Can corticosteroids improve the outcomes of patients with Covid-19? A retrospective cohort study of patients within and outside the epicentre

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Research

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Abstract

Background

The novel coronavirus disease 2019 (Covid-19) has been a worldwide pandemic with more than 300,000 deaths. Corticosteroids have been used in some patients with severe Covid-19 in order to control the systemic inflammation or cytokine storm, however, their effects and safety have not yet been elucidated.

Methods

Patients with confirmed Covid-19 were retrospectively included from both the epicentre and out of the epicentre. Patients were classified into two groups according to the use of systemic corticosteroids, and the mortality and the rate of virus clearance were compared between the two groups. In addition, independent factors associated with death after corticosteroids treatment were also identified.

Results

A total of 775 patients were included in our final analysis, of which 238 (30.7%) patients received systemic corticosteroids treatment. Compared with patients without corticosteroids treatment, patients with corticosteroids treatment had significantly higher mortality (19.3% vs. 3.7%, $P < 0.001$) and lower rate of virus clearance (43.2% vs. 66.7%, $P < 0.001$) although along with increase of SpO_2/FiO_2 and blood lymphocytes in patients with severe Covid-19. Corticosteroids treatment was associated with longer hospital length of stays and delayed virus clearance time. In patients with corticosteroids treatment, blood lymphocytes (odds ratio (OR) 0.792, 95% confidence interval (CI) 0.672–0.932, $P = 0.005$) and creatine kinase (CK) (OR 1.006, 95%CI 1.000-1.012, $P = 0.038$) were independent risk factors associated with death, with a sensitivity of 90.91% and 44.44% and a specificity of 70.75% and 94.05%, respectively.

Conclusions

In patients with Covid-19, corticosteroids treatment is associated with increased mortality and reduced rate of virus clearance.

Introduction

The coronavirus disease 2019 (Covid-19) is a severe acute respiratory syndrome (SARS) caused by the infection of a novel SARS coronavirus (SARS-CoV-2), which initially emerged in Wuhan, China in December, 2019.[1] Since the declaration of a public health emergency of international concern and subsequently a pandemic by the World Health Organization, the rapid outbreak of Covid-19 has led to a global anxiety with about 5 million infected cases and more than 300,000 deaths. Although numerous

trials of different medications have been made such as antiviral drugs including Favipiravir, Remdesivir, Lopinavir and Ritonavir, and chloroquine and hydroxycholoroquine, no convincing results have been reported due to the lack of proper study designs as well as data for peer review.[2,3] So far, there are no effective treatments for Covid-19 and the potential vaccines are still under clinical trials.

Cytokine storm syndrome has been identified as a key character in patients with Covid-19 and the levels of some specific cytokines are associated with disease severity and mortality such as IP-10, MCP-3, and IL-1 receptor antagonist.[4] Therefore, it is recommended that treatments of these hyperinflammations should be identified and addressed to reduce the mortality.[5,6] Corticosteroids are potent anti-inflammatory agents with the ability to modulate the inflammatory response, and they were reported to reduce the pro-inflammatory cytokines[7] and mortality[8] during 2002 SARS-CoV outbreak. However, there is a lack of study of corticosteroids in this novel coronavirus pandemic. In this study, we aimed to evaluate the effectiveness of systematic corticosteroids in patients with Covid-19, with the particular interests in any differences of treatment response within and out of the epicentre.

Methods

This study was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University. All patients were consented for publications.

Patients

We retrospectively collected the data of adult patients with confirmed Covid-19 from 2 centres in Wuhan and 46 centres in Sichuan (out of Wuhan) from January to March, 2020. In order to study the efficacy of corticosteroids treatment in patients with acute respiratory distress syndrome (ARDS) caused by Covid-19, we collected ARDS patients from another 2 centres in Wuhan.

Covid-19 and different disease severities were diagnosed in accordance with the published guidelines.[9] Covid-19 was confirmed if suspects met one of the etiological and serological evidences: 1) positive for SARS-CoV-2 by real-time fluorescent RT-PCR, 2) highly homologous to SARS-CoV-2 in viral gene sequence, or 3) serum SARS-CoV-2 specific IgM and IgG detectable or reaching a titration of at least 4-fold increase during convalescence. Four severity categories were classified: 1) Mild, mild symptoms without pneumonia; 2) Moderate, fever and respiratory symptoms with pneumonia; 3) Severe, respiratory rate (RR) $\geq$ 30 breaths/min, oxygen saturation $\leq$ 93% at rest in room air, or the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) $\leq$ 300mmHg; and 4) Critical, respiratory failure with the need for mechanical ventilation, shock, or organ failure requiring admission to intensive care unit (ICU).

Patients with ARDS was defined according to the following criteria: 1) acute onset of respiratory symptoms within 7 days, 2) bilateral infiltrates on chest imaging, 3) without evidence of left atrial

hypertension and cardiogenic pulmonary oedema, and 4) severe hypoxemia at PaO2/FiO2 ≤ 300mmHg.[10,11]

Study design and Outcomes

This study was designed as a retrospective cohort study to compare the outcomes between patients with and without corticosteroids treatment. Corticosteroids treatment was classified as systematic administration of corticosteroids including oral prednisolone and intravenous injection of dexamethasone or methylprednisolone. Patients were further stratified based on different severities and other characteristics to assess the effectiveness of corticosteroids treatment. We also endeavoured to identify any subgroups who might potentially benefit from corticosteroids treatment.

The primary outcomes of this study were patients' prognosis including mortality and rate of virus clearance. The secondary outcomes included hospital length of stay (LOS), virus clearance time, and change of ratio of pulse oximetric saturation to fraction of inspired oxygen (SpO_2/FiO_2) and percentage of blood lymphocytes. Virus clearance was defined as at least two consecutive negative results of real time-polymerase chain reaction (RT-PCR) in an interval of at least 24 hours, and virus clearance time was calculated from the date of confirmed diagnosis to the date of the second negative RT-PCR test.

Statistical analysis

SPSS Statistics V26 (© Copyright IBM Corporation and other(s) 1989-2019) was used for data analysis, and GraphPad Prism V8.4.2 was used for figure depiction. Continuous variables were shown as mean ± standard deviation, while dichotomous variables were reported as frequency and proportion.

Independent Student's t-test and Spearman Chi-square test or Fisher's exact test were performed to compare the variables and outcomes between the patients with and without corticosteroids. Analysis of variance (ANOVA) was conducted to compare the SpO_2/FiO_2 and blood lymphocytes among different time points in patients with corticosteroids treatment. Bivariate Pearson Correlation Matrix was used to analyse the correlation among various cofounding factors with potential influence on corticosteroids treatment related mortality. Univariate and multivariate logistic regressions were conducted to identify potential independent factors associated with corticosteroids treatment related deaths. We further performed receiver operating characteristics (ROC) curves of each independent risk factors for death to analyse the area under the curve (AUC), and calculated the cut-off values by Youden index (=sensitivity + specificity -1). Statistical significance was defined as a two-sided P value of < 0.05.

Results

A total of 775 patients were included in our final analysis, of which 490 patients were from Wuhan and 285 patients were from Sichuan. Eventually, 238 (30.7%) patients received systemic corticosteroids treatment including 201 (41.0%) patients from Wuhan and 37 (13.0%) from Sichuan. Excluding the

patients with ARDS separately collected from the 2 centres in Wuhan, the overall mortality rate was 5.4%, while the mortality rate in Wuhan and Sichuan was 7.7% and 1.3%, respectively.

Baseline demographics

Table 1 and 2 summarized the demographic characteristics and baseline blood test results between the patients with and without corticosteroids treatment. We found that, compared to the patients without corticosteroids treatment, patients with corticosteroids treatment were older patients (57±16 vs. 51±17, P<0.001) and there were more male patients (59.1% vs. 44.5%, P<0.001), more patients with symptoms (e.g. dyspnoea: 34.4% vs. 17.1%, P<0.001) and comorbidities (50.0% vs. 41.5%, P=0.030), and more severe patients (50.8% vs. 18.6%, P<0.001) and ARDS patients (26.9% vs. 5.8%, P<0.001). The patients in the corticosteroids treatment had significantly lower oxygenation (SpO_2/FiO_2: 194±96 vs. 303±81, P<0.001), blood lymphocytes (14.9±11.5% vs. 25.0±13.2%, P<0.001), and T cells (560±331 vs. 876±422, P<0.001) and its subsets (CD4 cells: 339±209 vs. 545±284, P<0.001; CD8 cells: 207±170 vs. 305±175, P<0.001), but higher neutrophils (76.6±16.8% vs. 64.9±14.3%, P<0.001), D-dimer (6.04±19.70mg/L vs. 2.39±9.31mg/L, P=0.015), and creatine kinase (CK) (155±365 vs. 98±126, P=0.036) than patients without corticosteroids treatment. Although significant differences could also be seen in RR, total bilirubin (TB), alanine aminotransferase (ALT), aspartate transaminase (AST), albumin (ALB), and blood urea nitrogen (BUN), however, they all fell into the normal ranges.

Due to the inconsistent baseline characteristics between patients with and without corticosteroids treatment, we tried to investigate whether these significant differences were derived from the different disease severities in each group. We found that almost all of these characteristics were significantly different between the two groups (Table S1). Therefore, we further compared the outcomes after stratification of the patients into different disease severities.

Primary outcomes

In total patients, compared with patients without corticosteroids treatment, patients with corticosteroids treatment had significantly higher mortality (19.3% vs. 3.7%, P<0.001) but lower rate of virus clearance (43.2% vs. 66.7%, P<0.001). (Table 3) After stratification of disease severities, corticosteroids treatment was associated with higher mortality in patients with severe-to-critical diseases (37.6% vs. 16.5%, P<0.001), while no significant difference was found in the patients with mild-to-moderate diseases (0% vs. 0.5%, P=0.302). However, there were no changes in the rate of virus clearance after stratification (mild-to-moderate: 47.0% vs. 67.4%, P<0.001; severe-to-critical: 37.7% vs. 63.2%, P=0.002). In patients with ARDS, no differences (mortality: 46.8% vs. 29.1%, P=0.090; rate of virus clearance: 38.1% vs. 62.5%, P=0.406) were shown in the two groups. (Table 3)

When compared the treatment outcomes of corticosteroids in patients from different regions, we found a similar pattern in patients from Wuhan, while in patients from Sichuan, no significant differences were shown in either disease severity groups. (Table 3)

Secondary outcomes

Significantly longer hospital LOS (18.7±12.0 vs. 15.0±8.9, P<0.001) and virus clearance time (11.9±9.2 vs. 9.4±8.3, P=0.011) were found in patients with corticosteroids treatments but not in the subgroup of severe-to-critical disease severities (hospital LOS: 18.3±13.4 vs. 15.0±10.3, P=0.051; virus clearance time: 11.5±10.5 vs. 10.5±8.9, P=0.626), which was also true in patients from Wuhan and Sichuan. (Table 3)

In terms of the improvement of oxygenation and blood lymphocytes over time (24h vs. 48h vs. 72h vs. 7d), we found that corticosteroids could not improve oxygenation (SpO_2/FiO_2) except for patients with ARDS (160±68 vs. 230±109 vs. 265±123 vs. 216±37, P=0.044), neither could it increase blood lymphocytes except for patients with severe-to-critical diseases (9.2±8.9% vs. 13.8±7.8% vs. 15.3±11.2% vs. 16.0±10.9%, P=0.008) and ARDS (6.8±7.8% vs. 14.7±10.4% vs. 12.4±12.6% vs. 13.3±11.1%, P=0.050). (Table S2 and Fig. 1 and 2) However, despite the improvement of oxygenation and blood lymphocytes after corticosteroids treatment, the levels were still significantly lower than those in patients without corticosteroids treatment. (Table S2 and Fig. 1 and 2)

Risk factors for death associated with corticosteroids treatment

Table 4 showed the potential factors associated with death in patients with corticosteroids treatment. We found that the factors with significant differences were similar to those demographics and characteristics identified as significantly different between the patients with and without corticosteroids treatment. Compared to survivals, patients who died with corticosteroids treatment were older (72±13 vs. 54±15, P<0.001) and there were more patients with symptoms (e.g. dyspnoea: 66.7% vs. 27.9%, P<0.001) and comorbidities (74.4% vs. 45.6%, P=0.001), and more severe patients (100.0% vs. 39.7%, P<0.001) and ARDS patients (67.4% vs. 21.9%, P<0.001). Interestingly, we also noticed more patients who received corticosteroids treatment within 48 hours of admission in the group of death (79.2% vs. 51.9%, P=0.012). The patients in the corticosteroids treatment had significantly lower oxygenation (SpO_2/FiO_2: 132±45 vs. 226±99, P<0.001), blood lymphocytes (5.2±4.0% vs. 17.9±11.4%, P<0.001), and T cells (341±237 vs. 597±331, P=0.016), but higher neutrophils (91.0±5.1% vs. 72.2±16.9%, P<0.001), D-dimer (17.53±43.76mg/L vs. 3.73±8.54mg/L, P=0.006), TB (20.4±17.1μmol/L vs. 12.2±7.4μmol/L, P=0.001), ALT (54.8±56.2U/L vs. 34.4±24.4U/L, P=0.011), AST (67.6±42.1U/L vs. 31.7±16.3U/L, P<0.001), CK (445±802U/L vs. 93±91U/L), and BUN (11.54±9.10mmol/L vs. 5.43±4.14mmol/L, P<0.001) than patients without corticosteroids treatment upon admission.

After the correlation matrix analysis of the above potential risk factors (Table S3), we finally chose the variates with less internal correlations in our multivariate logistic regression model, which included age, blood lymphocytes, D-dimer, ALT, CK, and the percentage of comorbidities and use of corticosteroids within 48 hours of admission. The multivariate logistic regression showed that blood lymphocytes (odds ratio (OR) 0.792, 95% confidence interval (CI) 0.672-0.932, P=0.005) and CK (OR 1.006, 95%CI 1.000-1.012, P=0.038) were independent risk factors associated with death in patients with corticosteroids treatment. (Table 5) The ROC curves identified a cut-off value of 10.45% for blood lymphocytes (AUC

0.863, 95%CI 0.778-0.947, P<0.001) with a sensitivity and specificity of 90.91% and 70.75%, and a cut-off value of 239.50 U/L for CK (AUC 0.672, 95%CI 0.504-0.840, P=0.023) with a sensitivity and specificity of 44.44% and 94.05%. (Figure 3 and Table 5)

Discussion

In this study, we found that corticosteroids inclined to be used in patients with severe and critical Covid-19, however, corticosteroids treatment was associated with higher mortality, lower rate of virus clearance, and increased days of hospital stay, although it could improve oxygenation and elevate the level of blood lymphocytes in severe patients. Low blood lymphocytes (<10.45%) and high blood CK level (>239.50U/L) were independent risk factors associated with mortality in patients receiving corticosteroids treatment.

Since the outbreak of SARS-CoV-2, debates have increased on the use of corticosteroids in patients with Covid-19.[12,13] Based on the experiences during the 2002 SARS and 2009 H1N1 pandemic, corticosteroids are expected to improve the outcomes if utilized in an early acute phase of infection.[14,15] However, controversial findings have been reported in the treatment of patients with Covid-19. Case reports and studies with small number of patients found that corticosteroids treatment did not shorten duration of symptoms or hospital length of stays, but associated with greater risk of ICU admission.[16,17,18] Furthermore, high-dose corticosteroids use has been reported to be associated with death in patients with severe Covid-19.[19] On contrary, a retrospective cohort study of 201 patients with Covid-19 found that treatment with methylprednisolone could significantly decrease the risk of death by 62% among patients with ARDS.[20] In our study, we found that corticosteroids treatment was associated with increased mortality, especially in patients with severe Covid-19 or ARDS. While, in patients with mild-to-moderate Covid-19, corticosteroids treatment could not bring any benefits. Although our results showed that corticosteroids could improve oxygenation in patients with severe Covid-19 and ARDS, but this increase of oxygenation still could not be able to change the final outcomes, which we think might be due to the limited extent of increase in oxygenation. Therefore, our results support the recommendations by the World Health Organization against the administration of systemic corticosteroids to patients with Covid-19.[21]

There is another concern of the commencement of corticosteroids in patients with Covid-19, which is the delay of virus clearance. Studies in patients with SARS-CoV, influenza A (H7N9), and Middle East Respiratory Syndrome (MERS) have already shown delayed viral clearance after systemic corticosteroids treatment.[22-24] In this study, we found that corticosteroids treatment was not associated with longer virus clearance time in patients with severe Cvoid-19 and ARDS, which is in consistent with the previous reports.[17,25] However, in patients with mild-to-moderate Covid-19, we noticed that the use of corticosteroids significantly delayed the virus clearance time. In addition, we also found that the rate of virus clearance was significantly lower in patients with corticosteroids regardless of the disease severities. Hence, the use of systemic corticosteroids in patients with Covid-19 should be cautious.

In terms of blood lymphocytes, previous studies have reported in consensus that lymphopenia is commonly developed in patients with Covid-19,[16,18] which is caused by upregulated cell apoptosis, autophagy, and migration to the lungs.[26,27] The level of lymphocytes has been found to be negatively associated with disease severity and a gradual increase of lymphocytes has been seen in recovered patients.[16,18,28] In addition, lymphopenia has also been reported to be an indicator for mortality in patients with Covid-19.[29,30] In our study, we found that the level of blood lymphocytes could also be served as a good predictor of death related to corticosteroids treatment. We also noticed an increase of lymphocytes after corticosteroids treatment especially in patients with severe Covid-19 and ARDS, however, it did not result in reduced mortality related to corticosteroids treatment even though the levels the lymphocytes were increased to by the corticosteroids were similar to those in patients without corticosteroids treatment. Thus, it seems the outcomes of the patients are determined by the severities of Covid-19 rather than the increase of blood lymphocytes, which is also true for the increase of oxygenation by corticosteroids. On the other hand, it is not clear how corticosteroids increase the blood lymphocytes. One possibility is the amelioration of inflammation by corticosteroids, which results in less cell migration to the inflammatory site. However, further studies are needed to address this phenomenon.

There are several limitations in our study. Firstly, albeit this is a study with relatively large numbers of patients, prospective controlled trials are needed for further validation, especially with comparable patients' baseline characteristics. Despite the stratification of different disease severities in our study, we could still notice the significant differences in oxygenation and blood lymphocytes between the patients with and without corticosteroids treatment, which might potentially underestimate the effects of corticosteroids. Secondly, due to the miscellaneous types, doses, and durations of corticosteroids used, it is not feasible for us to draw a clear conclusion whether any specific regime may potentially bring benefits or is associated with worse outcomes. Thirdly, some other cofounding factors such as the access to ICU have not been investigated or considered because of the shortage of medical sources. Finally, due to the small numbers of dead patients with corticosteroids treatment, limited variates were included in the multivariate logistic regression model, which might omit some clinically important causes associated with mortality such as complications and multiple organ dysfunction syndrome, as SARS-CoV-2 could infect other tissues besides the lungs due to the wide expression of the virus receptors in different tissues[31].

Conclusions

For patients with Covid-19, especially those with severe categories, corticosteroids treatment is associated with increased mortality and reduced rate of virus clearance. Therefore, commencement of corticosteroids in patients with Covid-19 should be cautious before more evidence. In addition, blood lymphocytes and CK levels could be used as predictors for corticosteroid treatment failure.

Abbreviations

ALB, albumin; ALT, alanine aminotransferase; ANOVA, analysis of variance; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; AUC, area under the curve; BUN, blood urea nitrogen; CI, confidence interval; CK, creatine kinase; Covid-19, coronavirus disease 2019; ICU, intensive care unit; LOS, length of stay; MERS, Middle East Respiratory Syndrome; OR, odds ratio; PaO_2/FiO_2, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; ROC, receiver operating characteristics; RR, respiratory rate; RT-PCR, real time-polymerase chain reaction; SARS, severe acute respiratory syndrome; SpO_2/FiO_2, ratio of pulse oximetric saturation to fraction of inspired oxygen; TB, total bilirubin.

Tables

Table 1 Demographics between patients with and without corticosteroids treatment.

Characteristics	Corticosteroid group			No corticosteroid group			P (Total)	P (Wuhan)	P (Out of Wuhan)
	Total (n=238)	Wuhan (n=201)	Out of Wuhan (n=37)	Total (n=537)	Wuhan (n=289)	Out of Wuhan (n=248)			
Gender (Male, %)	140 (59.1)	117 (58.2)	23 (63.9)	234 (44.5)	107 (38.1)	127 (51.8)	<0.001	<0.001	0.176
Age (years)	57±16	58±16	52±16	51±17	56±16	44±15	<0.001	0.299	0.005
Alcohol history (%)							0.028	0.013	0.568
Never	159 (86.4)	129 (87.2)	30 (83.4)	385 (84.1)	198 (91.2)	187 (77.6)			
Current alcoholist	10 (5.4)	7 (4.7)	3 (8.3)	51 (11.1)	15 (7.0)	36 (14.9)			
Ex-alcoholist	15 (8.2)	12 (8.1)	3 (8.3)	22 (4.8)	4 (1.8)	18 (7.5)			
Smoking history (%)							<0.001	0.054	0.085
Never	177 (85.1)	144 (83.7)	33 (91.7)	401 (85.9)	201 (88.2)	200 (83.7)			
Current smoker	12 (5.8)	11 (6.4)	1 (2.8)	52 (11.1)	18 (7.9)	34 (14.2)			
Ex-smoker	19 (9.1)	17 (9.9)	2 (5.5)	14 (3.0)	9 (3.9)	5 (2.1)			
Symptoms (%)									
Fever	164 (88.0)	135 (75.8)	29 (82.9)	335 (65.6)	173 (62.5)	162 (69.2)	0.002	0.003	0.098
Dry	66	51	15	156	67	89	0.816	0.241	0.585

cough	(32.4)	(30.0)	(44.1)	(31.5)	(24.9)	(39.2)			
Dyspnoea	72 (34.4)	62 (35.6)	10 (28.6)	87 (17.1)	67 (24.3)	20 (8.6)	<0.001	0.009	0.002
Fatigue	86 (41.7)	76 (43.4)	10 (32.3)	161 (31.8)	109 (39.6)	52 (22.4)	0.011	0.425	0.225
Wheeze	57 (27.4)	51 (29.3)	6 (17.6)	48 (9.5)	44 (16.0)	4 (1.7)	<0.001	0.001	<0.001
Chest tightness	62 (29.8)	56 (32.0)	6 (18.2)	89 (17.5)	66 (24.0)	23 (9.8)	<0.001	0.063	0.145
Muscle pain	33 (15.7)	26 (14.9)	7 (20.0)	64 (12.7)	35 (12.7)	29 (12.7)	0.284	0.520	0.287
Vital signs (upon admission)									
T (°C)	36.9±0.8	36.8±0.7	37.2±0.9	36.9±0.7	36.7±0.6	37.1±0.7	0.740	0.040	0.219
HR (bpm)	88±16	87±15	94±17	89±30	89±39	89±14	0.699	0.562	0.062
RR (bpm)	22±5	22±6	22±4	20±3	20±4	20±2	<0.001	0.001	<0.001
SBP (mmHg)	129±19	128±18	135±24	127±18	128±19	127±17	0.214	0.898	0.008
DBP (mmHg)	78±13	77±12	81±16	79±12	77±11	80±12	0.540	0.661	0.655
SpO_2 (%)	89.5±10.7	87.9±11.4	96.0±3.5	95.8±5.7	93.3±9.1	96.9±2.8	<0.001	0.002	0.182
Comorbidities (%)									
Any comorbidities	116 (50.0)	99 (49.5)	17 (53.1)	211 (41.5)	137 (48.4)	74 (32.7)	0.030	0.813	0.024

Hypertension	66 (28.3)	55 (27.4)	11 (34.4)	121 (23.9)	86 (30.4)	35 (15.7)	0.200	0.470	0.010
CHD	15 (6.4)	10 (5.0)	5 (15.6)	27 (5.3)	20 (7.1)	7 (3.1)	0.548	0.347	0.010
DM	36 (15.5)	30 (14.9)	6 (18.8)	48 (9.5)	34 (12.0)	14 (6.3)	0.018	0.351	0.026
COPD	19 (8.2)	11 (5.5)	8 (25.0)	17 (3.4)	13 (4.6)	4 (1.8)	0.005	0.661	<0.001
Asthma	11 (4.7)	5 (2.5)	6 (18.8)	13 (2.6)	9 (3.2)	4 (1.8)	0.125	0.654	<0.001
Dementia	7 (3.0)	6 (3.0)	1 (3.1)	5 (1.0)	4 (1.4)	1 (0.4)	0.059	0.332	0.236
Stroke	6 (2.6)	5 (2.5)	1 (3.1)	11 (2.2)	10 (3.5)	1 (0.4)	0.735	0.513	0.236
CKD	7 (3.0)	5 (2.5)	2 (6.3)	11 (2.2)	6 (2.1)	5 (2.2)	0.496	0.768	0.215
Carcinoma	8 (3.4)	7 (3.5)	1 (3.1)	13 (2.6)	10 (3.5)	3 (1.3)	0.511	0.976	0.417
Severities (%)									
Mild-to-Moderate	117 (49.2)	103 (51.2)	14 (37.8)	437 (81.4)	208 (72.0)	229 (92.3)	<0.001	<0.001	<0.001
Severe-to-Critically[#]	121 (50.8)	98 (48.8)	23 (62.2)	100 (18.6)	81 (28.0)	19 (7.7)	<0.001	<0.001	<0.001
ARDS	64 (26.9)	53 (26.4)	11 (29.7)	31 (5.8)	23 (8.0)	8 (3.2)	<0.001	<0.001	<0.001
Treatments									
Antiviral agents (%)	232 (97.5)	195 (97.0)	37 (100)	508 (94.6)	277 (95.8)	231 (93.1)	0.075	0.499	0.141

[#]Including ARDS. Abbreviations: ARDS, acute respiratory distress syndrome; CHD, chronic heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; SpO_2, pulse oximetric saturation; T, body temperature.

Table 2 Baseline (within 24h of admission) laboratory measurements between patients with and without corticosteroids treatment.

Characteristics	Corticosteroid group			No corticosteroid group			P (Total)	P (Wuhan)	P (Out of Wuhan)
	Total (n=238)	Wuhan (n=201)	Out of Wuhan (n=37)	Total (n=537)	Wuhan (n=289)	Out of Wuhan (n=248)			
ABG									
SpO_2/FiO_2	194±96	176±83	298±105	303±81	265±107	325±53	<0.001	<0.001	0.225
PaO_2/FiO_2	165±121	150±114	260±125	304±157	292±192	318±109	<0.001	<0.001	0.205
pH	7.40±0.11	7.39±0.12	7.44±0.03	7.40±0.08	7.38±0.09	7.41±0.05	0.919	0.646	0.091
$PaCO_2$ (mmHg)	41±12	42±12	34±7	43±24	43±11	43±31	0.430	0.577	0.291
HCO^{3-} (mmol/L)	29.0±28.3	30.5±32.6	24.7±6.2	23.1±22.6	25.7±3.8	21.2±29.8	0.132	0.254	0.667
Routine blood test									
Hb (g/L)	127±19	127±18	126±28	129±22	124±17	140±27	0.313	0.094	0.071
HCT	0.371±0.053	0.370±0.052	0.378±0.065	0.379±0.055	0.364±0.051	0.415±0.047	0.078	0.207	0.017
PLT (10^9/L)	209±93	212±94	157±58	215±92	229±96	181±71	0.439	0.070	0.235
WBC (10^9/L)	8.02±5.30	8.15±5.44	6.37±2.54	6.00±2.99	6.08±3.21	5.82±2.39	<0.001	<0.001	0.425
Lymphocytes (%)	14.9±11.5	15.2±11.7	10.7±6.8	25.0±13.2	25.5±11.9	23.7±16.0	<0.001	<0.001	0.006
	76.6±1	76.3±1	81.3±1	64.9±1	63.9±1	67.3±1	<0.001	<0.001	0.001

Neutrophils (%)	6.8	7.2	1.1	4.3	4.5	3.8			
Eosinophils (%)	0.6±1.2	0.6±1.2	0.4±1.0	1.1±1.5	1.3±1.5	0.5±0.7	<0.001	<0.001	0.670
Basophils (%)	0.2±0.2	0.2±0.2	0.1±0.1	0.3±0.3	0.4±0.4	0.2±0.2	<0.001	<0.001	0.032
Monocytes (%)	6.1±3.8	6.1±3.9	5.1±2.2	7.9±3.7	8.0±3.7	7.7±3.6	<0.001	<0.001	0.014
Coagulation test									
D-dimer (mg/L)	6.04±19.70	6.26±20.59	3.88±5.88	2.39±9.31	2.80±10.74	1.43±4.37	0.015	0.063	0.112
Fibrinogen (g/L)	6.99±12.07	7.26±12.69	4.53±1.42	5.19±22.71	3.79±3.54	8.15±39.73	0.432	0.001	0.764
APTT (s)	28.8±4.8	28.0±3.8	36.0±7.3	29.0±5.1	27.8±4.4	31.5±5.4	0.746	0.668	0.015
INR	1.05±0.12	1.05±0.11	1.08±0.16	1.03±0.12	1.03±0.13	1.05±0.10	0.245	0.233	0.317
Biochemical analysis									
TB (μmol/L)	13.4±9.9	13.6±10.2	10.9±4.9	11.0±6.5	11.4±6.5	10.1±6.3	0.003	0.020	0.689
ALT (U/L)	37.0±31.1	36.9±31.4	38.5±28.2	28.4±23.3	28.5±25.3	28.1±18.5	0.002	0.011	0.100
AST (U/L)	36.4±24.6	36.0±24.8	41.6±23.0	28.2±18.2	27.6±18.3	29.8±17.9	<0.001	0.011	0.051
ALB (g/L)	36.4±5.2	36.1±5.1	39.0±5.5	41.5±27.7	38.3±5.4	48.2±47.9	0.037	<0.001	0.513
CK (U/L)	155±365	161±382	94±33	98±126	91±131	114±114	0.036	0.035	0.588

Glu (mmol/L)	9.32±16.71	9.37±17.26	8.70±4.17	7.78±22.37	8.26±26.54	6.64±2.96	0.437	0.648	0.040
BUN (mmol/L)	6.81±6.14	6.98±6.36	4.86±1.74	5.10±4.97	5.50±5.73	4.15±2.11	0.001	0.017	0.235
Cr (μmol/L)	78.6±90.8	79.5±94.5	68.0±18.8	76.0±112.3	77.1±122.7	73.5±83.9	0.792	0.833	0.809
T cell subsets									
CD3 (cells/μL)	560±331	570±333	326±121	876±422	883±404	832±528	<0.001	<0.001	0.115
CD4 (cells/μL)	339±209	339±209	-	545±284	552±279	468±342	<0.001	<0.001	
CD8 (cells/μL)	207±170	207±170	-	305±175	300±156	360±337	<0.001	<0.001	
CD4/CD8	1.99±1.16	2.05±1.16	0.71±0.35	2.04±1.08	2.08±1.10	1.85±0.96	0.741	0.849	0.053
Complement 3 (g/L)	1.109±0.215	1.105±0.215	-	1.047±0.208	1.044±0.208	1.143±0.178	0.048	0.054	
Complement 4 (g/L)	0.289±0.116	0.288±0.116	-	0.262±0.102	0.262±0.103	0.256±0.084	0.086	0.115	
Pro-BNP (pg/mL)	885.34±2946.43	926.73±3018.63	107.24±206.03	590.50±2917.51	672.24±3215.60	261.01±1047.65	0.431	0.550	0.748

[#]Including ARDS. Abbreviations: ABG, arterial blood gas; ALB, albumin; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate transaminase; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CK, creatine kinase; FiO_2, fraction of inspired oxygen; Glu, glucose; Hb, haemoglobin; HCO3-, bicarbonate; HCT, haematocrit test; INR, the international normalized ratio; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PLT, platelet; SpO_2, pulse oximetric saturation; TB, total bilirubin; WBC, white blood cell.

Table 3 Primary outcomes between patients with and without corticosteroids treatment.

Outcomes	Corticosteroid group			No corticosteroid group			P (Total)	P (Wuhan)	P (Out of Wuhan)
	Total (n=238)	Wuhan (n=201)	Out of Wuhan (n=37)	Total (n=537)	Wuhan (n=289)	Out of Wuhan (n=248)			
Overall									
Endpoint (%)							<0.001	<0.001	0.007
Recovery	161 (70.6)	137 (70.3)	24 (72.7)	433 (88.5)	244 (86.5)	189 (91.3)			
No change	23 (10.1)	15 (7.7)	8 (24.2)	38 (7.8)	22 (7.8)	16 (7.7)			
Death	44 (19.3)	43 (22.1)	1 (3.0)	18 (3.7)	16 (5.7)	2 (1.0)			
Hospital LOS	18.7±12.0	18.1±12.5	23.3±6.4	15.0±8.9	15.0±10.3	15.1±6.8	<0.001	0.003	<0.001
Rate of virus clearance (%)	83 (43.2)	65 (41.4)	18 (51.4)	311 (66.7)	159 (59.3)	152 (76.8)	<0.001	<0.001	0.002
Virus clearance time (days)	11.9±9.2	14.5±8.3	6.9±8.9	9.4±8.3	11.5±9.1	7.8±7.3	0.011	0.020	0.543
Mild-to-Moderate									
Endpoint (%)							0.302	0.578	0.323
Recovery	99 (89.2)	90 (90.0)	9 (81.8)	363 (92.6)	188 (92.2)	175 (93.1)			
No change	12 (10.8)	10 (10.0)	2 (18.2)	27 (6.9)	15 (7.4)	12 (6.4)			
Death	0 (0)	0 (0)	0 (0)	2 (0.5)	1 (0.5)	1 (0.5)			

Hospital LOS	19.2±10.5	18.7±10.8	23.3±5.8	15.0±8.6	15.2±10.2	14.9±6.7	<0.001	0.005	<0.001
Rate of virus clearance (%)	54 (47.0)	47 (46.1)	7 (53.8)	263 (67.4)	122 (58.7)	141 (77.5)	<0.001	0.037	0.086
Virus clearance time (days)	12.2±8.4	13.9±7.8	5.9±7.5	9.3±8.2	11.5±9.2	7.8±7.1	0.012	0.114	0.373
Severe-to-Critical #									
Endpoint (%)							<0.001	0.001	0.898
Recovery	62 (53.0)	47 (49.5)	15 (68.2)	70 (72.2)	56 (71.8)	14 (73.7)			
No change	11 (9.4)	5 (5.3)	6 (27.3)	11 (11.3)	7 (9.0)	4 (21.1)			
Death	44 (37.6)	43 (45.3)	1 (4.5)	16 (16.5)	15 (19.2)	1 (5.3)			
Hospital LOS	18.3±13.4	17.4±14.1	23.3±6.9	15.0±10.3	14.5±10.5	17.6±8.5	0.051	0.139	0.050
Rate of virus clearance (%)	29 (37.7)	18 (32.7)	11 (50.0)	48 (63.2)	37 (61.7)	11 (68.8)	0.002	0.002	0.248
Virus clearance time (days)	11.5±10.5	16.3±9.4	7.6±9.8	10.5±8.9	11.5±8.9	8.1±8.8	0.626	0.074	0.868
ARDS									
Endpoint (%)							0.090	0.108	0.649
Recovery	30 (48.4)	23 (44.2)	7 (70.0)	17 (54.8)	11 (47.8)	6 (75.0)			

No change	3 (4.8)	1 (1.9)	2 (20.0)	5 (16.1)	3 (13.0)	2 (25.0)			
Death	29 (46.8)	28 (53.8)	1 (10.0)	9 (29.1)	9 (39.1)	0 (0)			
Hospital LOS	17.4±13.1	16.3±13.5	24.0±7.8	13.5±11.5	11.6±11.2	20.3±10.6	0.173	0.155	0.452
Rate of virus clearance (%)	8 (38.1)	3 (30.0)	5 (45.5)	5 (62.5)	1 (50.0)	4 (66.7)	0.406	1.000	0.620
Virus clearance time (days)	12.0±13.5	19.7±17.8	9.9±12.3	12.9±9.6	10.0	13.3±10.4	0.883	0.684	0.571

[#]Including ARDS. ARDS, acute respiratory distress syndrome; LOS, length of stay.

Table 4 Characteristics between survivals and deaths in patients with corticosteroids treatment.

Characteristics	Survival (n=184)	Death (n=44)	P	Characteristics	Survival (n=184)	Death (n=44)	P
Gender (Male, %)	105 (57.1)	31 (70.5)	0.104	*Treatments*			
Age (years)	54±15	72±13	<0.001	Antiviral agents (%)	180 (97.8)	42 (95.5)	0.327
Alcohol history (%)				Use of corticosteroids within 48h of admission (%)	84 (51.9)	19 (79.2)	0.012
Never	126 (86.3)	26 (86.7)	0.185	*ABG*			
Current alcoholist	10 (6.8)	0 (0)		SpO_2/FiO_2	226±99	132±45	<0.001
Ex-alcoholist	10 (6.8)	4 (13.3)		PaO_2/FiO_2	199±136	114±69	0.011
Smoking history (%)				pH	7.41±0.09	7.36±0.13	0.038
Never	138 (85.2)	32 (86.5)	0.573	$PaCO_2$ (mmHg)	39±9	45±15	0.024
Current smoker	11 (6.8)	1 (2.7)		HCO^{3-} (mmol/L)	25.6±5.2	40.9±60.2	0.098
Ex-smoker	13 (8.0)	4 (10.8)		*Routine blood test*			
Symptoms (%)				Hb (g/L)	127±17	127±25	0.949
Fever	130 (77.4)	28 (75.7)	0.823	HCT	0.370±0.050	0.374±0.064	0.681
Dry cough	57 (35.4)	6 (17.1)	0.036	PLT (10^9/L)	220±93	173±81	0.004
Dyspnoea	46 (27.9)	24 (66.7)	<0.001	WBC (10^9/L)	6.70±3.58	12.74±7.47	<0.001

Fatigue	59 (36.4)	25 (69.4)	<0.001	Lymphocytes (%)	17.9±11.4	5.2±4.0	<0.001
Wheeze	34 (20.7)	20 (55.6)	<0.001	Neutrophils (%)	72.2±16.9	91.0±5.1	<0.001
Chest tightness	46 (28.0)	15 (41.7)	0.108	Eosinophils (%)	0.7±1.3	0.2±0.6	0.030
Muscle pain	24 (14.5)	9 (25.0)	0.121	Basophils (%)	0.2±0.3	0.1±0.2	0.036
Vital signs				Monocytes (%)	6.9±3.8	3.2±2.1	<0.001
T (°C)	36.9±0.8	36.7±0.8	0.044	*Coagulation test*			
HR (bpm)	88±16	91±16	0.184	D-dimer (mg/L)	3.73±8.54	17.53±43.76	0.006
RR (bpm)	21±5	25±7	<0.001	Fibrinogen (g/L)	7.29±13.17	5.75±3.69	0.635
SBP (mmHg)	128±18	133±24	0.130	APTT (s)	28.7±5.1	29.6±3.1	0.480
DBP (mmHg)	77±12	81±13	0.050	INR	1.03±0.09	1.13±0.18	0.001
SpO_2 (%)	92.4±8.2	81.5±12.8	<0.001	*Biochemical analysis*			
Comorbidities (%)				TB (μmol/L)	12.2±7.4	20.4±17.1	0.001
Any comorbidities	82 (45.6)	32 (74.4)	0.001	ALT (U/L)	34.4±24.4	54.8±56.2	0.011
Hypertension	47 (26.1)	17 (38.6)	0.099	AST (U/L)	31.7±16.3	67.6±42.1	<0.001
CHD	13 (7.2)	2 (4.5)	0.741	ALB (g/L)	37.0±5.3	33.4±3.1	0.005
DM	27 (15.0)	9 (20.5)	0.377	CK (U/L)	93±91	445±802	<0.001

COPD	13 (7.2)	6 (13.6)	0.223	Glu (mmol/L)	9.13±19.03	10.09±5.62	0.758
Asthma	7 (3.9)	4 (9.1)	0.233	BUN (mmol/L)	5.43±4.14	11.54±9.10	<0.001
Dementia	1 (0.6)	6 (13.6)	<0.001	Cr (μmol/L)	73.7±98.1	95.4.4±62.4	0.193
Stroke	2 (1.1)	4 (9.1)	0.015	*T cell subsets*			
CKD	5 (2.8)	2 (4.5)	0.626	CD3 (cells/μL)	597±331	341±237	0.016
Carcinoma	4 (2.2)	4 (9.1)	0.050	CD4 (cells/μL)	365±210	174±103	0.006
Severities (%)				CD8 (cells/μL)	213±173	170±150	0.458
Mild-to-Moderate	111 (60.3)	0 (0)	<0.001	CD4/CD8	2.09±1.18	1.41±0.86	0.073
Severe-to-Critically[#]	73 (39.7)	44 (100)	<0.001	Complement 3 (g/L)	1.117±0.205	1.051±0.289	0.423
ARDS	33 (21.9)	29 (67.4)	<0.001	Complement 4 (g/L)	0.290±0.104	0.289±0.194	0.989
				Pro-BNP (pg/mL)	614.83±3101.43.99	1773.60±2485.49	0.100

[#]Including ARDS. Abbreviations: ABG, arterial blood gas; ALB, albumin; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CHD, chronic heart disease; CK, creatine kinase; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; DM, diabetes mellitus; FiO_2, fraction of inspired oxygen; Glu, glucose; Hb, haemoglobin; HCO^{3-}, bicarbonate; HCT, haematocrit test; HR, heart rate; INR, the international normalized ratio; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO2, arterial partial pressure of oxygen; PLT, platelet; RR, respiratory rate; SBP, systolic blood pressure; SpO_2, pulse oximetric saturation; T, body temperature; TB, total bilirubin; WBC, white blood cell.

Table 5 Univariate and multivariate logistic regression of factors associated with death in patients with corticosteroids treatment.

Characteristics	Univariate		Multivariate		Cut-off	Sensitivity	Specificity	PPV	NPV
	OR (95% CI)	P	OR (95% CI)	P					
Age (years)	1.105 (1.069, 1.143)	<0.001	1.044 (0.979, 1.114)	0.189					
Any comorbidities	3.477 (1.650, 7.325)	0.001	1.924 (0.244, 15.186)	0.535					
Use of corticosteroids within 48h of admission	3.529 (1.257, 9.906)	0.017	5.067 (0.720, 35.648)	0.103					
Lymphocytes	0.778 (0.709, 0.852)	<0.001	0.792 (0.672, 0.932)	0.005	10.45	90.91 %	70.75 %	48.19 %	96.30 %
D-dimer	1.030 (0.996, 1.066)	0.085	-	-					
ALT	1.015 (1.001, 1.030)	0.035	1.016 (0.990, 1.043)	0.230					
CK	1.006 (1.002, 1.009)	0.003	1.006 (1.000, 1.012)	0.038	239.50	44.44 %	94.05 %	61.54 %	88.76 %

[#]Including ARDS. Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; CK, creatine kinase; NPV, negative predict value; OR, odds ratio; PPV, positive predict value.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University.

Consent for publication

All patients were consented for publications.

Availability of data and material

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

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions:

HY and Z-AL designed the study; Huan Y, ZN, DL and HC collected and recorded the data; HY, RY and B-ML conducted the data analysis; HY, P-JL and TW drafted the manuscript; F-ML and Z-AL revised the manuscript critically for important intellectual content; Z-AL made the decision to submit report for publication. All authors read and approved the final manuscript.

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Figures

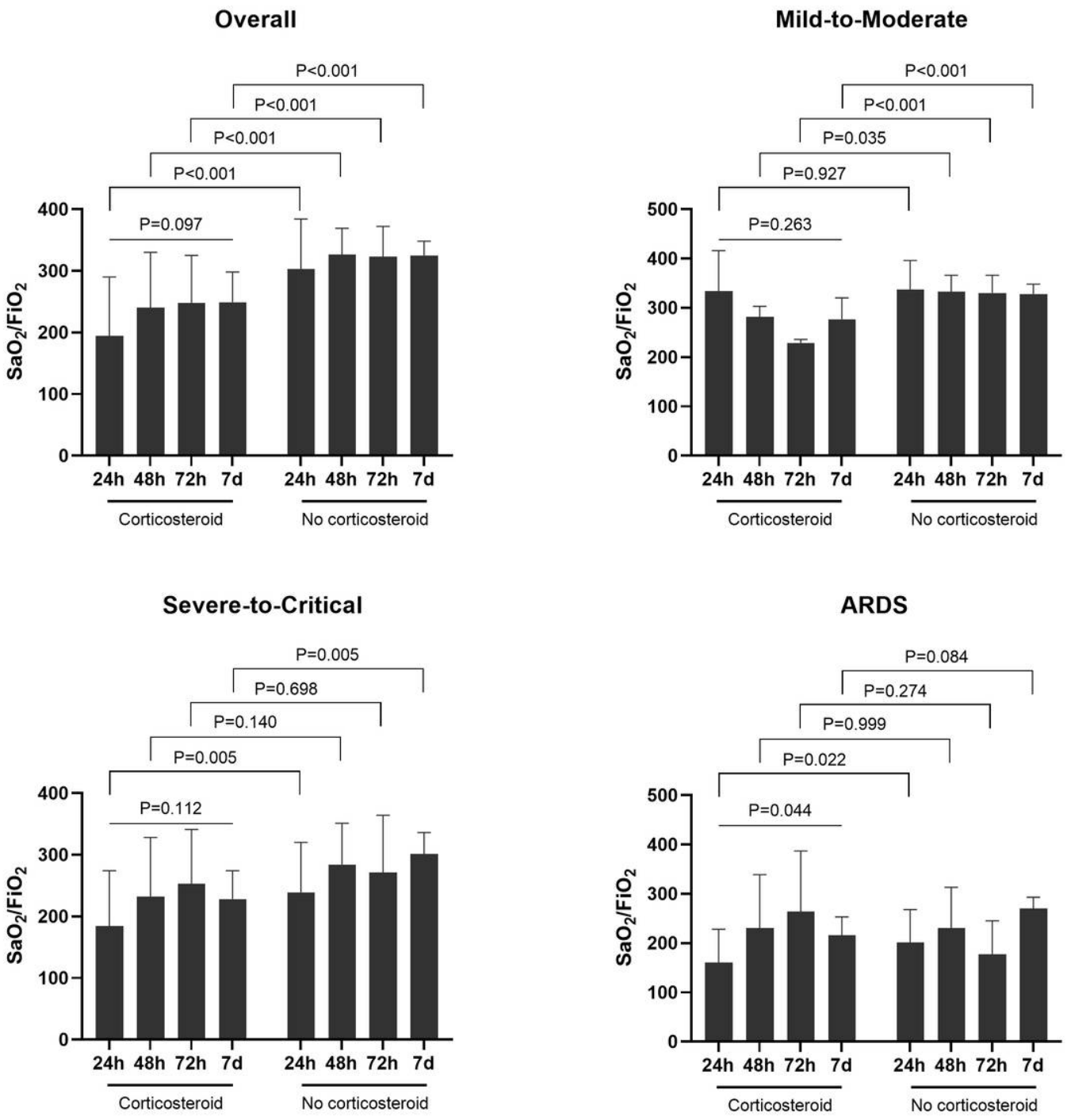

Figure 1

Change of SpO2/FiO2 in patients with and without steroids. FiO2, fraction of inspired oxygen; SpO2, pulse oximetric saturation.

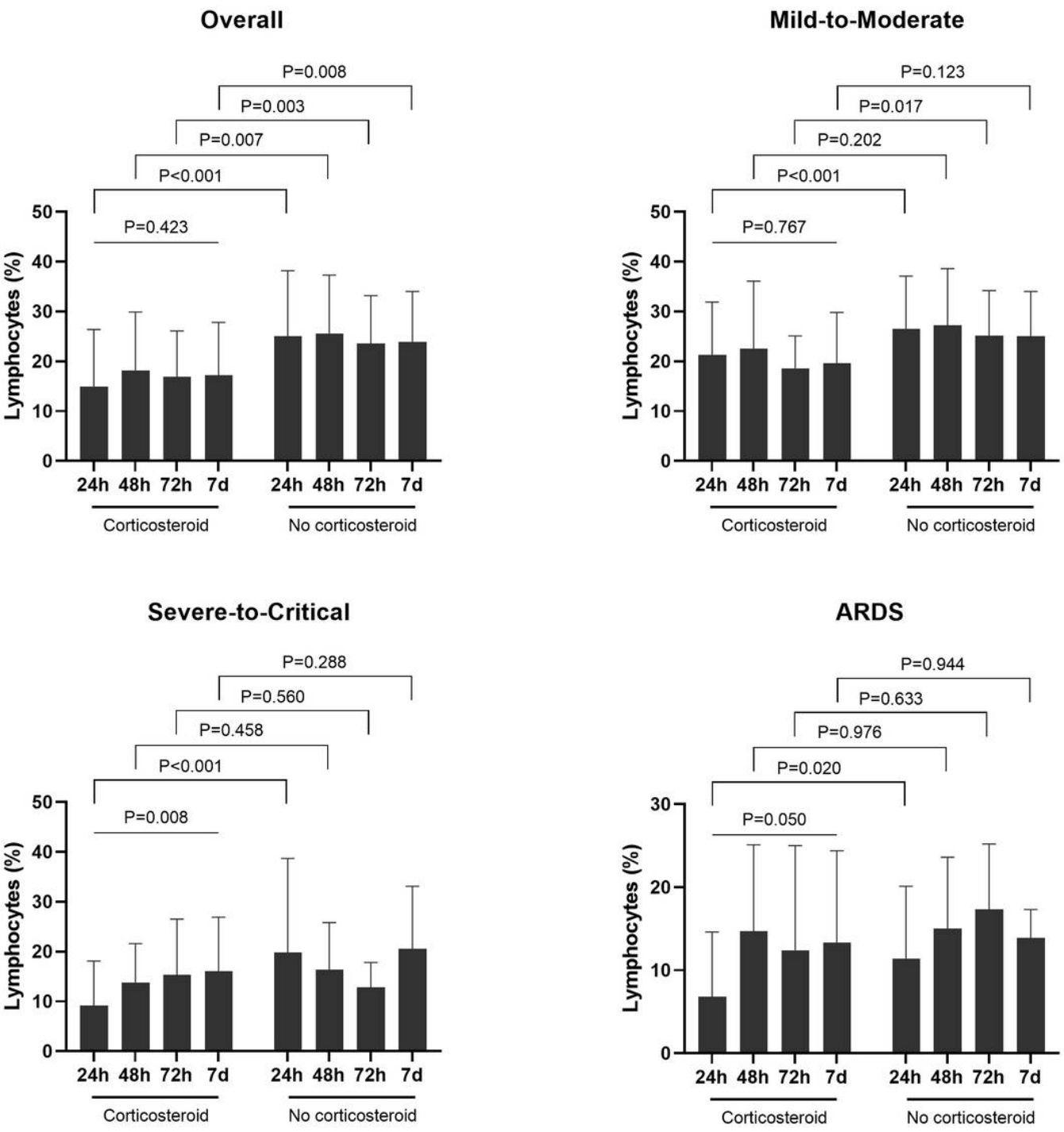

Figure 2

Change of Lymphocytes in patients with and without steroids.

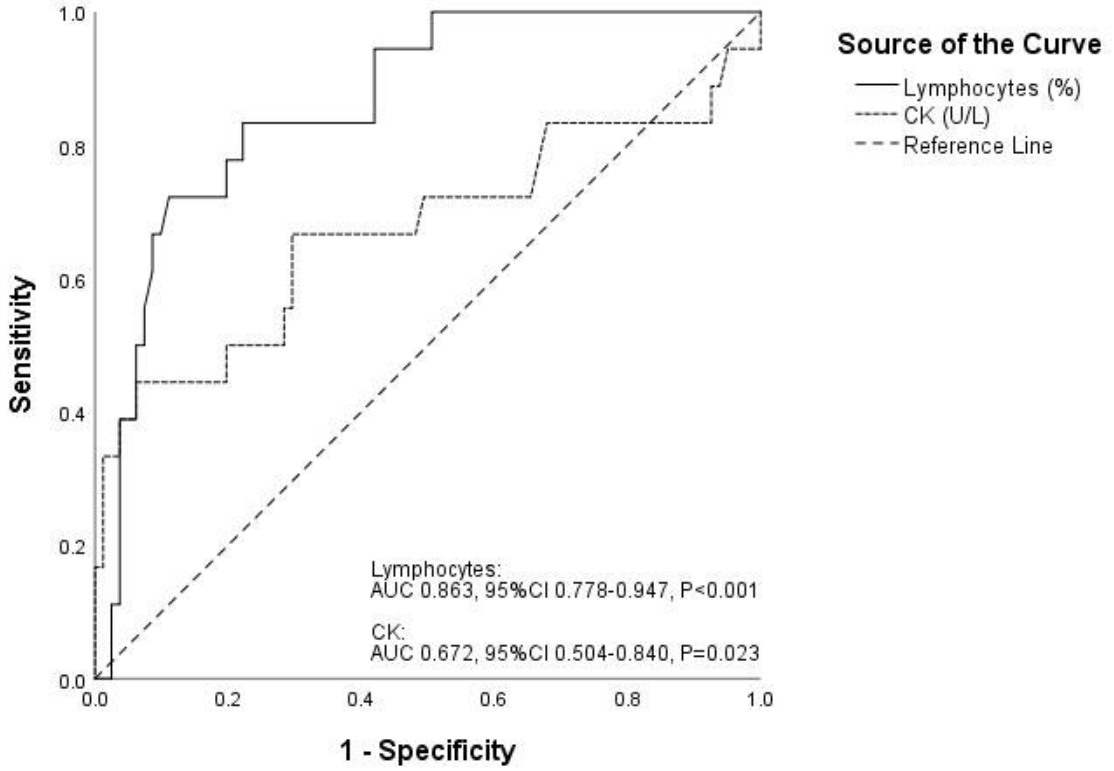

Figure 3

ROC curves of blood lymphocytes and CK. AUC, area under the curve; CI, confidence interval; CK, creatine kinase; ROC, receiver operating characteristics.

Supplementary Files

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- Supplementarymaterials.docx