The Effects of Steroids in Severe Hospitalized Patients with COVID-19: A Retrospective Cohort Study

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Abstract

The efficacy of corticosteroids in the treatment of patients with severe COVID-19 remains unknown. We evaluated the impact of corticosteroids on clinical improvement among severe COVID-19 patients. In this retrospective, two-centered, cohort study, we enrolled 101 patients with severe COVID-19: with 39 patients in the steroid group and 63 patients in the non-steroid group. The primary endpoint was Time to Clinical Improvement (TTCI) by up to 28 days after the treatment. Secondary endpoints included the rate of CAT scan improvement, the percentage of negative SARS-Cov-2 RT-PCR tests by Day 28, and the time to discharge. We found that patients in the steroid group did not have significant differences of TTCI from patients in the non-steroid group by 28 days after the treatment (median, 19 days vs. 20 days; hazard ratio, 1.07; p=0.797). The CAT scan improvement rate was not statistically different between the two groups by Day 28 (87.2% vs. 79.0%, p=0.170). The negative test of SARS-CoV2 RT-PCR by Day 28 was 68.4% in the steroid group, 87.1% in the non-steroid group (p= 0.060). Time to discharge was significantly longer in the steroid group than the non-steroid group (35 days vs 21 days, p=0.005). Our findings indicated the short-term corticosteroid at a low to moderate dose did not improve the clinical outcomes for patients with severe COVID-19. Further randomized clinical trials are needed to confirm the findings.

Background

Since December 2019, the novel coronavirus(COVID-19) has rapidly spread to many countries in the world and caused many deaths.[1,2] Clinical manifestations of COVID-19 include fever, dry cough, dyspnea, fatigue and lymphopenia.[3-5] Based on the presence and severity of symptoms, patients infected with COVID-19 can be divided into 3 clinical categories: mild (i.e. no pneumonia and mild pneumonia), severe, and critical.[6,7] While most patients (81%) with mild symptoms are often able to recover by themselves with less supportive care treatment, severe patients often have serious clinical symptoms such as low oxygen saturation rate, PaO2/FiO2 ≤300mm Hg, rapid respiratory rate, often with progressive imaging changes.[6,7] Without timely interventions, the patient's condition can become critical quickly, resulting in multiple organ failures and even death. While the overall case-fatality rate of COVID-19 is 2.3%, the mortality rate for critically ill patients is as high as 61%.[3,6]

The use of corticosteroids in the treatment of COVID-19 is controversial. Several observational studies and meta-analysis in patients with Severe Acute Respiratory Syndrome (SARS)-CoV, Middle East Respiratory Syndrome (MERS)-CoV, Influenza and Respiratory Syncytial Virus (RSV) have indicated that steroids do not provide any clinical benefits. Instead, it increased mortality and complications as well as delayed clearance of the viral RNA from respiratory tracts.[8-14] One preliminary case series reported that corticosteroids did not improve the survival rate in critical COVID-19 patients.[15] The World Health Organization (WHO) and Russell et al, therefore, did not recommend corticosteroid treatment for patients with COVID-19.[16,17] However, other retrospective data showed steroids lowered overall mortality in severe

cases of SARS and influenza A pneumonia.[18,19] Considering the toxicities involved with high doses of steroids, the expert consensus from the Chinese Thoracic Society stated that a low to moderate dose of steroids (≤0.5-1mg/kg per day methylprednisolone or equivalent) for a short duration (≤7 days) has the probability of reducing mortality in critically ill patients.[15,20]

This retrospective study evaluates the efficacy of corticosteroid at a low to moderate dose in the treatment of non-Intensive Care Unit (ICU) patients with severe COVID-19 in Wuhan, China.

Results

Patients and demographics

We reviewed the medical records of 760 hospitalized patients diagnosed with COVID-19 in two study hospitals in Wuhan, of which 659 patients were excluded because they had a mild to moderate disease. In total, 101 patients were included for data analysis, with 39 patients in the steroid group and 63 in the non-steroid group. Eligible patients were transferred from other hospitals or were admitted directly from the outpatient clinic. The average time from disease onset to the admission was 12 days. The median age was 68, and 81 (77.9%) patients were older than 60 years. 45 (43.6%) patients were men and 3 (3.0%) were smokers. Many patients had comorbidities such as diabetes (30.7%), hypertension (51.5%), cardiovascular disease, including CAD, arrhythmia, and CHF (24.9%). Positive tests for SARS-Cov2 RT-PCR were seen in 73 (70.2%) patients; positive IgM/IgG tests were seen in 66 (65.3%) patients. Some parameters were statistically different between two groups, including symptoms of shortness of breath, SpO2, higher WBC or neutrophils counts, and lower lymphocyte count. (Table 1)

Table 1. Demographic and clinical characteristics of the patients at baseline.

Characteristic	Total (N=101)	Steroid treatment (N=39)	No steroid treatment (N=62)	p-value
Age, yr – median (IQR)	68 (63 – 74)	67 (62 – 73)	68 (64 – 74)	0.5087
>60 yrs	80 (79.2)	31 (79.5)	49 (79.0)	0.9563
<=60 yrs	21 (20.8)	8 (20.5)	13 (21.0)	
Male sex – no. (%)	45 (44.6)	15 (38.5)	30 (48.4)	0.3285
Smoker – no. (%)	3 (3.0)	1 (2.6)	2 (3.2)	1.0000
Coexisting conditions – no. (%)				
Diabetes	31 (30.7)	9 (23.1)	22 (35.5)	0.1881
Hypertension	52 (51.5)	21 (53.9)	31 (50.0)	0.7065
CAD	15 (14.9)	4 (10.3)	11 (17.7)	0.3030
COPD	3 (3.0)	0 (0)	3 (4.8)	0.2818
Stroke	1 (1.0)	0 (0)	1 (1.6)	1.0000
Arrythmia	5 (5.0)	2 (5.1)	3 (4.8)	1.0000
CHF	5 (5.0)	2 (5.1)	3 (4.8)	1.0000
Renal dysfunction	2 (2.0)	2 (5.1)	0 (0)	0.1467
Liver dysfunction	5 (5.0)	0 (0)	5 (8.1)	0.1533
GI	29 (28.7)	14 (35.9)	15 (24.2)	0.2056
Dementia	1 (1.0)	0 (0)	1 (1.6)	1.0000
Bacterial infection	8 (7.9)	2 (5.1)	6 (9.7)	0.4803
Cancer	2 (2.0)	1 (2.6)	1 (1.6)	1.0000
Cough – no. (%)	72 (71.3)	31 (79.5)	41 (66.1)	0.1485
Fever – no. (%)	76 (75.3)	26 (66.7)	50 (80.7)	0.1130
Short of breath (SOB) – no. (%)	63 (62.4)	30 (76.9)	33 (53.2)	0.0167
Respiratory rate	22 (20 – 28)	24 (22 – 28)	22 (20 – 28)	0.0668
WBC count – median (IQR)				
>9.5 – no. (%)	22 (21.8)	17 (43.6)	5 (8.1)	<0.0001
3.5 – 9.5 – no. (%)	72 (71.3)	18 (46.2)	54 (87.1)	
<3.5 – no. (%)	7 (6.9)	4 (10.3)	3 (4.8)	

Neutrophils count – median (IQR)				
>6.3 – no. (%)	33 (32.7)	19 (48.7)	14 (22.6)	0.0055
1.8 – 6.3 – no. (%)	63 (62.4)	17 (43.6)	46 (74.2)	
<1.8 – no. (%)	5 (5.0)	3 (7.7)	2 (3.2)	
Lymphocyte count – median (IQR)				
>3.2 – no. (%)	2 (2.0)	0 (0)	2 (3.2)	0.0163
1.1 – 3.2 – no. (%)	26 (25.7)	5 (12.8)	21 (33.9)	
<1.1 – no. (%)	73(72.3)	34 (87.2)	39 (62.9)	
HgB – median (IQR)				
>150 – no. (%)	2 (2.0)	1 (2.6)	1 (1.6)	1.0000
115 – 150 – no. (%)	70 (69.3)	27 (69.2)	43 (69.4)	
<115 – no. (%)	29 (28.7)	11 (28.2)	18 (29.0)	
Platelet count – median (IQR)				
>350 – no. (%)	13 (12.9)	4 (10.3)	9 (14.5)	0.3686
125 – 350 – no. (%)	80 (79.2)	30 (76.9)	50 (80.7)	
<125 – no. (%)	8 (7.9)	5 (12.8)	3 (4.8)	
Serum creatinine – median (IQR)				
>84 – no. (%)	26 (25.7)	9 (23.1)	17 (27.4)	0.5506
45 – 84 – no. (%)	68 (67.3)	26 (66.7)	42 (67.7)	
<45 – no. (%)	7 (6.9)	4 (10.3)	3 (4.8)	
AST (U/liter) – median (IQR)				
>32 – no. (%)	37 (36.6)	15 (38.5)	22 (35.5)	0.7624
<=32	64 (63.4)	24 (61.5)	40 (64.5)	
ALT (U/liter) – median (IQR)				
>33 – no. (%)	35 (34.7)	12 (30.8)	23 (37.1)	0.5153
<=33 – no. (%)	66 (65.4)	27 (69.2)	39 (62.9)	
Lactate dehydrogenase (U/liter) – median (IQR)				
>214 – no. (%)	94 (93.1)	37 (94.9)	57 (91.9)	0.7036
135 – 214 – no. (%)	7 (6.9)	2 (5.1)	5 (8.1)	

IL-6				
>=7.0 – no. (%)	37 (36.6)	18 (46.2)	19 (30.7)	0.1153
<7.0 – no. (%)	64 (63.4)	21 (53.9)	43 (69.4)	
D-dimer – median (IQR)				
>=0.5 – no. (%)	88 (87.1)	36 (92.3)	52 (83.9)	0.2177
<0.5 – no. (%)	13 (12.9)	3 (7.7)	10 (16.1)	
C-reactive protein (CRP) – median (IQR)				
>=1.0 – no. (%)	98 (97.0)	39 (100.0)	59 (95.2)	0.2818
<1.0 – no. (%)	3 (3.0)	0 (0)	3 (4.8)	
SpO2 – median (IQR)	0.92 (0.89 – 0.92)	0.90 (0.84 – 0.91)	0.92 (0.91 – 0.93)	<0.0001

CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CHF: congestive heart failure; GI: gastrointestinal diseases; WBC: white blood cells; IQR: interquartile range; HgB: hemoglobin; AST: aspartate aminotransferase; ALT: alanine aminotransferase

The most common symptoms were fever (76, 75.3%), cough (72, 71.3%), and shortness of breath (66, 62.4%). All patients (100%) had SpO2 ≤ 93% on the diagnosis of severe disease. The median respiratory rate was 22/min. At the diagnosis of severe COVID-19, 45 (44.6%) patients received 2-4 liter/min nasal cannula oxygen, 47 (46.5%) patients received ≥ 5L/min nasal cannula oxygen; 9 (8.9%) patients received HFNC/NIV. All of the patients received Traditional Chinese Medicine (TCM) during the hospitalization, and the patients in each group received at least one antiviral medication: 78 (77.2%) patients received Arbidol, 38 (37.5%) received Lopinavir/Ritonavir, 31 (30.7%) received hydroxychloroquine/chloroquine. All but one patient survived. (Table 2)

Among the COVID-19 patients, systemic corticosteroid was used in 39 patients (38.6%), all of which received methylprednisolone. The median dose of methylprednisolone was 80 mg daily (40-160 mg daily), and 38 (90.5%) received methylprednisolone or equivalent < 150 mg. Corticosteroid was initiated within 13 days (9-22 days) from the onset of the disease and within 1 day of admission. The median duration of corticosteroid treatment was 7 days (4-10.0 days IQR). (Table 2)

Table 2. Patients' status and treatments received at enrollment

Characteristic	Total (N=101)	Steroid treatment (N=39)	No steroid treatment (N=62)	p-value
Seven-category scale (0-6) at day 0				0.0032
2. NASAL CANNULA < 5L/min – no. (%)	45 (44.6)	13 (33.3)	32 (51.6)	
3. NASAL CANNULA ≥ 5L/min – no. (%)	47 (46.5)	18 (46.2)	29 (46.8)	
4. Requiring HFNC or noninvasive mechanical ventilation – no. (%)	9 (8.9)	8 (20.5)	1 (1.6)	
Days from illness onset to disease severe status – median (IQR)	12 (7 – 19)	12 (9 – 20)	11 (7 – 17)	
Treatments during study period – no. (%)				
Arbidol	78 (77.2)	30 (76.9)	48 (77.4)	0.9538
Kaletra	38 (37.5)	14 (35.9)	24 (38.7)	0.7764
Ribavirin	18 (17.8)	8 (20.5)	10 (16.1)	0.5751
TCM	91 (90.1)	36 (92.3)	55 (88.7)	0.7368
Hydroxychloroquine	31 (30.7)	18 (46.2)	13 (21.0)	0.0075
γ-globulin	24 (23.8)	12 (30.8)	12 (19.4)	0.1895
Expectorants	38 (37.6)	16 (41.0)	22 (35.5)	0.5757
Days from illness onset to steroid therapy – median (IQR)	13 (9 – 22)	13 (9 – 22)	-	-
Days from admission to steroid therapy – median (IQR)	1 (1 – 4)	1 (1 – 4)	-	-
Days of steroid therapy – median (IQR)	7 (4 – 10)	7 (4 – 10)	-	-

IQR: interquartile range; TCM: traditional Chinese medicine.

Primary and Secondary Endpoints

For the primary endpoint, we first performed the univariate analysis using the Kaplan-Meier method. The median TTCI during the 28-day study period was 19 days in the steroid group, similar to 20 days in the non-steroid group (p=0.856). (Table 3, Figure 1). Further multivariate analysis with Cox Professional Hazards model showed no significant difference in TTCI between patients in the steroid group and those in the non-steroid group (hazard ratio for clinical improvement, 1.07; 95% confidence interval [CI] 0.62-1.86, p=0.797). (Table 5). When we evaluated the number of patients that achieved clinical improvement with a 2-point decrease in the score on Day 7, Day 14 and Day 21 after the treatment, there was no significant difference between the two groups on Day 7 and Day 21(p=1.000 and p=0.243 respectively). However, more patients in the steroid group achieved a 2-point decrease than those in the non-steroid group at Day 14 (p=0.015), suggesting a transient benefit. (Table 3)

For the secondary endpoints, the CAT scan improvement from the baseline was observed in 87.2% of patients in the steroid group by day 28, while CAT scan improvement was observed in 79.0% of patients in the non-steroid group. The difference was not statistically significant (p=0.170). The median time to CAT scan improvement from the admission was 16 days in the steroid group, longer than 14 days in the non-steroid group. The percentage of negative SARS-CoV2 RT-PCR results by day 28 was 68.4% in the steroid group, trending significantly lower than that (87.1%) in the non-steroid group (p= 0.060). Time to discharge was significantly longer in the steroid group than the non-steroid group (36 days vs 21 days, p=0.0005). (Table 3)

Table 3. Primary and secondary clinical outcomes

Characteristic	Total (N=101)	Steroid treatment (N=39)	No steroid treatment (N=62)	p-value
Time to clinical improvement – median no. of days (IQR)	20 (13 – 28)	19 (12 – 28)	20 (14 – 28)	0.8558
2-Score decreasing on seven-category scale at day 7 – no. of patients (%)				1.0000
Yes	3 (3.0)	1 (2.6)	2 (3.2)	
No	98 (97.0)	38 (97.4)	60 (96.8)	
2-Score decreasing on seven-category scale at day 14 – no. of patients (%)				0.0152
Yes	14 (13.9)	10 (25.6)	4 (6.5)	
No	87 (86.1)	29 (74.4)	58 (93.6)	
2-Score decreasing on seven-category scale at day 21 – no. of patients (%)				0.2429
Yes	20 (19.8)	10 (25.6)	10 (16.1)	
No	81 (80.2)	29 (74.4)	52 (83.9)	
Time to discharge – median no. days (IQR)	24 (18 – 36)	36 (21 – 41)	21 (15 – 31)	0.0005
CT improvement – no. (%)	83 (82.2)	34 (87.2)	49 (79.0)	0.1698
Virus negative transferring – no. (%)	80 (80.0)	26 (68.4)	54 (87.1)	0.0604

IQR: interquartile range.

Risk Factors

To evaluate whether factors other than steroid treatment could impact clinical improvement, we performed a univariate analysis with a log-rank test on other treatments and lab parameters. Treatment (Arbidol and Expectorants) and abnormal high laboratory findings (WBC, LDH, IL-6, D-dimer) significantly extended the time to clinical improvement. However, the time to clinical improvement was much shorter in

patients with high levels of hemoglobin (7.0±5.0 days) than in patients with normal (20.0±1.0 days) or low levels of hemoglobin (20.2±1.2 days) (p=0.004) (Table 4). All of the factors above except abnormally high WBC remained statistically significant as independent factors associated with the time to clinical improvement through multivariate analysis (Table 5).

Table 4. TTCLs of factors with borderline significance or above by Kaplan-Meier method.

	Time to clinical improvement, Mean (SD)	p-value (Log-rank test)
Arbidol		<0.0001
Yes	21.5 (0.8)	
No	14.1 (1.0)	
Expectorants		0.0260
Yes	20.8 (1.1)	
No	18.9 (0.9)	
WBC		0.0426
abnormal high	22.7 (1.5)	
normal	19.5 (0.9)	
abnormal low	15.0 (1.6)	
HgB		0.0004
High	7.0 (5.0)	
Normal	20.0 (0.9)	
Low	20.2 (1.2)	
LDH		0.0564
abnormal high	20.4 (0.8)	
normal	14.1 (1.9)	
IL-6		0.0168
abnormal high	21.7 (1.4)	
normal	18.8 (0.8)	
D-dimer		0.0026
abnormal high	20.7 (0.8)	
normal	15.1 (1.9)	

WBC: white blood cells; HgB: hemoglobin; LDH: Lactate dehydrogenase; IL-6: Interleukin-6.

Table 5. Cox PH model for decreasing 2 score on seven-category scale.

Variable		Estimate	SE	Chi-Square	p-value	Hazard Ratio (95% CI)
Steroid		0.07157	0.27873	0.0659	0.7974	1.07 (0.62 – 1.86)
Expectorants		-0.60606	0.29779	4.1421	0.0418	0.55 (0.30 – 0.98)
Arbidol		-0.92731	0.29266	10.0401	0.0015	0.40 (0.22 – 0.70)
Hemoglobin	Normal	0.13048	0.30159	0.1872	0.6653	1.14 (0.63 – 2.06)
Hemoglobin	High	3.06028	0.87592	12.2065	0.0005	21.33 (3.83 – 118.8)
LDH	Abnormal high	-1.08878	0.46473	5.4887	0.0191	0.34 (0.14 – 0.84)
IL-6	Abnormal high	-0.87793	0.31565	7.7359	0.0054	0.42 (0.22 – 0.77)
D-dimer	Abnormal high	-0.82894	0.33855	5.9952	0.0143	0.44 (0.22 – 0.85)

SE: standard error; LDH: Lactate dehydrogenase; IL-6: Interleukin-6.

Adverse effects

In terms of the side effects of corticosteroid, hyperglycemia was detected in a significantly higher percentage of patients in the steroid group (21, 53.9%) than in the non-steroid group (15, 23.4%) (p=0.003). No patient developed psychosis or avascular necrosis during the hospitalization. (Table 6).

Table 6. Summary of adverse events in the patients

Event	Steroid treatment (N=39)	No steroid treatment (N=62)	p-value
Hyperglycemia – no. (%)	21 (55.3)	15 (24.2)	0.0017
Avascular necrosis- no (%)	0	0	N/A
Psychosis – no (%)	0	0	N/A

Discussion

To our knowledge, this is the largest study to evaluate the efficacy of steroids in patients with severe COVID-19 by comparing treatment and control groups. The results showed that short-term, low to moderate dose of corticosteroids did not improve clinical outcomes, nor the requirement of oxygen, in severe non-ICU COVID-19 patients when measured by the time to clinical improvement. Because the mortality rate in this study was only 1% at Day 28, we could not determine if the use of corticosteroid could improve mortality.

Guidance on the use of corticosteroids in the treatment of patients with COVID-19 has been based on limited efficacy and safety data, which is mostly driven from studies in other respiratory viral infections such as SARS, MERS, and influenza. In a retrospective study, investigating the risk factor of SARS mortality, high-dose corticosteroid was found to increase 30-day mortality.[21] In another small randomized trial including 16 non-critical patients with SARS, hydrocortisone use in 9 patients led to greater viremia in the second and third weeks after infection as compared to the 7 patients receiving placebo.[11] Three other retrospective studies in SARS patients found that corticosteroid use was associated with significant toxicities including steroid-induced diabetes, psychosis, and avascular necrosis.[8,10,12] Based on the results above, WHO and Russel C discouraged systemic corticosteroid treatment of COVID-19 patients.[16,17] However, there has been published data that supports the use of corticosteroids in the treatment of viral pneumonia. In a retrospective chart review study, 17 patients receiving high-dose pulse corticosteroids followed by tapering had fewer oxygen requirements and a better imaging outcome than the 55 patients who received low doses of corticosteroids.[22] Another study showed that a low-dose of methylprednisolone (40-80mg daily) was associated with shorter hospital stay than high-dose methylprednisolone (320-640mg daily).[23] In a large retrospective study involving 401 SARS patients, the use of corticosteroids on critical patients resulted in a lowered mortality and a shorter hospital stay in critical patients. The author suggested that the steroid use should not be delayed until Acute Respiratory Distress Syndrome (ARDS) is fully developed.[19] Preliminary data showed that corticosteroids reduced inflammation in 15 critical COVID-19 patients, although there was no mortality improvement.[15] Considering the potential benefits and risks of corticosteroids, especially when given in high doses (>150mg prednisone or equivalent per day), experts in China formed a consensus to recommend low dose, short-term steroids in selected patients, most notably among patients with severe COVID-19.[7,20]

We studied clinical outcomes in a cohort of COVID-19 patients with severe symptoms and systemic inflammation as observed by the elevation of cytokines such as IL-6, CRP, or D-dimer, but without ARDS or secondary hemophagocytic lymphohistiocytosis (sHLH) induced multiorgan failure seen in critical condition.[24] Our data reveals that a short course of corticosteroids, at low to moderate dose did not significantly improve clinical symptoms and oxygen requirements by Day 28 of the treatment, although it provided the transient benefit on Day 14. Moreover, the use of corticosteroid prolonged the hospital stay

by up to 15 days and failed to improve viremia clearance. These results were consistent with recent small studies, suggesting that the steroid interferes with the ability of the distressed immune system to fight against viruses.[11,25]

The lack of benefits found in corticosteroid treatment is also possibly due to its incomplete inhibition of excessive inflammation in COVID-19 patients. Corticosteroids could not lower interleukin-6 (IL-6) significantly in SARS and COVID-19 patients.[15,26] In this study, we found IL-6 is an independent risk factor negatively associated with the clinical improvement, consistent with the finding that IL-6 is a predictor of COVID-19 fatality.[27] It is possible that IL-6 and IL-6 induced cytokine storm syndrome play an important role in the pathophysiology of COVID-19.[24] Indeed, preliminary studies showed that tocilizumab, an IL-6 receptor monoclonal antibody, was potentially effective in the treatment of patients with COVID-19 when used with or without steroids.[28,29] A multicenter, randomized clinical trial of tocilizumab in patients with severe COVID-19 is currently ongoing to address the anti-inflammatory treatment.

Besides IL-6, we found several other independent factors associated with the clinical improvement in patients with severe COVID-19. LDH and D-dimer were significantly higher among patients with severe disease than those with milder disease and were associated with poor prognosis. Interestingly, elevated HgB was significantly associated with clinical improvement. The underlying immunopathogenic mechanism is unknown. We also observed that treatment with Expectorant and Arbidol, an antiviral drug, was associated with extended time to clinical improvement. However, these observations were not the primary endpoint. Further study is needed to evaluate their potential associations with clinical outcome of COVID-19 infection.

There are several limitations to this study. As a retrospective chart review, we cannot address and balance all potential confounding factors completely. The exact reason for using corticosteroids has not always been recorded in the medical records. More patients in the steroid group were treated with HFNC or NIV than patients in the non-steroid group (8 vs. 1), indicating that some patients were in a more severe condition in the steroid group. The dose of corticosteroids varied among different patients. Finally, patients in this study had severe COVID-19 disease, but they were not critically ill, so the findings may not be generalized to patients in ICU.

Conclusions

In summary, our study demonstrated that the short-term corticosteroids at low to moderate doses did not improve the clinical outcomes for patients with severe COVID-19. Further randomized clinical trials are needed to confirm this finding.

Methods

Study Design and Participant Eligibility

This multiple-center, retrospective cohort study was conducted at two campuses of Wuhan Tongji Hospital, a designated hospital for treating patients with COVID-19. We reviewed charts of patients who were treated from February 11st, 2020 to March 27th, 2020. Patients were eligible for the study if they were at least 14 years old, with confirmed COVID-19 according to WHO and Chinese guidelines, and had a severe case of the disease.[7] Severe patients were defined as those who had at least at least one of three clinical criteria: PaO2/FiO2 ≤300mmHg, RR≥30/min, SpO2 ≤ 93%, or imaging study showed area of infection enlarged by 50% or more within 24-48 hours. Patients in the steroid group needed to receive the steroid for more than 24 hours to be eligible. Patients were excluded if they were < 14 years old, pregnant or postpartum, or had mild, moderate or critical COVID-19. The research was approved by the ethics commission of Xiang'an Hospital of Xiamen University and the Third Xiangya Hospital of Central South University. Written informed consent was waived due to the characteristics of this retrospective chart review study and the rapid spread of COVID-19.

Data Collection

Data were collected retrospectively from the electronic medical records, imaging studies and laboratory records, medication administration record (MAR) and nursing care documents to ensure accuracy and timely completion. Collected data were reviewed by two independent researchers. Any missing information or answers to questionable data was provided by the providers who were directly involved in patient care.

Data collected included demographic data (age, sex, disease onset, date of admission, data of diagnosis of severe COVID-19, date of discharge), smoking status, medical co-morbidities (diabetes, hypertension, coronary heart disease (CAD), chronic pulmonary obstructive disease (COPD), asthma, stroke, malignancy, dementia, chronic renal insufficiency, liver dysfunction, gastrointestinal disease, arrhythmia, congestive heart failure (CHF), dementia, cancer and bacterial infection), clinical signs and symptoms (cough, fever, shortness of breath (SOB), SpO2, respiratory rate), laboratory findings (blood glucose, serum creatine (Scr), hemoglobin (HgB), white blood cells (WBC), neutrophils, lymphocytes, platelets, aspirate aminotransferase (AST)/alanine aminotransferase (ALT), lactate dehydrogenase (LDH), interleukine-6 (IL-6), C-reactive protein (CRP), D-dime, CAT scan results, treatments (including use of anti-viral medications and corticosteroids), use of either extracorporeal membrane oxygenation (ECMO), intermittent mandatory ventilation (IMV), noninvasive ventilation (NIV), high flow nasal cannula (HFNC), or low flow nasal cannula (LFNC).

Outcomes

The primary endpoint was Time to Clinical Improvement (TTCI) by up to 28 days after the treatment. This endpoint was modified from the published method.[30] Clinical improvement was defined as a two-point drop of clinical score from the baseline level at the initiation of study treatment (with or without

corticosteroid treatment) by the treatment. A seven-category ordinal scale of clinical status is set as the following: 6.Death; 5.Intensive Care Unit (ICU)/hospitalization, requiring Extracorporeal Membrane Oxygenation (ECMO) and/or Intermittent Mandatory Ventilation (IMV); 4.ICU/hospitalization, requiring Non-Invasive ventilation (NIV)/High Flow Nasal Cannula (HFNC) Therapy; 3.Hospitalization, requiring ≥ 5L/min Low Flow Nasal Cannula (LFNC) Therapy with or without mask; 2.Hospitalization, requiring < 5L/min Low Flow Nasal Cannula (LFNC) therapy; 1. Hospitalization not requiring supplemental oxygen;

0.Hospital discharge or meet discharge criteria (discharge criteria are defined as clinical recovery, i.e. fever, respiratory rate, oxygen saturation returns to normal, and cough relief).

The modification was made due to changed clinical practice during COVID-19 outbreak in the studied hospital in February and March 2020. Medical devices routinely available in ICU or step-down units such as IMV, NIV, HFNC were limited and often saved for critically ill patients. As a result, non-ICU patients were often treated with lower flow oxygen (2-4L/min) on admission. If there was no clinical improvement of SpO2, oxygen rate was first escalated to 5L or above first through the nasal cannula. Upon a patient's worsening symptoms after this approach, the way of oxygen treatment was escalated to NIV/HFNC. Similarly, patients on NIV/HFNC with clinical improvement often de-escalated to ≥ 5L/min oxygen nasal cannula first before further decreasing the rate of oxygen. This approach maximized the usage of limited resources of NIV/HFNC during this crisis in Wuhan hospitals.

Secondary endpoints included the rate of CAT scan improvement, the percentage of negative SARS-Cov-2 RT-PCR test by Day 28, and time to discharge from the admission.

The sample size was calculated to be 72 to enable the detection of a minimum 25% difference in clinical improvement event rate between steroid group and non-steroid group at day 28, assuming a two-sided type I error of 5% and a power of 80%, steroid group could only have a two-thirds size of the non-steroid group enrolled, and 60% of the patients in the non-steroid group would reach clinical improvement. The number of eligible patients enrolled in this study was 101, giving enough power to detect the treatment difference if it existed.

Baseline characteristics data were summarized as the median and Interquartile Range (IQR) for continuous variables, counts and percentages for categorical variables. Nonparametric Wilcoxon Mann-Whitney test was used for analyzing the continuous variables, and Chi-square test or Exact Fisher test was used for categorical variables among different groups. Cumulative improvement rates were assessed using the Kaplan-Meier method and compared with a log-rank test. Patients were right-censored if they did not reach clinical improvement or had died before day 28. Finally, the Cox proportional hazard (Cox PH) regression model with covariates of treatments and other disease-related factors (lab test results) was used to calculate hazard ratio for clinical improvement while controlling for the confounding factors. Post hoc subgroup analysis for clinical improvement at day 7, day 14, and day 21 after treatment was performed by Chi-square test to evaluate the benefit of treatment.

CAT improvement and the negative test of SARS-CoV2 RT-PCR were assessed on the binary level at Day 28 by the Chi-square test. Statistical significance was pre-specified at a two-sided $p<0.05$. Statistical analysis software (SAS; v 9.4, SAS Institute, Inc, Cary, NC) was used for all statistical analyses.

Abbreviations

COVID-19: 2019 novel coronavirus disease

WHO: World Health Organization

SARS: Severe acute respiratory syndrome

MERS: Middle East respiratory syndrome

RSV: Rrespiratory syncytial virus

ICU: intensive care unit

MAR: medication administration record

CAD: coronary heart disease

COPD: chronic pulmonary obstructive disease

CHF: congestive heart failure

SOB: shortness of breath

Scr: serum creatine

HgB: hemoglobin

WBC: white blood cells

AST: aspirate aminotransferase

ALT: alanine aminotransferase

LDH: lactate dehydrogenase

IL-6: interleukine-6

CRP: C-reactive protein

ECMO: extracorporeal membrane oxygenation

IMV: intermittent mandatory ventilation

NIV: noninvasive ventilation

HFNC: high flow nasal cannula

LFNC: low flow nasal cannula

TTCI: time to Clinical Improvement

IQR: interquartile range

Cox PH: Cox proportional hazard

ARDS: acute respiratory distress syndrome

sHLH: secondary hemophagocytic lymphohistiocytosis

Declarations

Ethics approval and consent to participate

The research was approved by the ethics commission of XiangAn Hospital of Xiamen University and the Third Xiangya Hospital of Central South University

All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests

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Author's contributions

Quan Li, MD PharmD and Liwei Chen, MD MS contributed equally to the study design, data analysis, drafting, writing and final revision of the manuscript

Peifeng Guo, Xin Ma, Lan Cheng, Qun Hu, Zhenyu Yin, Jingjing Liu, Xi Liu, Zuoliang Liu, Xinlin Yin contributed to the data collection

Xianli Chen, MD PhD and Xuefei Xiao, MD PhD contributed equally to study design, data collection, reviewing, revision and approval of the manuscript.

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Figures

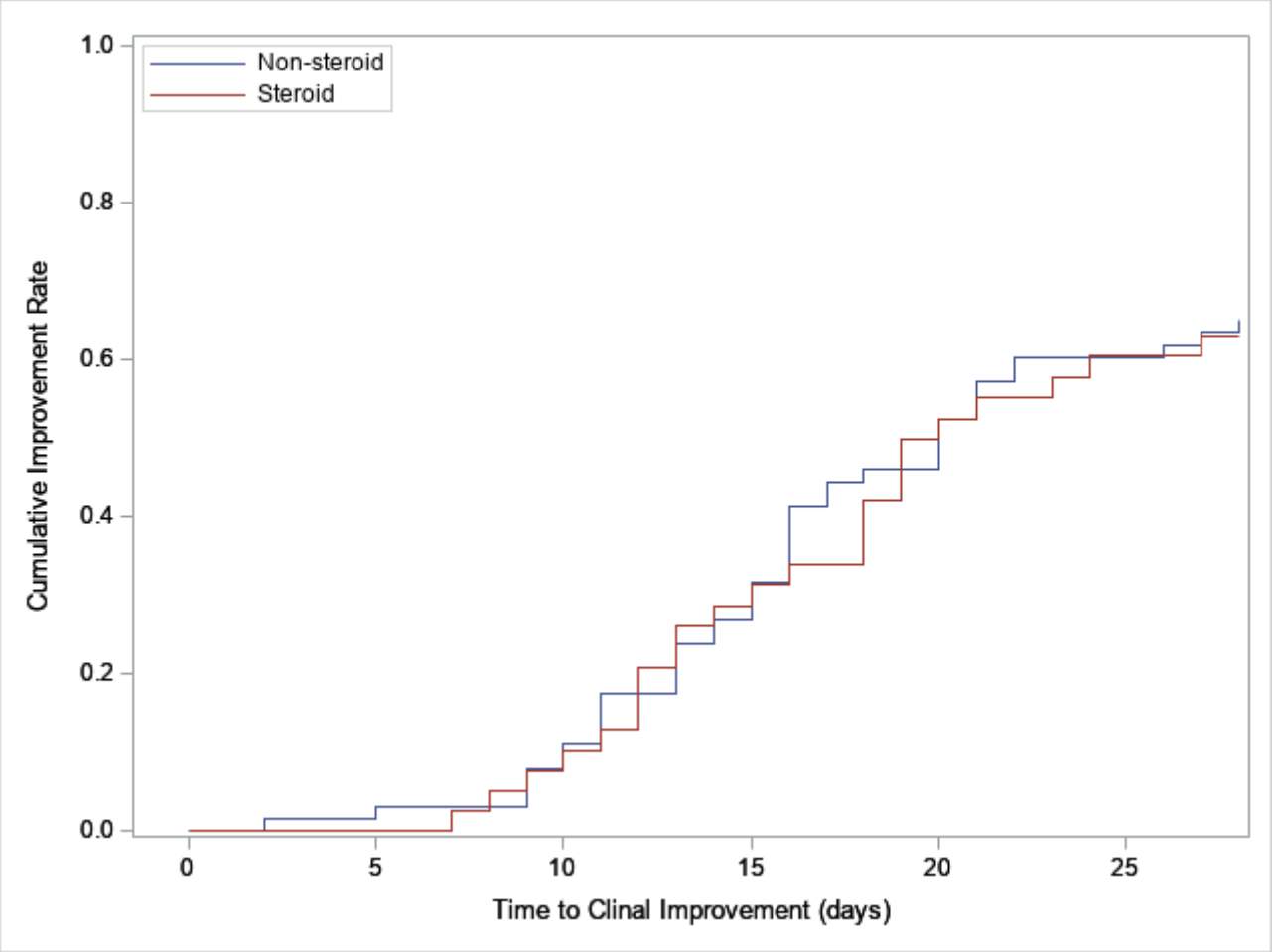

Figure 1

Time to Clinical Improvement Cumulative incidence function plot of the cumulative probability of clinical improvement from steroid and non-steroid treatment groups prior to day 28. The y-axis is the cumulative improvement rate and x-axis is the duration of the study in days