Early Versus Late Use of Dexamethasone in Critically Ill Patients With COVID-19: A Multicenter, Prospective Cohort Study

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Abstract

Background:

Corticosteroids, especially dexamethasone, showed a survival benefit in critically ill COVID 19 patients. However, it is unclear whether the timing of dexamethasone initiation is associated with positive outcomes. The aim of this study is to evaluate the timing of dexamethasone initiation and 30-day ICU mortality in critically ill patients with COVID19.

Methods:

A multicenter, non-interventional, prospective study for all adult COVID19 admitted to intensive care units (ICUs) who received systemic dexamethasone between March 01 to December 31, 2020. Patients were divided into two groups based on the timing for dexamethasone initiation (early vs. late). Early use defined as the initiation of dexamethasone within three days of ICU admission. Multivariate logistic and generalized linear regression were used. We considered a P value of < 0.05 statistically significant.

Results:

A total of 475 patients were included in the study; dexamethasone was initiated early within three days of ICU admission in 433 patients. Early initiation of dexamethasone was associated with lower 30-day ICU mortality (OR [95%CI]: 0.43 [0.23, 0.81], p-value = 0.01), and acute kidney injury during ICU stay, (OR [95%CI]: 0.45 [0.21, 0.94], p-value = 0.03). Additionally, among survivors, early initiation was associated with shorter MV duration (beta coefficient [95% CI]: -0.94 [-1.477, -0.395], p-value = 0.0001), ICU length of stay (LOS) (beta coefficient [95%CI]: -0.73 [-0.9971, -0.469], p-value = 0.0001), and hospital LOS (beta coefficient [95%CI]: -0.68 [-0.913, -0.452], p-value = 0.0001).

Conclusion:

Early initiation of dexamethasone within three days of ICU admission in COVID-19 critically ill patients was associated with a mortality benefit. Additionally, it was associated with shorter MV duration, hospital, and ICU LOS.

Introduction:

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China, in 2019. Coronaviruses (CoVs) are ribonucleic acid (RNA), positive-stranded viruses with nucleocapsid, which can spread rapidly.[1,2] The mortality rate reported is around 40% in critically ill patients with comorbidities who were infected with SARS-CoV-2.[3,4]

Severe COVID-19 disease can enhance the systematic inflammatory response in critically ill patients, causing a systemic hyperinflammatory state, leading to multiple complications such as acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and thrombosis, which can increase mortality rate[4,5,6]. To date, no available treatment can work specifically against the SARS-CoV-2 infection, and limited therapeutic options are showing a positive impact for reducing the complications secondary to COVID-19 infection.[7]

Patients with moderate to severe COVID-19 are treated with antiviral medications, inflammation inhibitors/antirheumatic drugs, plasma, and hyperimmune immunoglobulins. Treating with systematic corticosteroids was a debate, but the fact that COVID-19 patients can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction made this class a potential therapeutic option.[8,9] It has been proposed that the potent anti-inflammatory mechanism of corticosteroids might prevent or mitigate these deleterious effects. 10,

RECOVERY trial, a multicenter, randomized, open-label trial performed in the United Kingdom, showed that a significant mortality reduction at 28-days in hospitalized patients who received dexamethasone for up to 10 days compared to patients who received the standard of care.[10,29] This benefit was observed in patients who were mechanically ventilated or required supplemental oxygen at enrollment[29]. Moreover, 44 studies have used a variety of corticosteroid strategies in COVID-19 patients.[11,12] The most used corticosteroid in these studies was methylprednisolone, while the least used were prednisone, dexamethasone, and hydrocortisone. The outcomes varied between studies; some reported longer hospital stay in the corticosteroid group, and others reported the opposite or no effect on hospital stay. Many studies reported a positive effect of corticosteroids on ventilator-free days, the number of patients requiring mechanical ventilation for respiratory failure, and the mechanical ventilator timing.

The timing of using systemic corticosteroids in critically ill patients with COVID 19 patients evaluated by Li Y. et al., who investigated the association of corticosteroids, especially methylprednisolone timing, and 90-day mortality.[13] They found a higher 90-day mortality rate with early initiation of methylprednisolone. A recent meta-analysis of a randomized controlled study showed that using corticosteroids must be discouraged in COVID 19 patients not requiring oxygen therapy as it increased the mortality rate in those patients.[14]

There is limited and unclear data regarding corticosteroid initiation's appropriate timing, especially dexamethasone in COVID-19 critically ill patients. This study aims to evaluate the proper timing of systemic dexamethasone initiation in critically ill patients with COVID19 and its clinical outcomes.

Methods

Study design

This is a multicenter, non-interventional, prospective study in critically ill patients aged > 18-years with COVID-19 (diagnosed according to reverse transcriptase-polymerase chain reaction (RT-PCR) obtained from nasopharyngeal or throat swabs), who were admitted to the ICU at two tertiary hospitals in Saudi Arabia from March 01, 2020, until December 31, 2020. We aimed to enroll as many patients as possible, with no predefined sample size. Patients were excluded if they did not receive corticosteroid therapy during ICU stay. The ICU length of stay (LOS) was less than one day, labeled as "Do-Not-Resuscitate" code status within 24 hours of ICU admission.

Eligible patients were classified into two groups based on the timing of dexamethasone initiation during ICU stay (early initiation and late initiation group. Early initiation was defined as systemic dexamethasone initiation within three days of ICU admission, whereas late initiation was defined as dexamethasone after three ICU admission days. Patients were followed during ICU stay. The study was approved by King Abdullah International Medical Research Center in July 2020 (Ref.# RC20/430/R).

Setting

This study was conducted in two tertiary governmental hospitals; King Abdulaziz Medical City, Riyadh, and King Abdulaziz University Hospital, Jeddah. The primary site for this multicenter study was King Abdulaziz Medical City (Riyadh).

Data collection

We collected demographic data (See additional file 1), 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), acute kidney injury, fluid balance, the needs for mechanical ventilation (MV) and MV parameters (e.g., Pao2/Fio2 ratio, Fio2 requirement) within 24 hours of ICU admission. Also, renal profile, liver function tests (LFTs), coagulation profile (i.e., INR, aPTT, fibrinogen), and inflammatory markers (CRP, procalcitonin) within 24 hours of ICU admission were collected. Tocilizumab use was recorded for the eligible patients. All patients were followed until they were discharged from the hospital or died during the in-hospital stay, whichever occurred first.

Outcomes

The primary endpoint was to evaluate the timing of dexamethasone initiation and its association with 30-day ICU mortality in critically ill patients with COVID 19. The secondary endpoints were to assess the in-hospital mortality, hospital LOS, ICU LOS, MV duration, ICU re-admission within three months and, ICU-related complication (s) during ICU stay (i.e., AKI, acute liver injury, respiratory failure requires MV, thrombosis/infraction).

Definition (s)

- Acute kidney injury (AKI) was defined using Acute Kidney Injury Network (AKIN) definition[15].

- Thrombosis/infraction was defined using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD10-CM) code (i.e., myocardial infarction (MI), ischemic stroke, pulmonary embolism, deep vein thrombosis) during ICU stay[16].
- Respiratory failure was defined as either hypoxemic respiratory failure (PaO_2 < 60 mm Hg with a normal or low arterial carbon dioxide tension ($PaCO_2$) or hypercapnic respiratory failure ($PaCO_2$ > 50 mm Hg) that requires invasive mechanical ventilation.
- 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 hospital stay.

Data management and Statistical analysis

We presented categorical variables as number (percentage), numerical variables (continuous variables) as mean and standard deviation (SD), or median and lower quartile (Q1) and upper quartile (Q3), as appropriate. 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).

We compared categorical variables using the Chi-square or Fisher 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. Baseline characteristics, baseline severity, and outcome variables were compared between the two groups. Multivariate logistic and generalized linear regression were used to find out the relationship between the timing of initiation with different outcomes considered in this study after adjusting for the age, the needs for mechanical ventilation (MV) within 24 hours of ICU admission, and study centers[4]. The odds ratios (OR) and estimates with the 95% confidence intervals (CI) were reported for the associations.

We assessed model fit using the Hosmer-Lemeshow goodness-of-fit test. 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 we used SAS version 9.4 for all statistical analyses.

Results:

Demographic and Clinical Characteristics

A total of 758 critically ill patients with COVID-19 were screened, 475 patients with COVID-19 have received dexamethasone during their ICU stay. Among the 475 patients, 435 patients (91.5 %) received dexamethasone early within three days of ICU admission. The majority of the patients were men (71.8%), and the mean age of the patients was 61 ± 14.2 years (Table 1, Supplemental Digital Content 1). The most common comorbidities were diabetes mellitus (63.7%), hypertension (58%), and dyslipidemia (24.4%); comorbidities were not significantly different between the two groups (Table 1).

Table 1
Co-existing illness

Co-existing illness	Overall (475)	Early (N = 435)	Late (N = 40)	P-value
Dyslipidemia, n (%)	115 (24.4)	109 (25.2)	6 (15.4)	0.17^^
Diabetes mellitus, n (%)	300 (63.7)	275 (63.7)	25 (64.1)	0.96^^
Hypertension, n (%)	273 (58.0)	252 (58.3)	21 (53.8)	0.59^^
Acute coronary syndrome (ACS), n (%)	4 (0.9)	4 (0.9)	0 (0.0)	> 0.99**
Asthma, n (%)	38 (8.1)	37 (8.6)	1 (2.6)	0.35**
Atrial fibrillation, n (%)	15 (3.2)	13 (3.0)	2 (5.1)	0.36**
Chronic obstructive pulmonary disease, n (%)	9 (1.9)	9 (2.1)	0 (0.0)	> 0.99**
Cancer, n (%)	21 (4.5)	19 (4.4)	2 (5.3)	0.69**
Chronic kidney disease- (Non-Dialysis), n (%)	35 (7.4)	31 (7.1)	4 (10)	0.80**
Chronic kidney disease- (On Dialysis) n (%)	16 (3.4)	15 (3.5)	1 (2.6)	
Coronary artery bypass grafting, n (%)	12 (2.6)	11 (2.6)	1 (2.6)	> 0.99**
Heart failure, n (%)	32 (6.8)	31 (7.2)	1 (2.6)	0.50**
Hypothyroidism, n (%)	30 (6.4)	28 (6.5)	2 (5.1)	> 0.99**
Ischemic heart disease, n (%)	42 (9.0)	39 (9.1)	3 (7.7)	> 0.99**
Liver disease, n (%)	11 (2.4)	10 (2.3)	1 (2.6)	> 0.99**

-Denominator of the percentage is the total number of patients

^^ Chi-square/ ** Fisher's Exact teat is used to calculate P-value.

The baseline severity scores (i.e., APACHE II, SOFA, and NUTRIC scores), Glasgow coma score (GCS), lactic acid, platelets count, CRP, CPK, ferritin, procalcitonin, PaO2/FiO2 ratio, and acute kidney injury within 24 hours of ICU admission, were not significantly different between the two groups. The median APACHE II score was 12, while the median SOFA score was 5. Two-thirds of patients needed MV within 24 hours of ICU admission. The patients had high median serum CRP and ferritin (154 mg/L and 845 g/L, respectively). Additionally, the difference in tocilizumab use during ICU stay was not significant between the two groups (Table 1, Supplemental Digital Content 1).

ICU and in-hospital mortality

ICU mortality within 30 days in both groups was 38.6% (n = 178), early initiation of dexamethasone was significantly lower compared with late initiation after adjusting for age, the need of MV within 24 hours of

ICU admission, and different hospital centers (OR (95% CI): 0.43 (0.23, 0.81), p-value = 0.01) (Table 2). Moreover, the in-hospital mortality was lower in the early initiation of dexamethasone by 40 %; however, it was not statistically significant (OR (95%CI): 0.60 (0.29, 1.22), p-value = 0.16), as shown in Table 2.

Table 2
Regression analysis for the outcomes

Outcomes	Dexamethasone				
	Early	Late	P value	Odds Ratio (OR) (95%CI)	P-value
30-day ICU mortality, n (%)	166/421 (39.4%)	12/39 (30.7%)	0.29^^	0.43 (0.231,0.813)	0.01*^
Hospital mortality, n (%)	197/428 (46%)	16/39 (41%)	0.55^^	0.60 (0.294 ,1.227)	0.16*^
ICU readmission within 3 months, n (%)	26/334 (7.8)	2/32 (6.3)	> 0.99**	1.10 (0.244, 4.962)	0.90*^
Acute kidney injury during ICU stay, n (%)	210/433 (48.4)	25/40 (62.5)	0.09^^	0.45 (0.215, 0.940)	0.03*^
Liver injury during ICU stay, n (%)	54/433 (12.4%)	3/40 (7.5%)	0.45**	1.68 (0.493 ,5.794)	0.40*^
Respiratory failure required MV during ICU stay, n (%) $	318/433 (73.4%)	34/40 (85%)	0.11^^	0.56 (0.147, 2.093)	0.38*^
Thrombosis during ICU during ICU stay, n (%)	39/429 (9%)	7/40 (17.5%)	0.09**	0.44 (0.18 ,1.073)	0.07*^
				beta coefficient (Estimates) (95%CI)	P-value
MV duration during ICU (days), Median (Q1, Q3) &	3.5 (1.00, 11.00)	13.0 (8.50, 22.00)	< 0.001^	-0.94(-1.477,-0.395)	< 0.001**^
Hospital length of stay (days), Median (Q1, Q3) &	16.0 (11.00, 24.00)	34.0 (28.00, 45.00)	< 0.001^	-0.68 (-0.913, -0.452)	< 0.001**^
ICU Length of Stay (days), Median (Q1, Q3) &	8.0 (5.00, 13.00)	22.0 (17.0, 28.00)	< 0.001^	-0.73 (-0.9971, -0.469)	< 0.001**^

Outcomes	Dexamethasone				
	Early	Late	P value	Odds Ratio (OR) (95%CI)	P-value
-Denominator of the percentage is the total number of patients					
*T -Test / ^ Wilcoxon rank sum test is used to calculate the P-value.					
^^Chi-square test is used to calculate the P-value.					
**Fisher Exact test is used to calculate the P-value.					
*^Multivariate Logistic regression is used to calculate p-value after adjusting for patient's age, the needs of MV within 24 hours of ICU admission, and hospital center.					
**^Generalized linear regression is used to calculate p-value after adjusting for patient's age, the needs of MV within 24 hours of ICU admission, and hospital center.					
$ Denominator of the percentage is non-mechanically ventilated patients with 24 hours of ICU admission.					
& Denominator is patients who survived.					

Length of stay and MV duration

Among survived patients who received dexamethasone early, we observed a significant shorter hospital length of stay (beta coefficient [95%CI]: -0.68 [-0.913, -0.452], p-value = 0.0001), ICU LOS (beta coefficient [95%CI]: -0.73 [-0.9971, -0.469], p-value = 0.0001), and MV duration (beta coefficient [95% CI]: -0.94 [-1.477, -0.395], p-value = 0.0001) compared to the late initiation of dexamethasone after ICU admission (Table 2).

ICU Complications during ICU stay

Overall, there were no significant differences between the early versus late initiation group in terms of the risk for developing respiratory failure (OR (95%CI): 0.56 (0.14 ,2.09), p-value = 0.38), acute liver injury (OR (95%CI): 1.68 (0.49 ,5.79), p-value = 0.40), and thrombosis during ICU stay (OR (95%CI): 0.44 (0.18 ,1.07), p-value = 0.0.07). However, early initiation of dexamethasone is significantly associated with a lower risk of developing acute kidney injury (OR (95%CI): 0.45 (0.21, 0.94), p-value = 0.03) during ICU stay, as shown in Table 2.

Discussion

Our study aimed to evaluate the effect of dexamethasone initiation time on critically ill COVID-19 patients' clinical outcomes. A total of 475 patients were included in the analysis; dexamethasone was initiated early within three days of ICU admission in the majority of the included 435 (91.5%) patients. After adjusting for age, need for MV within 24 hours of ICU admission, and study centers, we found that dexamethasone early initiation is associated with lower 30-day ICU mortality. Additionally, it was associated with shorter hospital LOS, ICU LOS, and MV duration among survived patients.

The clinical presentation of COVID-19 ranges in severity from asymptomatic mild disease to severe pneumonia, leading to acute respiratory distress syndrome (ARDS) and associated with a high mortality rate. 17,18. In critically ill COVID-19 patients, the clinical presentation of ARDS, massive vascular inflammation, disseminated intravascular coagulation, and shock is triggered frequently, with an ARDS occurrence rate of 17–41% of all cases [19,20]. The dysregulated inflammatory immune response observed with COVID-19 is similar to multifactorial ARDS, where plenty of evidence has proven corticosteroids ability to down-regulate the inflammatory immune response and accelerate disease resolution [21,22,23]. Although the World Health Organization (WHO) initially did not recommend using corticosteroids for COVID-19 treatment, as of September 02, 2020, the WHO recommended using systemic corticosteroids in critically ill patients with severe COVID-19 over no use [24]. Furthermore, the surviving sepsis guideline recommends steroid administration in severe COVID19 cases with ADRS requiring MV and patients with refractory shock [25].

Our study found survival benefits with the early initiation of dexamethasone in critically ill COVID-19 patients. Several previous studies have mixed results regarding the benefits of corticosteroid use in COVID-19 patients. A recent systematic review and meta-analysis compared the effect of corticosteroids versus standard of care; the study suggested that corticosteroids were associated with a significant reduction in the mortality rates in COVID-19 patients [26]. Furthermore, another meta-analysis by Sterne et al., that included data from seven randomized clinical trials aimed to evaluate the association between corticosteroids administration and 28-day all-cause mortality reported that corticosteroids associated with lower mortality rates compared with standard of care [27]. However, none of these meta-analyses included studies that assessed the association between the corticosteroids, specifically dexamethasone initiation time and mortality benefits.

In our study, early dexamethasone initiation was associated with a significant reduction in 30 days ICU mortality (p-value = < 0.01). Our results are in line with the RECOVERY trial findings, which conclude that the use of dexamethasone was associated with lower 28-day mortality among patients who received respiratory support [10]. However, the RECOVERY trial did not assess the effect of early dexamethasone initiation on the 30 days mortality [10]. The definition of early versus late corticosteroids initiation is debatable in critically ill patients in general and, more specifically, in COVID-19 patients. We decided to choose three days cutoff margin for early vs. late initiation definition based on clinical judgment. It is well known that COVID19 related lung injury and its associated hyperinflammatory and overreacting immune response occur early in ARDS presentation. Typically, if critically ill patients fail other supportive measures, early corticosteroid initiation can mediate downregulation of systemic and pulmonary inflammation, restore homeostasis, and enhance disease resolution.

The present study found shorter hospital length of stay (LOS), ICU LOS, and MV duration in the early group compared to the late group of dexamethasone. In parallel to our findings, a recent prospective study by Monedero et al. compared outcomes between patients who received either early, delayed, or not received corticosteroids. They found that early corticosteroids use in critically ill COVID19 patients

associated with shorter MV duration and less ICU LOS [28] This study results could be limited by the fact that they combined no steroids and late initiation in one group, and they included patients who received steroids earlier before ICU admission in the early group. In our study, the two groups have similar baseline characteristics with a defined cutoff margin of corticosteroid initiation time based on the ICU admission timeframe. Moreover, we only included patients who received dexamethasone to have a consistent comparison with the RECOVERY trial [10]. Additionally, to further investigate if early dexamethasone initiation is different from just initiating dexamethasone at any given point.

In terms of ICU complications during ICU stay, our study found that early initiation of dexamethasone was associated with a lower incidence of acute kidney injury. That could be related to dexamethasone's prolonged and potent anti-inflammatory effect on downregulation of the inflammation and enhancing disease resolution. Our findings are consistent with Monedero et al. [28]; they reported a lower rate of acute renal failure in the early group. Moreover, in our study, we assessed the complication of having respiratory failure required MV during ICU stay for patients who were not initially ventilated and found no difference between the groups. However, Monedero et al. [28] reported a lower rate of mechanical ventilation in the early steroids group.

We believe that our multicenter prospective cohort study is the first study that highlights the appropriate time of dexamethasone initiation and its effects on critically ill COVID19 patients' mortality and morbidity. It is prospective design allows to prospectively explore the association between the time of dexamethasone therapy initiation in COVID-19 patients with ICU mortality. Additionally, it had a predefined cutoff margin of early vs. late initiation time, and it assessed several important clinical outcomes in the final analysis. Nevertheless, we also determined some limitations to our study. First, the observational nature of the study design and some residual confounding factors are still possible. Second, this study only focused on the ICU-related outcomes, but the safety outcomes and steroids-related side effects need to be addressed in further studies. Third, we cannot exclude missing data for some variables due to the observational design. Lastly, there was a dynamic change in the national and international COVID-19 management guidelines as more evidence continued to emerge, which affected the general practice.

Conclusion

Our multicenter, prospective cohort study showed that early initiation of dexamethasone within three days of ICU admission in COVID19 critically ill patients was associated with a 30-day ICU mortality benefit. Further randomized clinical and interventional studies are needed to confirm our findings.

Declarations

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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 July, 2020 by King Abdullah International Medical Research Center Institutional Review Board, Riyadh, Saudi Arabia (Reference No: RC20/430/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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Tables

Table 1: Co-existing illness

ng illness	Overall (475)	Early (N=435)	Late (N=40)	P-value
lemia, n (%)	115 (24.4)	109 (25.2)	6 (15.4)	0.17^^
s mellitus, n (%)	300 (63.7)	275 (63.7)	25 (64.1)	0.96^^
nsion, n (%)	273 (58.0)	252 (58.3)	21 (53.8)	0.59^^
oronary syndrome (ACS), n (%)	4 (0.9)	4 (0.9)	0 (0.0)	>0.99**
n (%)	38 (8.1)	37 (8.6)	1 (2.6)	0.35**
brillation, n (%)	15 (3.2)	13 (3.0)	2 (5.1)	0.36**
obstructive pulmonary disease, n (%)	9 (1.9)	9 (2.1)	0 (0.0)	>0.99**
n (%)	21 (4.5)	19 (4.4)	2 (5.3)	0.69**
kidney disease- (Non-Dialysis), n (%)	35 (7.4)	31 (7.1)	4 (10)	0.80**
kidney disease- (On Dialysis) n (%)	16 (3.4)	15 (3.5)	1 (2.6)	
y artery bypass grafting, n (%)	12 (2.6)	11 (2.6)	1 (2.6)	>0.99**
ilure, n (%)	32 (6.8)	31 (7.2)	1 (2.6)	0.50**
roidism, n (%)	30 (6.4)	28 (6.5)	2 (5.1)	>0.99**
c heart disease, n (%)	42 (9.0)	39 (9.1)	3 (7.7)	>0.99**
sease, n (%)	11 (2.4)	10 (2.3)	1 (2.6)	>0.99**

nator of the percentage is the total number of patients
quare/ ** Fisher's Exact teat is used to calculate P-value.

Table 2: Regression analysis for the outcomes

nes	Dexamethasone				
	Early	Late	P value	Odds Ratio (OR) (95%CI)	P-value
ICU mortality, n (%)	166/421 (39.4%)	12/39 (30.7%)	0.29^^	0.43 (0.231,0.813)	0.01*^
al mortality, n (%)	197/428 (46%)	16/39 (41%)	0.55^^	0.60 (0.294 ,1.227)	0.16*^
admission within 3 months, n	26/334 (7.8)	2/32 (6.3)	>0.99**	1.10 (0.244, 4.962)	0.90*^
kidney injury during ICU (%)	210/433 (48.4)	25/40 (62.5)	0.09^^	0.45 (0.215, 0.940)	0.03*^
njury during ICU stay, n (%)	54/433 (12.4%)	3/40 (7.5%)	0.45**	1.68 (0.493 ,5.794)	0.40*^
atory failure required MV ICU stay, n (%) $	318/433 (73.4%)	34/40 (85%)	0.11^^	0.56 (0.147, 2.093)	0.38*^
bosis during ICU during ICU (%)	39/429 (9%)	7/40 (17.5%)	0.09**	0.44 (0.18 ,1.073)	0.07*^
				beta coefficient (Estimates) (95%CI)	P-value
ration during ICU (days), n (Q1, Q3) &	3.5 (1.00, 11.00)	13.0 (8.50, 22.00)	<0.001^	-0.94(-1.477,-0.395)	<0.001**^
al length of stay (days), n (Q1, Q3) &	16.0 (11.00, 24.00)	34.0 (28.00, 45.00)	<0.001^	-0.68 (-0.913, -0.452)	<0.001**^
ength of Stay (days), Median)3) &	8.0 (5.00, 13.00)	22.0 (17.0, 28.00)	<0.001^	-0.73 (-0.9971, -0.469)	<0.001**^

minator of the percentage is the total number of patients
t / ^ Wilcoxon rank sum test is used to calculate the P-value.
·square test is used to calculate the P-value.
er Exact test is used to calculate the P-value.

ivariate Logistic regression is used to calculate p-value after adjusting for patient's age, the needs of MV within rs of ICU admission, and hospital center.

neralized linear regression is used to calculate p-value after adjusting for patient's age, the needs of MV within 24 of ICU admission, and hospital center.

minator of the percentage is non-mechanically ventilated patients with 24 hours of ICU admission.

ominator is patients who survived.

Supplementary Files

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- Additionalfile1Table1.docx