapy in patients with atherosclerotic vascular disease (ASCVD) risk factors or existing ASCVD/CVD as primary or secondary prevention or cholesterol-lowering [12–14]. Statins have pleiotropic anti-inflammatory, antithrombotic and immunomodulatory effects which may decrease the endothelial dysfunction and inflammatory dysregulation present in patients with COVID-19[15–17]. Moreover, statin therapy has been reported to have antiviral activity through their immunomodulation and the suppression of viral replication suggesting that statins may have a role in treating viral infections[18]. These effects of statins suggest that they might have a promising role in preventing or treating patients with COVID-19.

Several observational studies reported inconsistent results about the benefit of statin use in patients with COVID-19[19–22]. However, only limited studies looked into their benefit in critically ill patients with severe COVID-19[23]. Hence, the benefit of statin therapy use in this population remains questionable. Thus, the aim of this study is to investigate the impact of statin use on the outcome of critically ill patients with COVID-19.

Methods

Study design

This was a multicenter, retrospective cohort study including adults critically ill patients confirmed COVID-19 and admitted to the Intensive care unit (ICU) from March 01, 2020, until March 31, 2021. The study was approved by King Abdullah International Medical Research Center (KAIMRC) in January 2021 (Ref.# NRC21R/015/R). Informed consent from the study patients was waived due to the retrospective observational nature of the study.

Study participants

We included adults (age \geq 18 years) admitted to the ICU with confirmed COVID-19. Patients were diagnosed with COVID-19 using Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) nasopharyngeal and/ or throat swabs. Patients were excluded if they were $<$ 18 years old, had ICU length of stay (LOS) \leq one day, or died or were labeled as "Do-Not-Resuscitate" within 24 hours of ICU admission (Fig. 1). Eligible patients were then classified into two groups based on the statin therapy use during ICU stay. Statins were prescribed in the ICU as part of the medication reconciliation process if they had been

prescribed in the pre-ICU period or were initiated in the ICU for various indications at the discretion of the ICU treating team.

Study setting

The study took place at four hospitals in Saudi Arabia; King Abdulaziz Medical City (Riyadh), King Abdulaziz University Hospital (Jeddah), King Abdullah bin Abdulaziz University Hospital (Riyadh), and King Salman Specialist Hospital (Hail). The primary site for this multicenter retrospective study was King Abdulaziz Medical City (Riyadh).

Data collection

Each patients' data were collected and managed using Research Electronic Data Capture (REDCap®) software hosted by King Abdullah International Medical Research Center (KAIMRC). We collected patients' demographic data, comorbidities, vital signs and laboratory tests, Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and Nutrition Risk in Critically ill (*NUTRIC*) scores, Glasgow Coma Score (GCS), statin therapy use (type and dose), acute kidney injury, use of prone positioning, receipt of mechanical ventilation (MV) and MV parameters (e.g., PaO₂/FiO₂ ratio, FiO₂ requirement) within 24 hours of ICU admission. Moreover, renal profile, liver function tests (LFTs), coagulation profile (i.e., INR, aPTT, fibrinogen, D-dimer), and inflammatory markers (Ferritin, procalcitonin and creatine phosphokinase (CPK)) within 24 hours of ICU admission were collected. Tocilizumab and corticosteroids use were recorded for the eligible patients. All patients were followed until they were discharged from the hospital or died during in-hospital stay, whichever occurred first.

Outcomes

The primary endpoint was the in-hospital mortality. The secondary endpoints were 30-day mortality, hospital LOS, ICU LOS, receipt of MV, ventilator-free days (VFDs) at 30 days, and ICU-acquired complications (new onset atrial fibrillation, AKI, liver injury, hospital-acquired pneumonia, and secondary fungal infection).

Outcome definition (s)

- The 30-day mortality was defined as a death occurring for any cause within 30 days of the admission date during hospital stay; patients who were discharged from the hospital alive were presumed to be survived. All patients were followed until they were discharged from the hospital or died during the in-hospital stay, whichever occurred first.
- 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[24].
- 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.
- Hospital-acquired pneumonia was defined as pneumonia that occurs ≥ 48 hours after admission and did not appear to be incubating at the time of admission[25].
- Secondary fungal infection was identified through the blood, urine, wound, drainage, cerebrospinal fluid, and/or respiratory cultures. The fungal growth was considered significant if the growth was $\geq 100,000$ colony forming units (CFUs)/ml in sputum or endotracheal aspiration, $\geq 10,000$ CFUs of single organism/ml in bronchoalveolar lavage or ≥ 1000 CFUs of single organism/ml in protected specimen brushes. Additionally, urinary cultures were considered significant if showing a growth $\geq 100,000$ CFUs/ml of no more than two species of microorganisms. Cultures were excluded if the laboratory reported them as a "contaminant sample." [26, 27]
- 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.

Statistical analysis

We presented numerical variables (continuous variables) as mean and standard deviation (SD), or median and lower quartile (Q1) and upper quartile (Q3), as appropriate and categorical variables as number (percentage). The normality assumptions were assessed for all numerical variables using a statistical test (i.e., Shapiro–Wilk test) and graphical representation (i.e., histograms and Q-Q plots). Model fit assessed using the Hosmer-Lemeshow goodness-of-fit test.

Baseline characteristics and outcome variables were compared between the two study groups. For categorical variables, we used the Chi-square or Fisher's exact test. We compared the normally distributed continuous variables using student t-test and other non-normally distributed continuous variables with the Mann-Whitney U test. Multivariable Cox proportional hazards regression analyses were performed for the 30-day and in-hospital mortality. Additionally, Kaplan-Meier (KM) plots were generated for these outcomes. Multivariable regression analysis and negative binomial regression were used for the other outcomes considered in this study. The odds ratios (OR), hazard ratio (HR), or estimates with the 95% confidence intervals (CI) were reported as appropriate. 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.

Propensity score matching procedure (Proc PS match) (SAS, Cary, NC) was used to match patients who received statin therapy (active group) to patients who did not (control group) based on patient's age and baseline severity scores (APACHE II and SOFA scores) within 24 hours of ICU admission. A greedy nearest

neighbor matching method was used in which one patient who received statin therapy (active) group matched with one patient who did not (control), which eventually produced the smallest within-pair difference among all available pairs with treated patients. Patients were matched only if the difference in the logits of the propensity scores for pairs of patients from the two groups was less than or equal to 0.5 times the pooled estimate of the standard deviation.

Results

A total of 1049 patients met our inclusion criteria. Of these patients, 279 (26.6 %) patients received statins during ICU stay. After propensity score matching, 502 patients were included (1:1 ratio) according to the selected criteria. The majority of the patients (86.4 %) received statin as a continuation due to underlying coexisting illness (e.g., DLP, IHD). Only twenty patients (8.6 %) required statin discontinuation during ICU stay, most often due to rhabdomyolysis (9 patients), followed by liver damage (8 patients). Atorvastatin (81.3 %) with a median dose of 20 mg was the most often used statin, followed by Rosuvastatin (14.1 %) with a median dose of 20 mg.

Demographic and Clinical Characteristics

The majority of the included patients in both arms were male (68.9 %) with a mean age of 61.6 (SD + 14.79). The predominant underlying comorbidities were diabetes mellitus (59.0 %), followed by hypertension (55.2 %) and dyslipidemia (19.3 %). There were some notable differences between the two groups before propensity score matching; patients who did not receive statin therapy (control group) were younger, had a higher APACHE II score, proning position status, total WBC count, D-dimer, ferritin, and creatine phosphokinase (CPK) levels baseline. Conversely, patients who received statins had significantly higher MV needs within 24 hours of admission, C-reactive protein (CRP) baseline, and systemic corticosteroids use during ICU stay compared with the control group. Following the propensity score matching based on patient's age and baseline severity scores (APACHE II and SOFA scores), most of these baseline and demographic characteristics were similar between the two groups. Summary of the patients' baseline characteristics is available in the (Additional file-1)

30-day and in-hospital mortality

In a crude analysis, there was no significant difference in the 30-day mortality (44.2 % vs. 49.2 %, $P=0.27$) or in-hospital mortality (46.8 % vs. 53.0 %, $P=0.57$) between the statin and the control group, respectively (Table 1). However, using the cox proportional hazards regression analysis, patients who received statin had a lower 30-day mortality (HR 0.75 (95% CI 0.58, 0.98)), $P=0.03$) as well as in-hospital mortality (HR 0.69 (95% CI 0.54, 0.89, $P=0.004$)) compared with the control group (Table 1). The overall survival probabilities were higher during hospital stay among patients who received statin therapy before and after propensity score-matched (Fig. 2).

Table 1
The outcomes of critically ill patients with COVID-19 after Propensity score matching

Outcomes	Number of outcomes/Total number of patients			Hazard Ratio (HR) (95%CI)	P-value \$
	Control	Statin	P-value		
30-day mortality, n (%) ^Δ	122/248 (49.2)	111/251 (44.2)	0.27 ^{^^}	0.75 (0.58, 0.98)	0.03
In-hospital mortality, n (%) ^Δ	132/249 (53.0)	117/250 (46.8)	0.17 ^{^^}	0.69 (0.54, 0.89)	0.004
				beta coefficient (Estimates) (95%CI)	P-value \$*
Ventilator free days, Mean (SD)	10.2 (± 12.3)	10.6 (± 12.2)	0.61 [^]	0.03 (-0.38, 0.45)	0.87
ICU Length of Stay (Days), Median (Q1,Q3) &	9.0 (5.0, 14.0)	11.0 (6.0, 19.0)	0.03 [^]	0.24 (0.07, 0.42)	0.007
Hospital Length of Stay (Days), Median (Q1,Q3) &	17.0 (12.0, 28.0)	20.0 (13.0, 33.0)	0.03 [^]	0.39 (0.21, 0.58)	< 0.0001
<p>Δ Denominator of the percentage is the total number of patients</p> <p>& Denominator is patients who survived.</p> <p>[^] Wilcoxon rank sum test is used to calculate the P-value.</p> <p>^{^^} Chi-square test is used to calculate the P-value.</p> <p>\$ Cox proportional hazards regression analysis used to calculate HR and p-value.</p> <p>\$* Generalized linear model is used to calculate estimates and p-value.</p>					

Ventilator free days and Length of stay

During the ICU stay, the mean ventilator-free days (VFD) was 10.6 days (± 12.2) and 10.2 days (± 12.3) in patients who received statin therapy compared to the control group respectively; however, it was not significant between the two groups (beta coefficient : 0.03 (95% CI -0.38, 0.45), $P = 0.87$). On the flip side, among those who survived during ICU stay, we observed that critically ill patients who received statin had a longer ICU length of stay (LOS) and hospital LOS with a (beta coefficient 0.24 (95% CI 0.07, 0.42), $P = 0.007$), and (beta coefficient 0.39 (95% CI 0.21, 0.58), $P < 0.0001$ respectively)) (Table 1).

Complications during ICU stay

Complications during ICU stay were reported in (Table 2). During ICU stay, we observed that patients who received statin were shown to have statistically significantly lower odds of hospital-acquired pneumonia

(bacterial or fungal) (OR 0.48(95% CI 0.32, 0.69), $P= 0.001$)). On the other hand, statin users have a higher odds for secondary fungal infection (OR 2.48(95% CI 1.44, 4.24), $P= 0.001$) compared with the control group. In terms of other complications during ICU stay, a respiratory failure that received MV, liver injury, AKI, and new-onset atrial fibrillation were not statistically significant between the two groups (Table 2).

Table 2
The ICU complications of critically ill patients with COVID-19 during stay

Outcomes	Number of outcomes/Total number of patients		P-value	Odds Ratio (OR) (95%CI)	P-value \$
	Control	Statin			
Respiratory Failure Required MV, n (%) \$*	47/85 (55.3)	28/58 (48.3)	0.41 ^{^^}	0.80 (0.40, 1.59)	0.53
New onset A fib., n (%) Δ ^	25/248 (10.1)	33/238 (13.9)	0.19 ^{^^}	1.44 (0.83, 2.50)	0.21
Acute kidney injury, n(%) Δ	98/251 (39.0)	100/251 (39.8)	0.85 ^{^^}	1.03 (0.72, 1.48)	0.87
Liver injury, n(%) Δ	32/251 (12.8)	19/251 (7.6)	0.05 ^{^^}	0.55 (0.30, 1.01)	0.05
Hospital acquired pneumonia, n(%) Δ	101/251 (40.2)	61/251 (24.3)	< 0.001 ^{^^}	0.48 (0.32, 0.69)	< 0.001
Secondary fungal infection, n(%) Δ	29/180 (16.1)	44/137 (32.1)	0.001 ^{**}	2.48 (1.44, 4.24)	0.001
Follow-up markers (Highest during ICU stay)			P-value ^	beta coefficient (Estimates) (95%CI)	P-value \$*
Ferritin level (ug/l), Median (Q1, Q3) Δ	936.9 (466.6, 1650.0)	732.3 (332.0, 2132.1)	0.18	0.18 (-0.06, 0.42)	0.14
D-dimer level (mg/l), Median (Q1, Q3) Δ	4.4 (1.98, 19.6)	3.0 (1.36, 8.15)	< 0.001	-3.00 (-3.40, -2.60)	< 0.001
Procalcitonin level (ng/ml), Median (Q1, Q3) Δ	0.45 (0.13, 1.76)	0.49 (0.13, 1.58)	0.77	-1.46 (-2.01, -0.91)	< 0.001
Creatine phosphokinase (CPK) level (U/l), Median (Q1, Q3) Δ	180.0 (71.0, 544.0)	180.0 (84.0, 540.0)	0.81	-0.07 (-0.37, 0.23)	0.65
Total WBC count (10 ⁹ /L), Median (Q1, Q3) Δ	16.5 (11.0, 23.7)	15.3 (11.0, 20.6)	0.13	-0.09 (-0.19, -0.005)	0.04

Outcomes	Number of outcomes/Total number of patients		P-value	Odds Ratio (OR) (95%CI)	P-value
	Control	Statin			
<p>§* Denominator of the percentage is non-mechanically ventilated patients with 24 hours of ICU admission.</p> <p>Δ^ Denominator of the percentage is non-atrial fibrillation as comorbidity.</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/** Fisher's Exact test is used to calculate P-value.</p> <p>^ Wilcoxon rank sum test is used to calculate the P-value.</p> <p>§ Cox proportional hazards regression analysis used to calculate HR and p-value.</p> <p>§* Generalized linear model is used to calculate estimates and p-value..</p>					

Follow-up inflammatory markers during ICU stay

The follow-up inflammatory markers such as D-dimer (p-value < 0.001), procalcitonin (p-value < 0.001), and total WBC count (p-value 0.04) were significantly lower during ICU stay in patients who received statin compared with the control group. In contrast, creatine phosphokinase (CPK) and ferritin levels were similar among the groups, as described in Table 2.

Discussion

In this retrospective, multicenter study, we investigated the impact of statin's use on the outcome of critically ill patients with COVID-19. Additionally, we evaluated the statins' effects on the ICU-acquired complications, including safety outcomes. After using cox proportional hazards regression analysis, patients who received statins had a lower 30-day mortality (HR 0.75 (95% CI 0.58, 0.98), $P=0.03$) as well as in-hospital mortality (HR 0.69 (95% CI 0.54, 0.89), $P=0.004$). Also, patients who received statins had significantly lower hospital-acquired pneumonia and inflammatory markers with no difference in liver injury ($P=0.05$).

This study demonstrated that statin therapy in ICU patients with COVID-19 was associated with reduced risks of 30-day and all cause in-hospital mortality. This benefit of statin might be attributed to its pleiotropic anti-inflammatory properties reducing the CPR levels and interleukin-6[28]. These inflammatory markers are known to increase during COVID-19 disease and increase the risk of mortality[28]. In addition, statins have an antioxidant effect and improves endothelial dysfunction, which might help decrease the CV events due to the hyper-coagulopathy status during the course of COVID-19[28]. Theoretically, statins can help reduce the cytokine storm that is usually associated with the poor prognosis of patients infected with COVID-19 [17]. They could also help in up-regulating ACE receptors, thus protecting the lung tissues from the harmful effects of the coronavirus[17]. Similar to our findings, a

meta-analysis conducted by *Kow et al.* reported a significant reduction in fatal or severe COVID-19 disease with the use of statins[17]. However, not all the included studies in this meta-analysis had critically ill patients in their study population[21]. On the other hand, another meta-analysis by *Scheen et al.* and an observational study by *Russo et al.* showed that the use of statins was not associated with mortality benefits in patients with COVID-19.[29, 30] This variation from our findings might be because studies were underpowered to detect such a difference[22, 30]. Also, they only included non-severe COVID-19 cases compared to our study that evaluated critically ill patients. A randomized controlled trial (INSPIRATION-statin trial) presented in the American College of Cardiology Virtual Annual Scientific Session (ACC 2021) comparing atorvastatin 20 mg daily vs. placebo showed that initiating statin in critically ill patients with COVID-19 was not associated with improvement in the primary outcome (all-cause death, venous or arterial thrombosis, or treatment with extracorporeal membrane oxygenation)[31] However, we are still awaiting the full report.

We found that the use of statins was not associated with any significant reduction in MVFD or in preventing respiratory failures that require MV eventually. Contrary to our findings, a preliminary study demonstrated a significant reduction in the risk of MV in patients using statin among patients infected with COVID-19 [32]. It is noteworthy that that study included non-ICU patients with COVID-19[32]. Additionally, we observed that critically ill patients who received statins had significantly longer ICU and in-hospital LOS. The higher survival rate could explain the prolonged ICU and hospital LOS in our cohort in the statins group due to several proposed mechanisms such as anti-inflammatory, pleiotropic effects, and antibacterial or antiviral effects[15–18]. Another explanation, the more prolonged ICU and in-hospital LOS may be secondary to higher odds of secondary fungal infection in patients who received statin therapy.

Besides the observed survival benefits in our study with statins therapy use in critically ill patients with COVID-19, we did not report any safety concerns related to statins' side effects or complications. Even though earlier reports from a cohort of 1099 patients with COVID-19 from China showed that up to 39.4% had AST > 40 U/L and 28.1% had ALT > 40 U/L, and most of these elevations occurred in critical COVID-19 cases[33]. We did not find any significant differences in liver injury among the statins and non-statins critically ill groups with COVID-19. Statin showed a good safety profile in our cohort. Still, its use might be hindered by clinicians' reluctance to utilize it in critically ill patients with COVID-19 due to (liver injury, myotoxicity, and rhabdomyolysis-related kidney injury). Therefore, continuing statin therapy as primary or secondary prevention is advisable prior to ICU admission and during ICU stay unless contraindicated.

We believe that our multicenter cohort study is one of few studies that evaluated statins' clinical and safety outcomes in COVID-19 critically ill patients using propensity score matching and multiple regression analysis to minimize the bias. Nevertheless, we also determined some limitations in our study. The retrospective nature of our study may have been affected by missing documentation that could be translated to unmeasured confounders. Also, the medication history use before admission might be affected by limited reconciliation during COVID-19 pandemics. Even though we observed mortality benefits, we did not assess the long-term benefit of statin use after COVID-19 survival. Thus a large

randomized controlled trial is needed to investigate the efficacy and safety of statin use in critically ill patients with COVID-19.

Conclusion

Statin use during ICU stay in COVID19 critically ill patients was associated with lower mortality risk with no safety concerns. The continuation or the initiation of statin therapy during the ICU stay in patients with COVID-19 might be a reasonable approach unless statins are contraindicated. The result of this multicenter retrospective study motivates prospective clinical studies to confirm our findings.

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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None.

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 January 2021 by King Abdullah International Medical Research Center Institutional Review Board, Riyadh, Saudi Arabia ((Ref.# NRC21R/015/R).

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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Figures

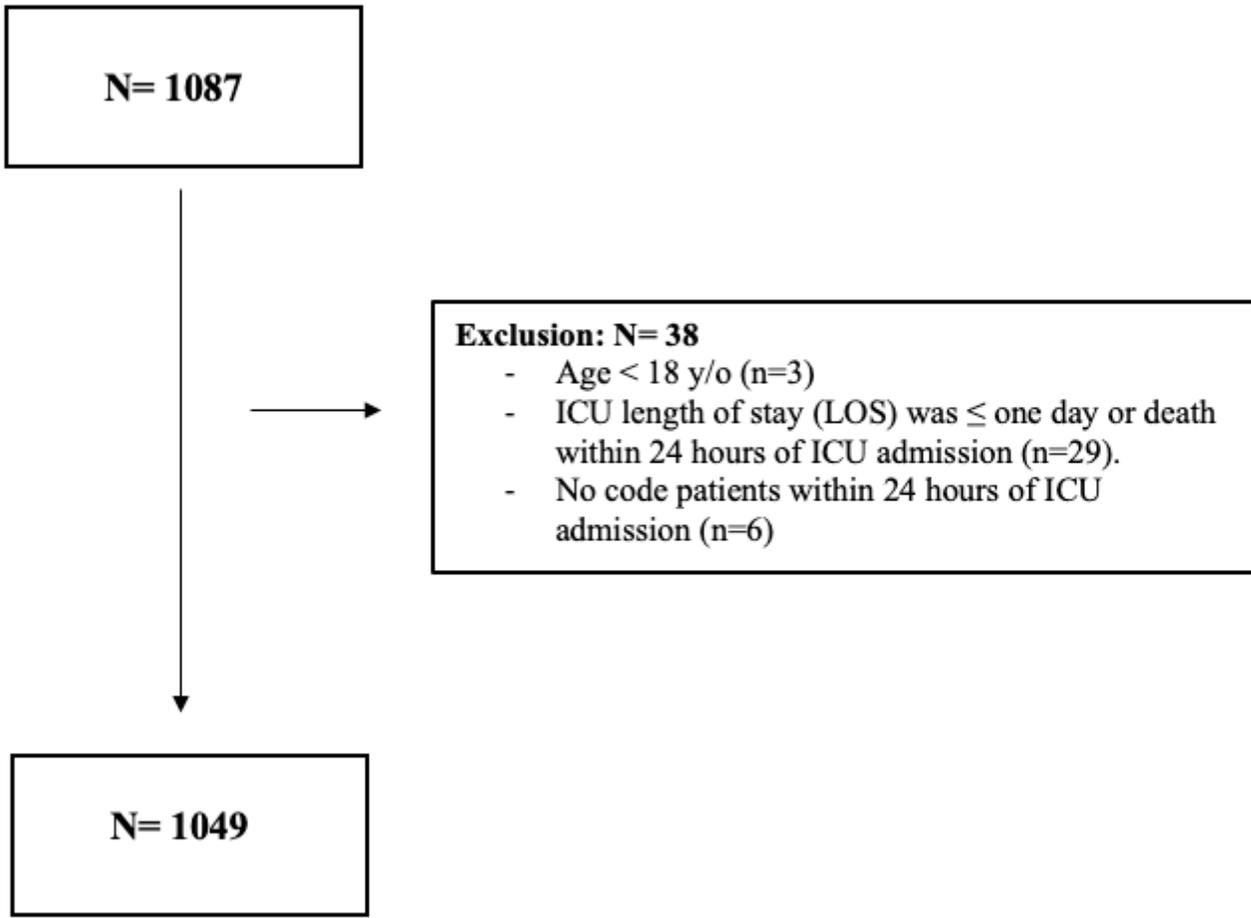


Figure 1

Critically ill patients with COVID-19 flowchart

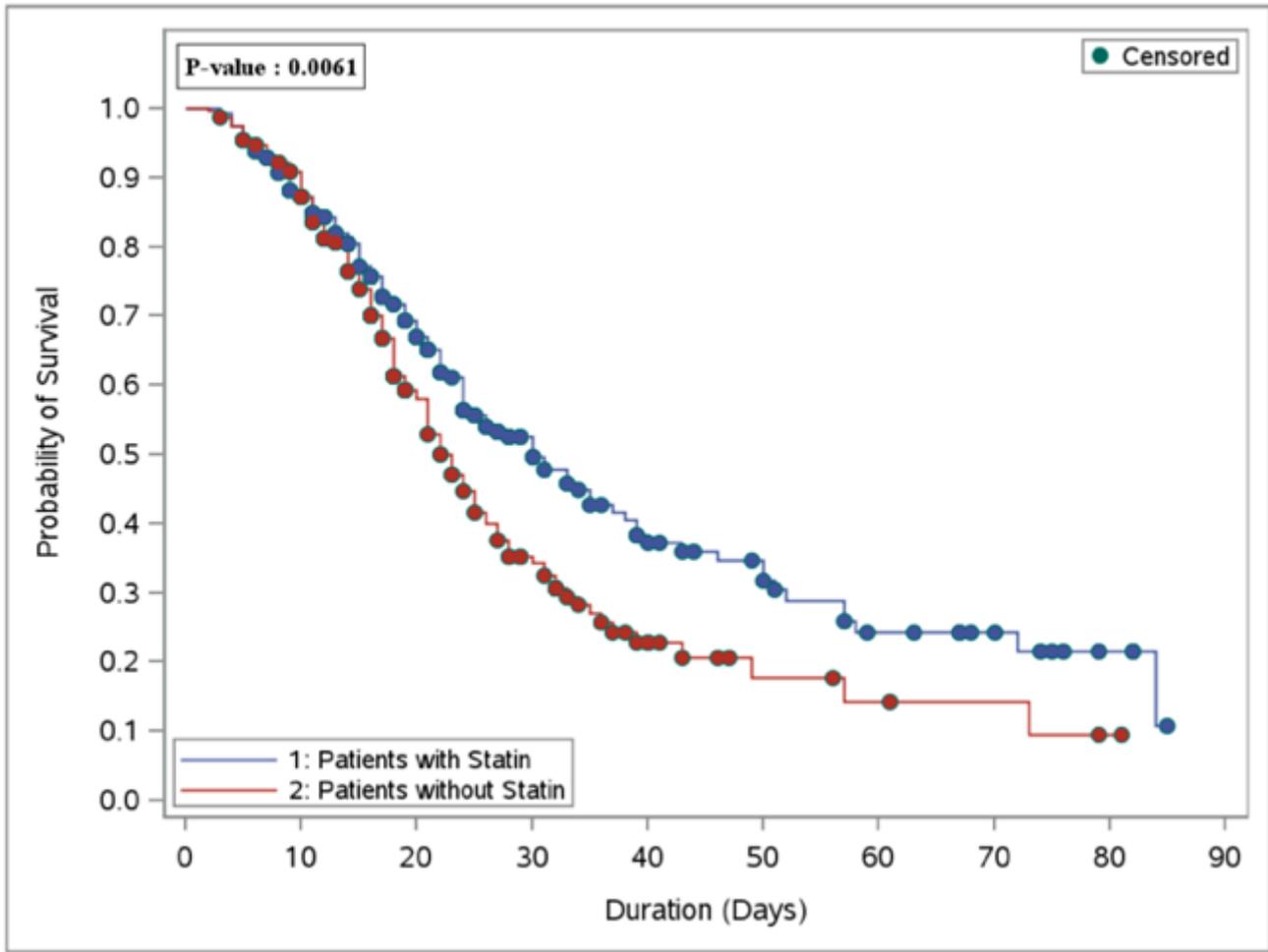


Figure 2

Overall survival plot during the hospital stay after PS matching comparing patients who received statin therapy (251 patients) versus the control group (251 patients).