Corticosteroid Therapy of Patients in ICU with Coronavirus Disease 2019(COVID-19): A Single-center, Retrospective, Observational study

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Research

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Abstract

Background

In December 2019, Coronavirus Disease 2019(COVID-19)occurred in Wuhan, China. The disease is a rapidly spreading to the world. Corticosteroid therapy is used among critically ill patients with COVID-19, but value of corticosteroid therapy is uncertain.

Objective

To investigate the association of corticosteroid therapy on intubation rates.

Methods

This was a retrospective, single-center, observational study performed in ICU at Jin Yin-tan hospital, Wu Han, China. 102 patients with COVID-19 admitted to ICU from 2019.12.31 to 2020.03.31 were selected as the research objects. The clinical data were collected to analyze the general characteristics, clinical symptoms, blood test and corticosteroid therapy. The intubation rate between corticosteroid therapy and non-corticosteroid therapy was compared.

Results

Baseline characteristics of patients between corticosteroid therapy and non-corticosteroid therapy were similar.($p > 0.05$). We found that there was no significant difference of intubation rate between corticosteroid therapy and non-corticosteroid($P = 0.575$), but there was a significant difference in noninvasive ventilation time between the two groups($P = 0.02$).

Conclusion

Corticosteroid therapy cannot reduce intubation rate in ICU patients with COVID-19.

Background

In December 2019, a kind of acute respiratory illness, known as Coronavirus Disease 2019(COVID-19), occurred in Wuhan, Hubei Province, China. The disease is a rapidly spreading to the world. COVID-19 is a rapidly spreading infectious disease that can may cause acute respiratory distress syndrome (ARDS)[1, 2].The current treatment strategies of COVID-19 with ARDS are mainly anti-viral therapy and oxygen therapy. Noninvasive respiratory support is often given first in patients with COVID-19 who have ARDS. Some studies suggest that corticosteroid therapy may have some effects in patients with ARDS[3, 4].The purpose of this study is to explore the value of corticosteroid therapy in ICU of patients with non-invasive respiratory support for COVID-19.

Methods

Study design

This was a retrospective, single-center, observational study performed in intensive care unit (ICU) at Jin Yintan hospital (Wuhan, China), which was a designated Grade hospital to treat patients with COVID-19. The research was conducted in accordance with the Declaration of Helsinki. We retrospectively investigated critical patients who had been diagnosed with COVID-19 from December 31, 2019 to March 31 2020. Critical patients were defined as those admitted to ICU who required noninvasive respiratory support encompasses strategies included noninvasive ventilation(NIV) and high-flow nasal cannula (HFNC) therapy. The data used in analysis were obtained from all available electronic medical records and nursing record. This study protocol was approved by the Research Ethics Committee of Jin Yintan hospital（KY-2020-06.01）.

We evaluated whether the corticosteroid therapy could reduce the tracheal intubation rate in critical patients.

Definition of study procedures

COVID-19 is a highly infectious disease, the blood gas analysis can not be measured continuously and in real time. But SpO_2 is real-time detection and more able to reflect the state of patients. Instead, we used SpO_2/FiO_2 (S/F) which can be obtained objectively. Studies have shown that SpO_2/FiO_2 (S/F) can also be used as an important indicator for predicting the prognosis of ARDS [5-7]

All included patients received noninvasive respiratory support encompasses strategies including noninvasive ventilation(NIV), and high-flow nasal cannula (HFNC) therapy[8]. For patients who were treated with corticosteroid, the therapy was initiated after they admitted to ICU. The main exposure was corticosteroid therapy, defined as the use of systemic corticosteroids. Corticosteroid therapy in this retrospective study was methylprednisolone.

Inclusion and exclusion criteria

Study participants met the following inclusion criteria: (1) aged >= 18 years, (2) patients were diagnosed with COVID-19, (3) patients were admitted to ICU, (4) patients received noninvasive respiratory support including noninvasive ventilation(NIV) and high-flow nasal cannula (HFNC) therapy[8], and (5) $SpO_2/FiO_2<315$ [7].

The exclusion criteria were as follows: (1) Patient data were incomplete and did not meet the trial design requirements. (2) Patients received chronic corticosteroid therapy before the onset of critical illness. (3) Worsening of the condition due to other causes.(4) Patients who admitted to ICU required invasive ventilation in 2 hours.

Outcome measures

Our main outcome was the intubation rate in patients after corticosteroid therapy.

Statistical analysis

Patient baseline characteristics were collected from the patients entering the ICU. Data analysis was performed by use of IBM SPSS for Windows, version 22 (SPSS Inc., Chicago, IL, United States). Normal or non-normal distribution of the data was determined with the Shapiro Wilk test. Levene's test was used to evaluate homogeneity of variances. If the differences and variations between groups were found not significant, a parametric Independent-sample T test was performed. If parametric tests were not acceptable, non-parametric statistical methods (Mann–Whitney test) were used in evaluation of the data. Data are expressed as mean±standard deviation (SD) or median(quartile) for continuous data. The counting data have been given as number of cases and/or as percentage (%), and chi square test was used for comparison between groups. Survival curves were generated by the Kaplan–Meier method. A p-value less than 0.05 was considered as statistically significant.

Results

General characteristics

Collected from 2019.12.31 to 2020.3.31, ICU eligible patients were total of 125 patients. Nine patients were excluded because their data were incomplete and did not meet the trial design requirements. Two patients received chronic corticosteroid therapy before the onset of critical illness were excluded. Nine patients were intubated within 2 hours after entering the ICU and were excluded. Finally, three people were excluded because of worsening of the condition due to other causes.We eventually included 102 critically ill patients, as figure 1. Among them, 65 patients were males (63.7%) and 37 females (36.3%). The age range was 34-89 years, with a median of 64 years. 79 patients had tachypnea, 24 patients had tachycardia, and 37 had a fever. Some patients had comorbidities, including hypertension (n=38[37.3%]), coronary heart disease (CHD)(n=13[12.7%]), diabetes (n=19[18.6%]), chronic lung disease (n=5[4.9%]), chronic gastrointestinal disease (n=9[8.8%]), tumor (n=5[4.9%]). See table 1.

Laboratory characteristics

Among the 102 patients, there were 48 patients(47.1%) with increased leukocytes, while 5 patients had leukopenia, but 87 patients(85.3%) with lymphocytes decreased. CRP median was 126.0mg/L and was increased in 97 patients(95.1%). AST median was 44.5U/L, ALT median was 45.0U/L, TBil median was 16.1umol/L and DBil median was 6.3umol/L. 60 patients(58.8%) demonstrated liver injury with elevated aspartate aminotransferase, and 46 patient (45.1%) had increased alanine aminotransferase. Some patients demonstrated kedney injury with elevated BUN and Cr. Among them, the abnormal increase in TNI accounted for 38.2%. The clinical features of cardiac function injury in ICU patients were also observed, and TNI and BNP were significantly increased. DDimer abnormally increased in 73.5% of ICU patients. See table 1 and table 2.

Corticosteroid therapy and survival curve

A total of 102 patients met the eligibility criteria for this study. Within the study period, 52 of these patients received corticosteroid therapy. Table 2 showed characteristics between patients with and without corticosteroid therapy. The median age of the patients in the corticosteroid group was 63, the median age of the non-corticosteroid group was 65.5(P=0.062). In addition, males(69.2%) were in the corticosteroid group and males(58%) were in the non-corticosteroid group , and there was no difference between the two gender groups(P=0.238). We also compared basic vital signs, including heart rate, respiration, and temperature, but there was no significant differences between the corticosteroid and the non-corticosteroid group. In addition, the patients' white blood cells, hemoglobin, lymphocytes and platelets were similar. There was no difference in liver, kidney, and heart function indicators between the corticosteroid and the non-corticosteroid group(AST、ALT、TBil、DBil). We found that there was no significant difference of SpO_2/FiO_2 (P=0.09) between the corticosteroid and the non-corticosteroid group. We also compared patients with various underlying disease, and also found no significant difference in the use of corticosteroid or not. Fig 2 showed the patient's onset of corticosteroid therapy initiation from ICU admission. Patients with corticosteroid therapy were divided into three groups based on the daily dosage of the therapy they received (Table 3): 1) 40mg, 2)80mg, and 3)160mg. We found that there was no significant difference of intubation rate between corticosteroid therapy and non-corticosteroid(P=0.575), but there was a significant difference in noninvasive ventilation time between the two groups(P=0.02). As shown in Table 3, in 52 patients with corticosteroid therapy group, more than a half of patients (27, 51.9%) started methylprednisolone at a daily dose of 80mg, 21 patients(40.4%) initiated methylprednisolone at a daily dose of 40mg, Only 4 patients initiated methylprednisolone at a daily dose of 160mg.

The median survival time of non-corticosteroid group was 8 days (95%CI;3.67,12.33), and the median survival time of the non-corticosteroid group was 11 days (95%CI;4.82,17.18). No significant survival difference was found between the two groups (χ^2=0.131, P=0.717). Inconsistent patient admission times can lead to differences in observation time and can also lead to bias in survival time results.

Discussion

ARDS is a pulmonary manifestation of a severe systemic inflammatory response. A variety of inflammatory cells, inflammatory mediators and cytokines are involved in this complex pathophysiological process[9].ARDS are mainly manifested as inflammatory disorders, inappropriate accumulation and activation of leukocytes and platelets, uncontrolled coagulation activation and permeability of the alveolar-capillary barrier damage.

Methylprednisolone is the most commonly used corticosteroid therapy for ARDS, and many studies have controversy on using of Methylprednisolone. Despite improvements some parameters in the cardiopulmonary, a study published in the new england journal of medicine[10] suggested that it is not routine use of methylprednisolone for persistent ARDS. In addition, the research found that methylprednisolone treatment more than two weeks after the onset of ARDS may increase the risk of death. One research have even found that[11], long-term application of used a methylprednisolone dose of 0.125-2 mg/kg/day reduced patient immunity. Other research found that[12], using high-dose methylprednisolone(1 g/d) could not improve the prognosis of patients, or even increase the 60-day mortality and decrease the number of ventilator-free days of patients. There was no difference in the number of mechanical ventilation, blood and biochemical parameters between SARS induced high-dose pulse methylprednisolone (> = 500 mg/day) and nonpulse (< 500 mg/day) [13]. In our study, methylprednisolone was used at a low dose of 0.5-2 mg/kg/day. The methylprednisolone dose used of this study was 0.5-2 mg/kg/day. Our results showed low-dose methylprednisolone did not decrease the intubation rate of patients. It may be due to the new coronavirus is different from previous pathogens.

The mechanism of COVID-19 leading to ARDS is not clear. The most common manifestations of patients are fever, weakness, respiratory distress and respiratory failures[1, 14]. A few of anatomical results [12] showed that the pathological changes of COVID-19 were associated with ARDS. The lungs showed diffuse alveolar injury and pulmonary hyaline membrane formation, which were similar to ARDS. The pulmonary pathology are similar to SARS and MERS. Lymphocyte-dominated mononuclear cells infiltration of inflammatory infiltration were in both pulmonary interstitium. In the alveolus cavity, multinucleated giant cells and atypically enlarged alveolar cells appear. Among them, the atypically enlarged alveolar cells have a larger nucleus, amphiphilic intracytoplasmic particles and obvious nucleoli, showing viral cytopathy Like change. The current research can only confirm that the final performance of COVID-19 is similar to ARDS, but it is not certain that it has the same pathophysiological mechanism.

In addition to treating severe patients, it is also important to choose appropriate treatments for patients with milder symptoms to prevent disease progression[15, 16]. Similar studies of viral pneumonia showed that the use of corticosteroid did not improve their prognosis[17–19].

From our results, the study show that the non-invasive ventilation time between the two groups is different, which may indicate that the corticosteroid has the potential to delay the invasive ventilation, but it does not improve the prognosis.

One of the characteristics of COVID-19 are a series of immunosuppression, including lymphopenia as the main manifestation[1, 14, 20]. Whether the timing and dose of corticosteroid would cause further immunosuppression and

delay the elimination of the virus may be a question worthy of our more attention[19]. A significant increase in DD dimer was also suggested in our data analysis, which may be due to extensive endothelial cell damage caused by COVID-19 pneumonia. Corticosteroid may have coagulation effect, and whether it would further aggravate the disorder of coagulation function also needs attention.

This study only analyzed the phenomenon and the possible pathophysiological effects of corticosteroid therapy based on the current retrospective analysis, does not involve the analysis of the pathophysiology of COVID-19.

We are aware of some limitations in this study. First, The sample size of this clinic research is small. Jin yin tan Hospital is the designated Grade III hospital for critically ill patients and our results may not be applied in the patient populations with milder symptoms. Second, at present, the disease develops rapidly from occurrence to development, our treatment and observation time is short, therefore, we could not use the 28-day mortality rate as the main result. Instead, we used the intubation rate after the use of corticosteroid as the main observation result. This main result may also lead to erroneous evaluations of the potential therapeutic effects of corticosteroid. Additionally, the pathophysiology of COVID-19 is unclear. The current speculation on pathophysiology is mainly based on a small amount of anatomical research and limited epidemiological investigations. It can also interfere with the interpretation of the results. Moreover, in the current data, there are insufficient cases with high-dose steroid pulse therapy, thus the effects of different dosages on intubation rate have not been evaluated.

Conclusions

Our study shows that the use of corticosteroid in ICU patients with COVID-19 who are given non-invasive respiratory support does not decrease patients' intubation rates.

Declarations

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Ethics approval: This study protocol was approved by the Research Ethics Committee of Jin Yintan hospital（KY-2020-06.01）.

Availability of data and material (data transparency): This study data will be transparent after the article is published.

Consent to participate: Written informed consent was obtained from all patients.

Consent for publication: Written informed consent was obtained from all patients.

Authors' contributions: Study design, data analysis, data interpretation: Jinjun Jiang, Junhua Zheng and Zhengshang Ruan. Collection, analysis of the data:Zhengshang Ruan, Rongrong Ren, Si Xuan, Aihua Qian, Ming Wei, Bin Xu, Lijun Liu and Jing Xu. Drafting the article: Zhengshang Ruan and Rongrong Ren. Critically revising the article: Zhengshang Ruan, Rongrong Ren, Si Xuan, Aihua Qian, Ming Wei. Reviewed submitted version of manuscript and approved the final version of the manuscript on behalf of all authors: Jinjun Jiang, Junhua Zheng. Statistical analysis:

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Tables

Table 1. Demographic Characteristics of ICU Patients With COVID-19

Study population	**No.**			
Gender				
Male(%)	65(63.7%)			
Female(%)	37(36.3%)			
Comorbidity(%)				
Chronic lung disease	5(4.9%)			
Hypertension	38(37.3%)			
CHD	13(12.7%)			
Intestinal disease	9(8.8%)			
Cancer	5(4.9%)			
Diabetes	19(18.6%)			
	Reference values	**Below normal(%)**	**No. of normal range (%)**	**Above normal(%)**
Temperature	36-37℃	0	65(63.7)	37(36.3)
Breath	12-20 /min	0	23(22.5)	79(77.5)
HR	60-100 /min	0	78(76.5)	24(23.5)
Hematologic				
WBC	3.5-9.5×10^9/L	5(4.9)	49(48.0)	48(47.1)
Lymphocytes	1.1-3.2×10^9/L	87(85.3)	15(14.7)	0
Platelets	125-350×10^9 /mL	22(21.6)	76(74.5)	4(3.9)
Biochemical				
TBIL	0-26umol/L	0	81(79.4)	21(20.6)
DBil	0-8umol/L	0	71(69.6)	31(30.4)
AST, U/L	15-40u/L	3(2.9)	39(38.2)	60(58.8)
ALT, U/L	9-50U/L	3(2.9)	53(52.0)	46(45.1)
BUN	3.1-8mmol/L	1(1.0)	62(60.8)	38(37.3)
Cr	57-97umol/L	15((14.7)	62(60.8)	25(24.5)
TNI	0-28pg/ml	0	63(61.8)	39(38.2)
BNP	0-100pg/ml	0	68(66.7)	34(33.3)
DDimer	0-1.5ug/ml	0	27(26.5)	75(73.5)
CRP	0-5mg/L	0	5(4.9)	97(95.1)

Table 2. Laboratory characteristics of ICU Patients With COVID-19				
	Overallcohort (n=102)	Corticosteroid (n=52)	Non-corticosteroid (n=50)	P value
Age, median (IQR), years	64.0(14)	63.0(18.0)	65.5(12.0)	0.062
Sex (%)				0.238
Male	65(63.7)	36(69.2)	29(58.0)	
Female	37(36.3)	16(30.8)	21(42.0)	
SpO_2/ FiO_2, median (IQR)	160(160)	150(150)	180(170)	0.090
NIV days, median (IQR)	6.0(10)	8.0(10)	4.5(11)	0.020
WBC(*10^9/L), median (IQR)	9.1(8.4)	10.2(6.7)	8.6(9.6)	0.857
Lymphocytes(*10^9/L) median (IQR)	0.6(0.5)	0.6(0.4)	0.7(0.6)	0.187
Platelet(*10^9/L), mean (SD)	185.7(75.9)	176.2(73.6)	195.6(77.7)	0.198
CRP(mg/L) , median (IQR)	126.0(121.6)	135.3(115.0)	120.0(127.2)	0.334
Hb(g/L), median (IQR)	120.0(25.0)	122.5(31.0)	118.5(23.0)	0.355
AST(U/L), median (IQR)	44.5(36.0)	44.0(34.5)	47.0(36.0)	0.680
ALT(U/L), median (IQR)	45.0(35.5)	49.0(34.8)	45.0(38.5)	0.102
TBil (μmol/L), median (IQR)	16.1(13.7)	15.7(12.5)	16.4(15.1)	0.880
DBil(μmol/L), median (IQR)	6.3(5.7)	6.7(5.7)	5.7(5.5)	0.393
BUN(mmol/L) , median (IQR)	7.4(5.1)	6.6(3.0)	8.7(5.4)	0.051
Cr(μmol/L), median (IQR)	75.0(31.9)	71.8(26.6)	78.1(55.3)	0.051
TNI(μg/L), median (IQR)	16.9(119.9)	12.8(32.5)	19.6(187.9)	0.186
BNP(μg/L), median (IQR)	69.2(123.8)	67.1(174.5)	72.4(90.8)	0.797
D-Dimer (μg/L), median (IQR)	5.9(16.3)	6.3(25.8)	5.2(11.3)	0.231
HR(/min), median (IQR)	89.5(16.5)	90.0(19.5)	89.0(14.5)	0.768
Temp(°C) , median (IQR)	36.8(1.3)	36.9(1.8)	36.8(0.9)	0.224
Respiration(/min), median (IQR)	23.0(7)	22.5(10)	24.0(7)	0.602
Comorbidity(%)				
Chronic lung disease[a]	5(4.9)	4(7.7)	1(2.0)	0.383
Hypertension	38(37.3)	18(34.6)	20(40.0)	0.574
CHD	13(12.7)	5(9.6)	8(16.0)	0.334
Intestinal disease[a]	9(8.8)	3(5.8)	6(12.0)	0.447
	5(4.9)	4(7.7)	1(2.0)	0.383

Cancer[a]				
Diabetes	19(18.6)	8(15.4)	11(22.0)	0.391
Rate of IV (%)	68(66.7)	36(69.2)	32(64.0)	0.575

[a] Continuity correction

IV = invasive ventilation

NIV = noninvasive ventilation

Table 3. Corticosteroid therapy (n=52)					
Methylprednisolone	40mg		80mg		160mg
	n/mean/median	%/sd/quartile (Q1-Q3)	n/mean/median	%/sd/quartile (Q1-Q3)	n/mean/median
No. of patients	21		27		4
Age	62.0	16	68.0	11	58.0
Sex, Male	15	71.4	19	70.4	2
SpO_2/FiO_2	210	310	150	100	150
WBC	11.0	6.4	8.9	7.5	8.6
Lymphocytes	0.6	0.4	0.6	0.5	0.5
Platelets	209.2	84.9	152.7	53.5	161.3
Hb	125.0	37.0	120.0	26.0	110.5
AST	44.0	41.0	42.0	33.0	58.5
ALT	43.0	59.0	51.0	34.0	60.5
TBil	15.5	8.1	20.5	14.3	15.4
DBil	6.0	4.8	7.0	8.1	6.2
BUN	6.6	2.8	6.6	5.5	5.8
Cr	73.9	32.6	72.0	23.3	66.5
CRP	97.2	137.1	160.0	86.2	149.3
TNI	10.3	30.8	24.2	168.9	6.3
BNP	57.7	203.3	69.4	171.3	73.3
DDimer	5.4	12.4	13.5	34.5	2.0
Heart rate	89.0	20.0	90.0	26.0	87.0
Temperature	38.0	2.0	36.7	0.5	38.5
Breaths	22.0	14	22.0	10	24.0

Figures

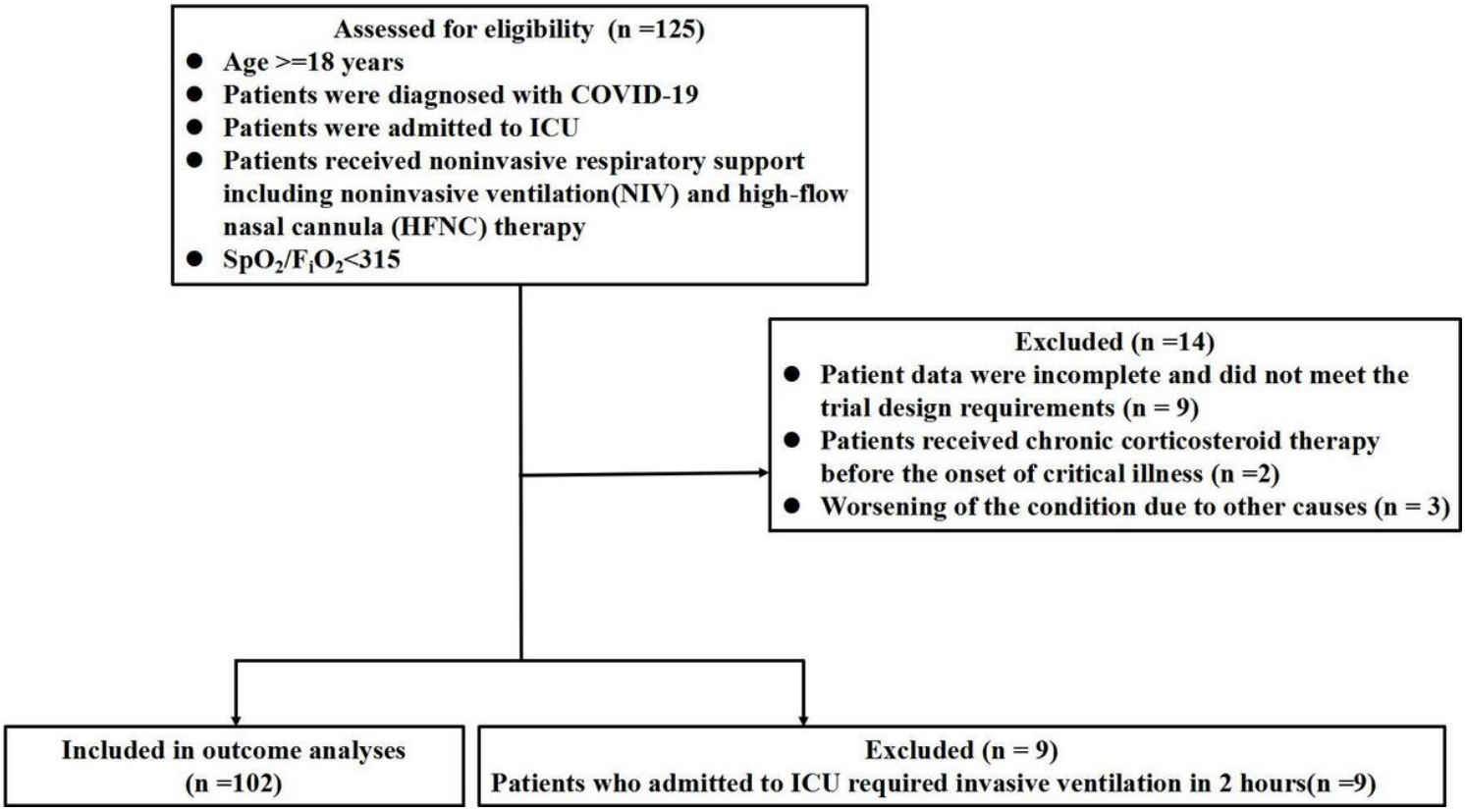

Figure 1

Trial Procedures flow chart.

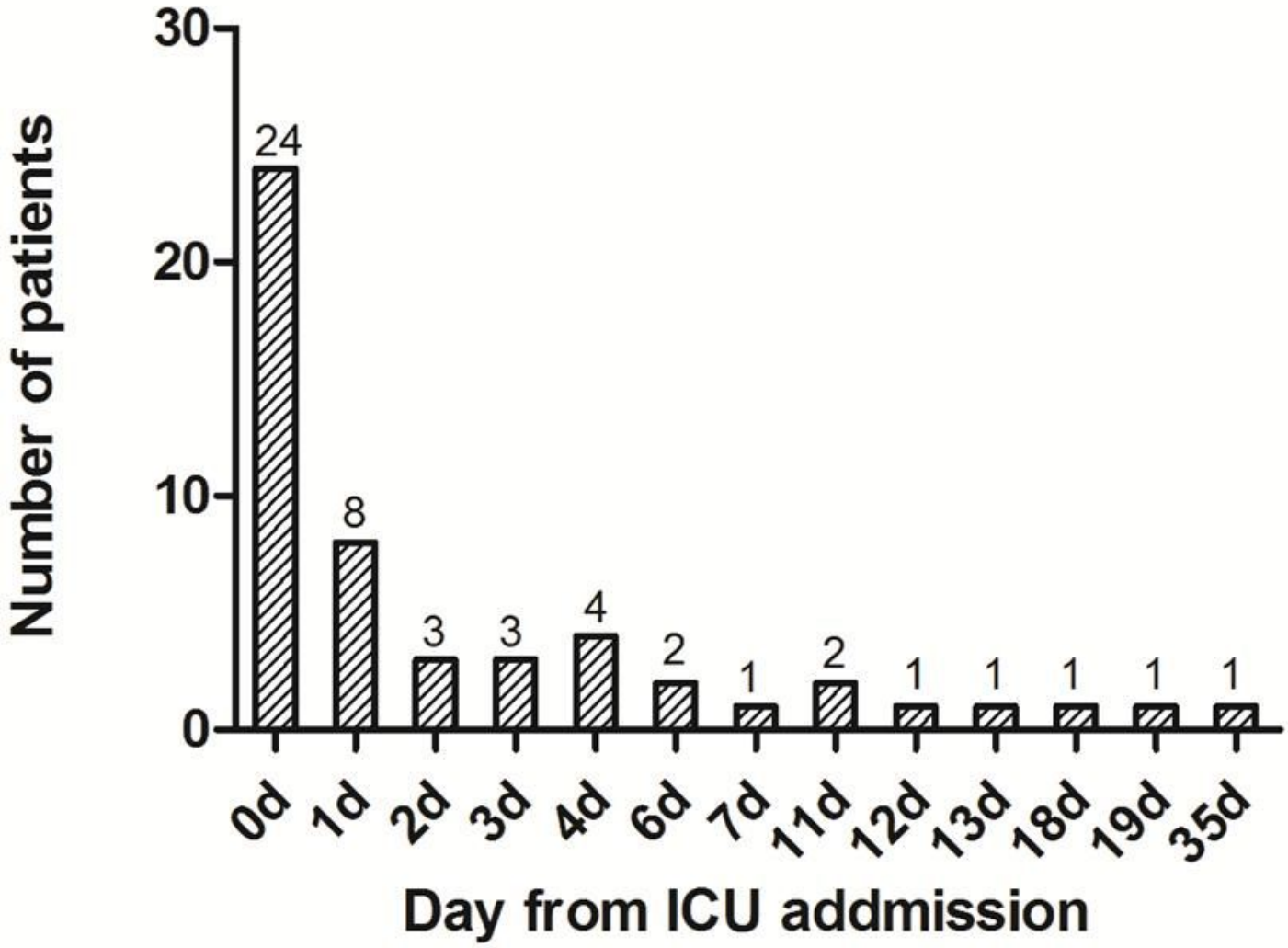

Figure 2

Time to corticosteroid therapy initiation from ICU admission. Day 0 includes patients who were already on corticosteroid therapy when admitted to the ICU.

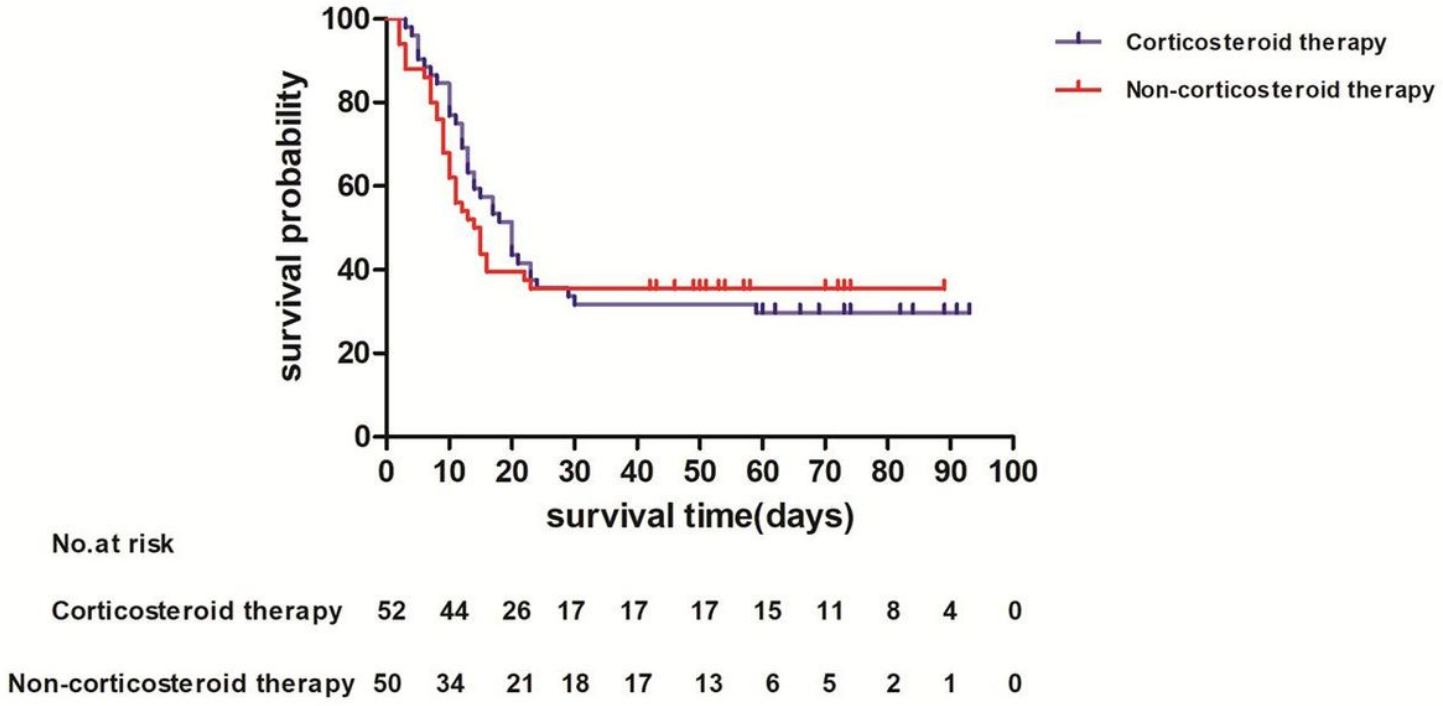

Figure 3

Figure 3