Corticosteroids treatment in severe patients with COVID-19: a propensity score matching study

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Research

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Abstract

Objectives Explore the efficacy of corticosteroid treatment in patients with severe COVID-19 pneumonia and the association between corticosteroid use and patient mortality.

Methods A retrospective investigation was made on the medical records of the patients with severe and critical patients with COVID-19 pneumonia from January to February 2020. First, the patients who received corticosteroid treatment were compared with patients without given corticosteroid treatment. Then a propensity score matching method was used to control confounding factors. Cox survival regression analysis was used to evaluate the effect of corticosteroid therapy on the mortality of severe and critical patients with COVID-19.

Results A total of 371 severe and critical patients were enrolled in our statistics. 209 patients were treated with corticosteroid therapy. Most of them were treated with methylprednisolone (197[94.3%]). The median corticosteroid therapy was applied 3(IQR 2–6) days after admission, 13(IQR 10–17) days after symptoms appeared. Temperature on admission(OR = 1.255,[95%CI 1.021–1.547],p = 0.032), ventilation(OR = 1.926, [95%CI 1.148–3.269],p = 0.014) and ICU admission(OR = 3.713, [95%CI 1.776–8.277],p < 0.001) were significantly associated with corticosteroids use. After PS matching, the cox regression survival analysis showed that corticosteroid use was significantly associated with a lower mortality rate (HR = 0.592, [95%CI 0.406–0.862], p = 0.006).

Conclusion Corticosteroid therapy use in severe and critical patients with COVID-19 pneumonia leads to lower mortality but may cause other side effects. Corticosteroid therapy should be used carefully.

1. Introduction

The coronavirus disease 2019 (COVID-19) has been considered as an urgent public health crisis worldwide with the rapidly increasing number of confirmed cases and death tolls, since the outbreak in December 2019. It is reported that more than 16 million have contracted the disease, around 540 thousand died, in 188 countries or areas up to July 7, 2020[1]. The outbreaks lead to huge demand for hospital beds and impose great challenges for physicians as well. However, clinical course and predictors for outcome of the patients remain to be fully investigated. Currently, while no specific antiviral or immunomodulatory treatment for COVID-19 have proven effective, therapies recommended for patients with COVID-19 are largely aligned with that of other viral pneumonia, mostly consisting of a set of supportive care strategies [2].

Data from several clinical observational investigations shows a significant fraction of the hospitalization patients with COVID-19 received corticosteroid treatment as supportive care. The proportion of patients received corticosteroid treatment varied from 18.6%[3], 22.0%[4], 30%[5], 35.5%[6], to 51.0%[7] depending on the settings and severity of illness. However, the role of corticosteroids in COVID-19 patients is controversy. While the guidance for critical care management from World Health Organization advocates against their use, there are expert consensus and guidelines incorporate corticosteroids in clinical management of COVID-19 in severe conditions[8]. For instance, Chinese experts consensus recommend short term therapy with low-to-moderate dose corticosteroids in COVID-19 ARDS[9, 10]. Waleed Alhazzani, et al suggest using systemic corticosteroids in mechanically ventilated adults with COVID-19 and ARDS[11]. The debate on the use of

corticosteroids in patients with COVID-19 indicates the knowledge gap in understanding the benefits and associated adverse effects of these clinical interventions.

Current knowledge base on corticosteroid treatment in viral pneumonia is largely built upon previous experience with severe patients infected by SARS, MERS and H1N1, and the treatment effect on clinical outcomes is inconclusive. A retrospective study revealed that proper use of corticosteroids in critical SARS patients were associated with lowered mortality and shorter length of hospital stay without significant secondary lower respiratory infection and other complications[12]. In an observational study in patients with MERS, corticosteroid therapy did not result in a difference in mortality after adjustment for time-varying confounders but led to delayed MERS coronavirus RNA clearance[13]. Inconsistent results also exist in the studies of influenza viral pneumonia[14, 15]. To date, few studies have investigated the impact of corticosteroid treatment in patients with COVID-19. Experience from Korea suggests that low dose steroid oral tablets/inhalers at the earlier stage of COVID-19 and high dose steroid treatment according to the severity of the disease can play important roles in decreasing the fatality and pulmonary fibrosis[16]. Zheng et al analyzed 55 medical records of COVID-19 patients and concluded that early and short-term use of low-dose methylprednisolone was beneficial and did not delay SARS-CoV-2 RNA clearance and influence IgG antibody production[17]. An observational study in 31 patients reported there were no associations between corticosteroid therapy and outcomes in patients without acute respiratory distress syndrome[6]. However, these findings may not be reliable due to the very small sample size and weakness in study design.

Coping with the pandemic of COVID-19 is extremely challenging for clinicians. Those who considering corticosteroids for severe patients with COVID-19 must balance the potential reduction in mortality with the potential downsides. Understanding the evidence for harm or benefit from corticosteroids in COVID-19 is of immediate clinical importance. However, data from studies on corticosteroid treatment in COVID-19 of sufficient sample size and carefully controlling potential confounding factors and biases are lacking. Therefore, The objective of this study is to identify the factors associated with corticosteroid use and its impact on outcomes in severe patients with COVID-19 accounting for potential selection bias by propensity score matching analysis.

2. Materials And Methods

2.1 Study settings and participants

This is a retrospective observational study. We enrolled all the 718 cases confirmed with COVID-19 admitted to Zhongfa Xincheng Branch of Tongji Hospital affiliated to Tongji Medical College, Huazhong University of Science and Technology, from Jan 28 to Feb 29, 2020. Zhongfa Xincheng Branch of Tongji Hospital was temporarily designated to offer 800 beds in refitted isolation wards for severe and critical patients with COVID-19 by local government during the outbreak. All the test, procedures, therapies were ordered by the attending physician.

The study was approved by the Ethics Committee of Tongji Hospital (IRB#). Patient identities were protected via anonymization, and the requirement for informed consent was waived due to the observational nature of the study.

2.2 Data Collection

The inclusion criteria were patients with definite diagnosis of COVID-19 based on the World Health Organization interim guidance; patients with a definite outcome (dead or discharged). The exclusion criteria were patients taking chronic corticosteroid therapy for the pre-existing health conditions; patients receiving corticosteroid therapy as rescue therapy (i.e. due to shock).

Data were collected from the electronic medical records using the standardized ISARIC case report forms. The extracted variables included patients demographic characteristics, co-morbidities existing prior to the admission, time of illness onset and hospital admission, signs and symptoms on admission, radiology findings, laboratory test results, medications and supportive care, complications during the hospital stay, and clinical outcomes. Data on the type, maximum daily dose, and duration of corticosteroids were collected.

Four internists (Yipeng Zhang, Lu Han, Jingru Liu, Mengyu Yang) performed the data extraction and data entry independently. The differences between them were detected in database via R software package, and finally adjudicated by the corresponding author TW.

2.3 Study definitions

Coronavirus disease 2019 (COVID-19) was defined in accordance with World Health Organization interim guidance. Nasal and pharyngeal swab specimens were collected for detecting SARS-COV-2, which were tested via rt-PCR according to the World Health Organization interim guidance on laboratory testing for COVID-19 in suspected human cases.

Severe and critical patients with COVID-19 were defined in accordance with Chinese interim guidelines for diagnosis and treatment for COVID-19 patients (version 7.0). Severe patients were those who had at least one of clinical features including respiratory rate exceeding 30 breaths/minute at rest, oxygen saturation $\leq$ 93% without oxygen support, arterial oxygen partial pressure/fractional inspired oxygen (PaO2/FiO2) $\leq$ 300 mmHg at rest, the total lesions on chest CT rapid progress $\geq$ 50% within 24–48 hours. Critical patients were those who had at least one of the clinical features including respiratory failure requiring mechanical ventilation, presence of shock, complicating with other organ failure.

Corticosteroid treatment was defined as the use of systemic corticosteroids ordered by the attending physician. All the dosages were converted into methylprednisolone equivalent doses (hydrocortisone 5:1, dexamethasone 1: 5, prednisolone 5: 4). High-dose corticosteroid therapy was defined as highest daily dose of $\geq$ 80 mg of methylprednisolone equivalent. Low to moderate dose corticosteroid therapy was defined as highest daily dose of < 80 mg of methylprednisolone equivalent. Early use of corticosteroid was defined as corticosteroid therapy within 7 days after hospital admission.

2.4 Endpoints

The primary objective of this study is to determine whether corticosteroid use was associated with hospital mortality. Additionally, the primary outcome was examined in the following subgroups according to clinical features on hospital admission: (1) severity of illness (severe group vs critical group based on previous definition); (2) requiring mechanical ventilation on hospital admission (yes vs no); (3) Asthma/chronic

pulmonary disease (yes or not); and (4) inflammatory response to C-reactive protein (CRP < 25 vs. ≥ 25 mg/dL).

The secondary objective of this study is to investigate risk factors associated with corticosteroid use in severe patients with COVID-19. Hospital length of stay, ICU length of stay, mechanical ventilation days, SARS-COV-2 RNA clearance and presence of complications were also examined in survivors between groups receiving and not receiving corticosteroid treatment.

2.5 Statistical analysis

Continuous variables were presented as means with standard deviation (SD) or medians and interquartile range 25–75% (IQR) and categorical variables as counts (percentage). For demographic variables, baseline clinical characteristics, co-interventions, and outcome variables, differences between patients received corticosteroid treatment during hospitalization and those who did not receive any corticosteroid treatment were compared via Student t test or Mann-Whitney U test for continuous variables and chi square test or Fisher exact test for categorical variables as appropriate.

Multiple logistic regression model was used to examine the association between baseline Variables on hospital admission and corticosteroid use. A set of priori–decided variables of clinical interest and all significant variables at the univariable level (P < 0.2) were included in the multivariate model. The probabilities for the entry and removal of variables in a stepwise forward manner were 0.05 and 0.10, respectively. Model integrity was tested by standard diagnostic statistics and plots, goodness of fit for each model was assessed with the Hosmer–Lemeshow test. Cox proportional hazards models were used to examine outcomes as a time to event (i.e., death, hospital discharge, SARS-COV-2 RNA clearance, presence of complications), with corticosteroid therapy as a time-varying covariate and adjusting for the same above-mentioned baseline covariates.

To minimize the effect of a corticosteroid treatment selection bias and to control for potential confounding factors, a propensity score matching procedure was performed. Treatment group (patients received corticosteroid treatment) and control group (those who did not received corticosteroid treatment) were full matched 1:1with weights based on a full-matching propensity score analysis. The propensity scores were determined using multivariate logistic regression models, which included a set of prespecified covariates without considering the outcomes. C-statistics were used to assess the model's discrimination. The treatment and control pairs were matched via nearest neighbor matching approach. To ensure balanced matches, a caliper, maximum acceptable difference between two groups, was set as 0.2 (i.e., 0.2 X standard deviation of the logit of the propensity scores) resulting in a relatively narrow difference between matched patients. In addition, the paired t-test or Wilcoxon signed rank test for continuous as appropriate, and the McNemar test for categorical variables were conducted respectively to assess the covariate balance between the treatment and control groups.

After the matching, a Kaplan–Meier survival plot was generated to track hospital mortality over time for the treatment and control group. And the Cox regression model mentioned above were performed again to examine the impact of corticosteroid treatment on patient outcomes after balancing the potential confounding factors and controlling for selection bias.

Finally, a series of sensitivity analysis was conducted. Because a corticosteroid therapy effect may be dose dependent and may vary according to the time of initiation, we performed all previous models on the following stratified groups: patients who received high-dose corticosteroid therapy, patients who received low to moderate dose corticosteroid therapy and patients who had early use of corticosteroid, each compared with patients who did not receive any corticosteroid therapy. We also compared corticosteroid therapy started after Day 7 since hospital admission compared with no corticosteroid therapy.

All tests were two-sided, and p-values < 0.05 were considered statistically significant. Results from logistic or Cox regression analysis were reported as odds ratios (OR) or hazard ratios (HR) with 95% confidence intervals (CIs) as appropriate. Data analysis was performed with R software package (cran.r-project.org).

3. Results

During the observation period, a total of 762 patients were admitted for COVID-19 infection. After data cleaning, 371 samples met our inclusion criteria of severe or critical patients and were included in this study. Data cleaning path was shown in Fig. 1.

3.1 Comparison between subjects with and without corticosteroid treatment

Clinical characters between the corticosteroid group and the non-corticosteroid group are given in Table 1. According to the initial condition, laboratory tests, and clinical records, patients with corticosteroid treatment are more severe than patients without corticosteroid treatment. Compared with non-corticosteroid group, corticosteroid group had higher LDH($P < 0.001$), CRP($P < 0.001$) and D-dimer($P < 0.001$), and lower platelets($P = 0.025$). Antiviral($P = 0.029$), interferon($P < 0.001$), antibiotics($P < 0.001$), and inotropes/vasopressors use($P = 0.001$) are more frequent than the non-corticosteroid group. Renal replacement($P = 0.002$) and non-invasive ventilation therapy use($P = 0.007$) more than non-corticosteroid group. Complications($P < 0.001$), ICU admission($P < 0.001$), length of hospitalization($P = 0.001$), and overall death rate($P < 0.001$) are larger than non-corticosteroid group. All of this suggests that patients with corticosteroid therapy are more critical.

Table 1
Clinical characteristics of patients with COVID-19 in the study

variable	corticosteroid group (n = 209)	non-corticosteroid group (n = 162)	statistics	p value
age median (IQR)	65.00(54.00–72.00)	63.00(55.00–71.00)	17198	0.443
gender, male, n (%)	133(63.6)	87(52.4)	2.403	0.017
Pregnancy, n (%)	0	0		
Days from onset of symptoms to the emergency room, mean ± SD	-			
Days from onset of symptoms to the hospital admission, mean ± SD	9.292 ± 5.598	10.864 ± 7.586	-2.212	0.028
Oxygen saturation on admission, mean ± SD	90.584 ± 14.943	92.771 ± 11.653	-0.620	0.536
Temperature on admission, median (IQR)	37.40(36.70–38.50)	37.15(36.50–38.00)	1.839	0.067
Chest pain	8(3.8)	6(3.7)	0.004	0.950
Myalgia	30(14.4)	18(11.1)	0.852	0.356
Shortness of breath	66(31.6)	36(22.2)	4.008	0.045
Quadrants with infiltrates in chest X-ray, median (IQR)	64(30.6)	41(25.3)	1.270	0.260
Creatinine	91.167 ± 86.123	98.191 ± 151.783	-0.562	0.574
LDH, median (IQR), UI	402.00(298.00–524.00)	288.50(231.50–401.00)	4.772	0.000
PCT, median (IQR) (ng/mL)	0.12(0.07–0.34)	0.08(0.03–0.22)	-1.506	0.133
CRP, median (IQR) (mg/dL)	83.30(43.90–121.90)	36.05(8.30–91.42)	5.165	0.000
WBC count	7.784 ± 4.332	7.118 ± 4.054	1.511	0.132
Platelets	197.615 ± 86.368	219.673 ± 102.113	-2.249	0.025
INR	1.233 ± 0.908	1.149 ± 0.292	1.126	0.261
ALT/SGPT	39.737 ± 58.620	56.691 ± 218.323	-1.074	0.283

Mann-Whitney U test

*Chi-squared test with continuity correction

**Fishers' exact test

***Not all patients took laboratory test of IL-6, 289 patients were included Student-t test

variable	corticosteroid group (n = 209)	non-corticosteroid group (n = 162)	statistics	p value
D-dimer D-D	5.574 ± 7.679	2.916 ± 5.272	3.935	0.000
IL-6	88.899 ± 235.905	49.453 ± 97.543	1.752	0.081***
Comorbidities				
Any comorbidity, n (%)	114(54.5)	94(58.0)	0.448	0.503
Diabetes, n (%)	41(19.6)	28(17.3)	0.328	0.567
Chronic cardiac disease, n (%)	29(13.9)	22(13.6)	0.007	0.935
Hypertension,	76(36.4)	57(35.2)	0.055	0.814
Asthma/chronic pulmonary disease, n (%)	15(7.2)	5(3.1)	2.994	0.084
Liver disease, n (%)	7(3.3)	7(4.3)	0.237	0.626
Renal disease, n (%)	7(3.3)	9(5.6)	1.076	0.299
Malignancy, n (%)	7(3.3)	7(4.3)	0.237	0.626
Rheumatological disease, n (%)	2(1.0)	1(0.6)	0.049	0.824*
Chronic neurological disease/hemiplegia or paraplegia or dementia, n (%)	2(1.0)	4(2.5)	0.533	0.465*
Antiviral, n (%)	109(52.2)	66(40.7)	4.770	0.029
Ribavirin	16(7.7)	11(6.8)	0.101	0.750
Lopinavir/Ritonavir	56(26.8)	41(25.3)	0.104	0.747
Neuraminidase inhibitor	16(7.7)	18(11.1)	1.309	0.253
Interferon	54(25.8)	13(8.0)	19.568	0.000
Antibiotic	177(84.7)	94(58.0)	32.955	0.000
ACE inhibitors)	4(1.9)	1(0.6)	0.385	0.535*
Angiotensin II receptor blockers (ARBs)	5(2.4)	8(4.9)	1.749	0.186
Oxygen therapy	196(93.8)	158(97.5)	2.937	0.087
Non-invasive ventilation	63(30.1)	29(17.9)	7.334	0.007

Mann-Whitney U test

*Chi-squared test with continuity correction

**Fishers' exact test

***Not all patients took laboratory test of IL-6, 289 patients were included Student-t test

variable	corticosteroid group (n = 209)	non-corticosteroid group (n = 162)	statistics	p value
Invasive ventilation	20(9.6)	8(4.9)	2.805	0.094
ECMO	1(0.5)	0(0.0)		1**
Renal replacement therapy	31.0(14.8)	8.0(4.9)	9.497	0.002
Prone position	9.0(4.3)	3.0(1.9)	1.756	0.185
Inotropes/vasopressors	81.0(38.8)	36.0(22.2)	11.555	0.001
ICU admission, Yes, n(%)	53(25.4)	11(6.8)	22.044	0.000
Complications				
Any complications, n(%)	109(52.2)	44(27.2)	23.524	0.000
Acute Respiratory Distress Syndrome	64(30.6)	15(9.3)	5.438	0.000
Myocarditis/Pericarditis	8(3.8)	2(1.2)	1.456	0.228
Acute renal injury	25(12.0)	9(5.6)	4.499	0.034
Liver dysfunction	21(10.0)	13(8.0)	0.668	0.504
Cardiomyopathy	1(0.5)	0(0.0)		1**
Death	102.0(48.8)	43.0(26.5)	18.995	0.000
Discharged alive	107.0(51.2)	119.0(73.5)	18.995	0.000
Length of Hospitalization	17.675 ± 10.162	14.574 ± 7.362	3.406	0.001
Length of symptoms onset to RNA clearance	20.319 ± 6.847	21.462 ± 8.926	-1.103	0.271
Mann-Whitney U test				
*Chi-squared test with continuity correction				
**Fishers' exact test				
***Not all patients took laboratory test of IL-6, 289 patients were included Student-t test				

209 patients received corticosteroid therapy during hospitalization. Of these, 197(94.3%) patients were treated with Methylprednisolone, 39(18.7%) prednisone, 6(2.8%) methylprednisolone tablets, and 1(0.5%) dexamethasone. After admission, the median(IQR) corticosteroid therapy was applied 3(2–6) days later, 13(10–17) days after symptoms appeared. Among all patients with corticosteroid treatment, the median duration of corticosteroid therapy is 7(4–12) days and 5(3-8.75) for survivor group and 10(7–14) for the death group. Details are shown in Table 2.

Table 2
Administration of corticosteroids in patients with COVID 19

Drug administered, n (%)*	
Prednisone	39(10.5)
Methylprednisolone	197(53.1)
Methylprednisolone tablet	6(1.6)
Dexamethasone	1(0.3)
Initial dosage (equivalent Methylprednisolone), mg/d	
Mean± SD	49.456 ± 24.361
Median (IQR)	40.00(40.00–80.00)
Maximum dosage (equivalent Methylprednisolone), mg/d	
Mean± SD	63.785 ± 41.838
Median (IQR)	40.00(40.00–80.00)
Time to initiation from hospitalization, d	
Mean± SD	4.833 ± 4.818
Median (IQR)	3.00(2.00–6.00)
Time to initiation from symptoms onset, d	
Mean± SD	14.124 ± 6.420
Median (IQR)	13.00(10.00–17.00)
Duration of therapy (d)(all patients)	
Mean± SD	9.144 ± 7.501
Median (IQR)	7.00(4.00–12.00)
Duration of therapy (d) (Survivors)	(n = 107)
Mean± SD	11.533 ± 7.745
Median (IQR)	5.000(3.000–8.750)
Duration of therapy (d) (Non-Survivors)	(n = 102)
Mean± SD	6.637 ± 6.365
Median (IQR)	10.000(7.000–14.000)
PaO2/FIO2 before corticosteroid initiation	(n = 34)

*Some patients changed corticosteroid type during treatment process. For rigors' sake, here is the statistics of patients who have used this kind of corticosteroid drug.

Drug administered, n (%)*	
Mean± SD	379.267 ± 212.574
Median (IQR)	323.81(247.62–440.48)
*Some patients changed corticosteroid type during treatment process. For rigors' sake, here is the statistics of patients who have used this kind of corticosteroid drug.	

3.2 Factors for corticosteroid use in patients with COVID-19

To clarify which factors influencing corticosteroid treatment use, we selected indicators for patients before corticosteroid therapy with discretion to build a stepwise logistic regression model. Age, critical, the temperature on admission, ventilation, and ICU admission were included finally. Temperature on admission(OR = 1.255,[95%CI 1.021–1.547],p = 0.032), ventilation(OR = 1.926,[95%CI 1.148–3.269],p = 0.014) and ICU admission(OR = 3.713, [95%CI 1.776–8.277],p < 0.001) are significant. Detail results are shown in Table 3.

Table 3
Multivariate analysis for factors associated with corticosteroid therapy (stepwise)

Variable	OR	95%CI	p-value
age	0.988	0.971–1.004	0.148
critical	1.576	0.872–2.856	0.132
Temperature on admission	1.255	1.021–1.547	0.032
Ventilation	1.926	1.148–3.269	0.014
ICU admission	3.713	1.776–8.277	< 0.001

3.3 Mortality analysis

102 of 209(48.8%) patients with corticosteroid treatment died, which mortality rate is higher than the non-corticosteroid group (43 of 162, 26.5%, chi-squared test p < 0.001). After controlling the factors that may affect the outcome, there is no significant evidence for corticosteroid therapy affects outcome (OR = 0.969, [95%CI 0.352–2.606], p = 0.950).

To minimization selection bias, a PS-full matching model was applied to our dataset and every sample in the non-corticosteroid group and corticosteroid group were given a PS full matching weights. Age, gender, the temperature on admission, days from symptom onset to admission, critical on admission, LDH ≥ 225U/L, CRP ≥ 1 mg/L, D-Dimer ≥ 0.5ug/mL, any complications, chronic heart disease, chronic liver disease, chronic renal disease, chronic neurological disease, hypertension, hyperlipidemia, renal replacement therapy, ICU on admission were the independent variables included in the logistic regression analysis of the PS-full matching model. Summaries of balance for matched data and unmatched data are shown in Table 4.

Table 4
Comparison of baseline characteristics between treated and untreated subjects in the original sample and in the propensity score-matched sample

Baseline variables	Original sample			Matched sample		
	Treated group (n = 209)	Control group (n = 162)	Mean difference	Treated group (n = 209)	Control group (n = 162)	Mean difference
Global distance	0.6263	0.4821	0.1441	0.6263	0.6258	0.0005
Demographic data						
age	62.5502	62.4259	0.1243	62.5502	62.4707	0.0796
temperature	37.5694	37.3642	0.2052	37.5694	37.5960	-0.0267
female	0.6364	0.5123	0.1240	0.6364	0.6295	0.0068
male	0.3636	0.4877	-0.1240	0.3636	0.3705	-0.0068
Severity of illness						
serious	0.4067	0.2037	0.2030	0.4067	0.3322	0.0745
critical	0.5933	0.7963	-0.2030	0.5933	0.6678	-0.0745
Service Utilization						
Days from onset of symptoms to the hospital admission	9.2919	10.8642	-1.5723	9.2919	9.0814	0.2104
ICU admission	0.2584	0.0741	0.1843	0.2584	0.2416	0.0167
Laboratory						
LDH	450.7368	343.6049	107.1319	450.7368	423.5441	27.1927
CRP	92.4766	58.1926	34.2840	92.4766	74.1692	18.3073
ALT	39.7368	56.6914	-16.9545	39.7368	72.4182	-32.6814
D-Dimer	5.5530	3.0003	2.5526	0.1800	2.4204	18.0200
Comorbidities						
Any comorbidity	0.5598	0.6111	-0.0513	0.5598	0.5921	-0.0323
Diabetes	0.2010	0.1790	0.0219	0.2010	0.2498	-0.0489
Chronic cardiac disease	0.1435	0.1481	-0.0046	0.1435	0.1277	0.0159
Hypertension	0.3732	0.3580	0.0152	0.3732	0.3408	0.0324
Asthma/chronic pulmonary disease	0.0718	0.0432	0.0286	0.0718	0.0399	0.0319

Baseline variables	Original sample			Matched sample		
	Treated group (n = 209)	Control group (n = 162)	Mean difference	Treated group (n = 209)	Control group (n = 162)	Mean difference
Liver disease	0.0335	0.0494	-0.0159	0.0335	0.0386	-0.0051
Renal disease	0.0383	0.0617	-0.0235	0.0383	0.0183	0.0200
Malignancy	0.0287	0.0432	-0.0145	0.0287	0.0407	-0.0120
neurological disease	0.0096	0.0247	-0.0151	0.0096	0.0070	0.0026
Complications						
Any complications	0.5215	0.2778	0.2438	0.5215	0.5230	-0.0015
Acute Respiratory Distress Syndrome	0.3062	0.0926	0.2136	0.3062	0.2241	0.0821
Myocarditis/Pericarditis	0.0431	0.0123	0.0307	0.0431	0.0215	0.0215
Acute renal injury	0.1196	0.0556	0.0641	0.1196	0.1313	-0.0117
Liver dysfunction	0.1005	0.0802	0.0202	0.1005	0.1581	-0.0576

After PS-full matching, we performed a logistic regression model and a Cox regression model to determine the impact of corticosteroid use in severe patients with COVID-19. With PS-full matching, the logistic regression model showed that corticosteroid use linked to a lower mortality rate (OR = 0.308, [95%CI 0.112–0.771], p = 0.016). Our cox regression model (Table 5.) and adjusted cox regression survival plot (Fig. 3.) confirms that corticosteroid use was significantly associated with a lower mortality rate (HR = 0.592, [95%CI 0.406–0.862], p = 0.006).

Table 5
Cox survival regression result after PS-full matching

Variable	HR	95%CI	p-value
Corticosteroid group	0.592	0.406–0.862	0.006
age	1.034	1.014–1.054	0.000
Temperature on admission	1.018	0.858–1.208	0.835
Gender male	1.497	0.961–2.329	0.073
critical	1.370	0.680–2.760	0.378
ventilation	2.632	1.879–3.685	0.000
LDH ≥ 225U/L	1.979	0.624–6.266	0.245
CRP ≥ 1 mg/L	0.913	0.238–3.498	0.894
D-Dimer ≥ 0.5ug/mL	2.135	0.926–4.919	0.074
ARDS	1.564	0.909–2.690	0.105
Acute renal failure	1.003	0.586–1.716	0.991
Liver dysfunction	1.159	0.599–2.238	0.661
Renal replacement therapy	0.774	0.496–1.206	0.257
Chronic liver disease	1.181	0.425–3.279	0.749
Chronic renal disease	1.566	0.600-4.084	0.359
Bacterial pneumonia	0.449	0.124–1.613	0.219
Bacteremia	6.309	2.872–13.857	0.000
hypertension	1.627	1.016–2.603	0.042
hyperlipidemia	2.804	0.466–16.855	0.259
Chronic neurological disease	1.766	2.344–14.581	0.000
Antivirus	0.770	0.517–1.146	0.198
Antibiotic	1.349	0.620–2.932	0.450
ICU admission	1.382	0.770–2.478	0.278

To make the results more robust, we performed several subgroup analyses. First, we separated the corticosteroid group by maximum dosage of corticosteroid use, days from admission to corticosteroid use, and total days of corticosteroid use. The subgroup logistic results showed that longer the duration corticosteroid use (OR = 37.032, [95%CI 2.042–3461.331], p = 0.040) links to higher survival rate, while the maximum dosage (OR = 0.969, [95%CI 1.215–1631.377], p = 0.081) and early or late start of treatment (OR =

21.539, [95%CI 0.160–6.273], p = 0.973) are not significant (Fig. 2 part1). In subgroup of patients who survived with clear timeline for virus clearance, corticosteroid therapy have no significant influence(β = 1.148, [95%CI -32.223–17.662], p = 0.131) on virus clearance, but long-term use(β = 1.738, [95%CI -0.017–3.493], p = 0.052, weak significance) and late-use(β = 3.729, [95%CI 0.871–6.587], p = 0.011) may cause more day for virus clearance. As for the death group, corticosteroid therapy earned more survival time(β = 3.463, [95%CI 0.591–6.336], p = 0.019) for other clinical interventions. Details are shown in Fig. 2 part2.

4. Discussion

Our results confirm that corticosteroid therapy in severe and critical patients with COVID-19 is associated with a lower mortality rate. Although it appears that the mortality rate of the corticosteroid group is higher than the control group, we found that corticosteroid therapy reduces the mortality rate after balancing the condition of patients by PS full matching.

Corticosteroids therapy in pneumonia and COVID-19 pneumonia remains a controversy. Corticosteroid has functions of anti-inflammatory, anti-allergic and hypothermic. Cytokine release syndrome (CRS) in COVID-19 often leads to multi-organ dysfunctions and links to severity of syndrome and the outcome[18–20]. Therefore, it is suggested that using corticosteroid as adjunctive therapy in COVID-19 treatment. On the other hand, due to its immunosuppression property, potential risks of corticosteroid therapy including secondary infections, long-term complications, and delayed virus clearance prevent doctors from using Corticosteroid therapy[19].

Scientists have ambiguous opinions on corticosteroid therapy that affect COVID-19 pneumonia. A variety of articles claims it benefits or stays neutrality[21–27], meanwhile, there is also evidence that corticosteroid treatment is associated with high mortality and it is recommended not to use corticosteroid[28–31]. Given that above studies did not exclude endogenous problems well and COVID-19 is still in the epidemic, and based on conflicting perspectives, we aimed at severe and critical patients with COVID-19 pneumonia and balance patient conditions before corticosteroid treatment by PS full matching to perform a more robust result whether corticosteroid works on severe and critical patients with COVID-19.

Our results showed that corticosteroid treatment was significant benefits to survival of severe and critical patients with COVID-19 pneumonia after balancing the selection bias, although it seems that corticosteroid group has a higher mortality rate at first glance(unbalanced). Most of retrospective research have ignored the selection bias and did not provide robust results. However, physicians consider whether to use corticosteroid often refers to severity of illness, which leads to serious endogenous problems. To the best of our knowledge, no study using a similar analysis to examine corticosteroid treatment in severe and critical patients with COVID-19 pneumonia. Only one study uses 1:1 PS matching on not severe patients with COVID-19 infected. By a group of 70 matched patients, Yuan, et al[32] concluded that corticosteroid might harm lung injury recovery in non-severe COVID-19 pneumonia patients. However, more attention should be paid to severe and critical patients.

In our subgroup analysis, long-term use of corticosteroid is associated with a higher survival rate. The effect of large-dose use and late use on survival rate seems not significant. But in a group of discharged alive with a

clear timeline for virus clearance, long-term use (weak significant p = 0.522) and late use extend the duration of viral shedding, which is consistent with most existing studies and reflects the harm of corticosteroid therapy[24, 31, 32]. Even so, in the death group, corticosteroid also prolongs the survival time of the patients, which gives the doctor more buffer to perform clinical interventions.

This study collects a relatively large dataset to balance selection bias and endogenous by PS full matching method, which makes our research more robust. But there still exist limitations. First, data are collected from single-center and our hospital mainly receives patients with severe illness. Our results and conclusions are only applicable to severe and critical patients with COVID-19 pneumonia. Second, this is a retrospective study, some interesting clinical evidence is not collected such as CT source image, SOFA score, etc. Third, In the early stage, due to the lack of nucleic acid detection reagents, some patients did not have complete virus clearance trace, thus we lost part of data in our subgroup analysis. Finally, the common defect of all retrospective studies is that we can't completely control the existence of bias. However, as PS matching analysis can balance the selection bias and endogenous problems, it is the best evidence available for physicians.

5. Conclusion

In a group of severe and critical patients with COVID-19 pneumonia, after balancing selection bias and endogeneity, corticosteroid therapy was significantly associated with decreased mortality. Physicians should use carefully because it also prolongs the duration of virus clearance.

Abbreviations

COVID-19: Coronavirus disease 2019

OR: Odds ratio

HR: Harzard ratio

PSM: Propensity score matching

ICU: Intensive care unit

CT: Computerized Tomography

ARDS: Acute respiratory distress syndrome

SARS: Severe Acute Respiratory Syndrome

MERS: Middle East Respiratory Syndrome

rt-PCR: Reverse transcription-polymerase chain reaction

PaO2: Partial pressure of arterial oxygen

FiO2: Fraction of inspired oxygen

SOFA: Sequential organ failure assessment

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Tongji Hospital (IRB#). Patient identities were protected via anonymization, and the requirement for informed consent was waived due to the observational nature of the study.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

The dataset used and analyzed 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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Authors' contributions

Study design: Tao Wang, Jingdong Ma

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Data analysis: Jingdong Ma, Yang Song

Drafting manuscript: Jingdong Ma, Yang Song

Revising manuscript content: Tao Wang, Jingdong Ma, Yang Song

Approving the final version of the manuscript: Tao Wang, Jingdong Ma, Yang Song

All authors read and approved the final manuscript.

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Figures

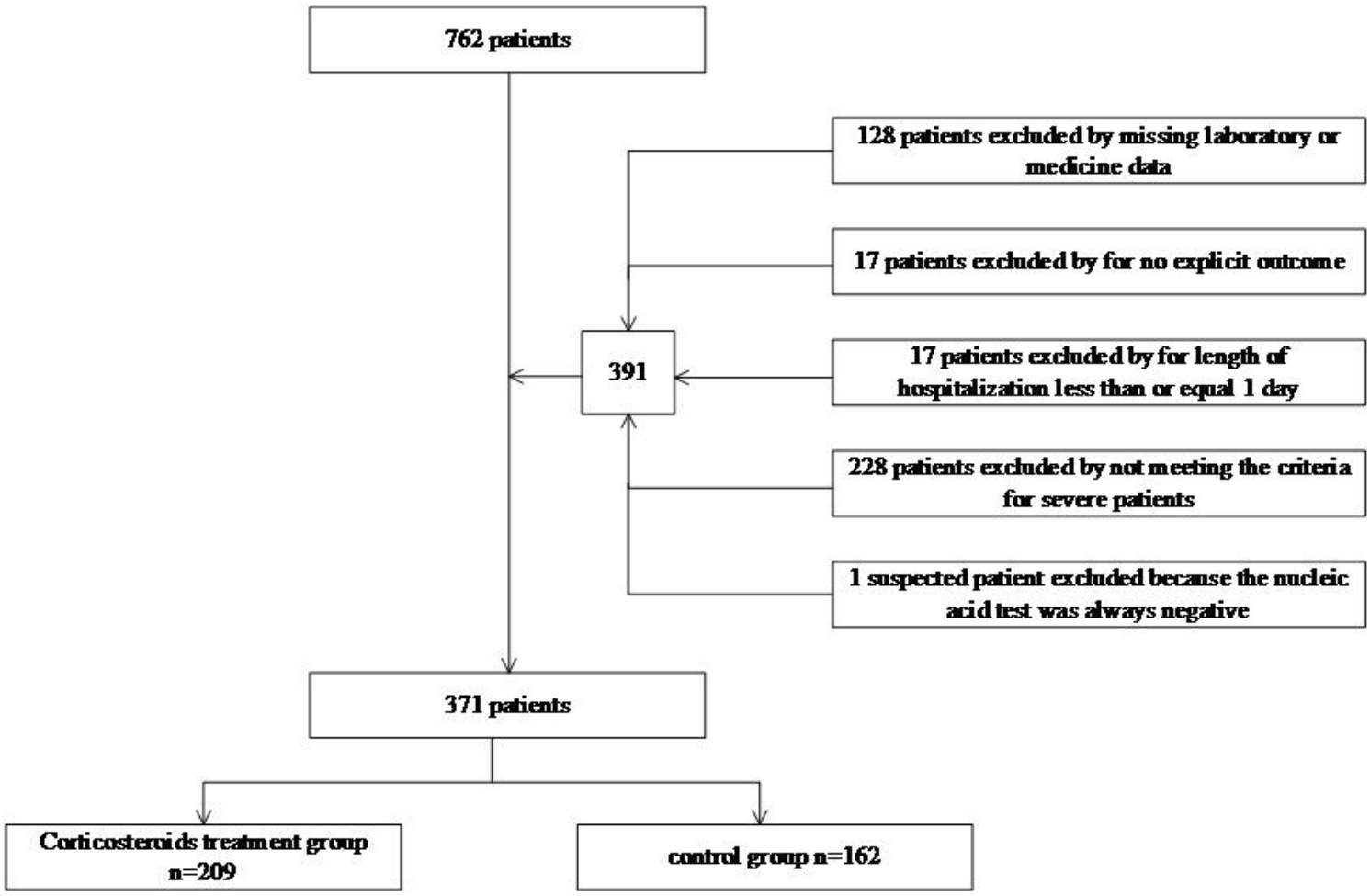

Figure 1

Data cleaning path for all excluded and included patients.

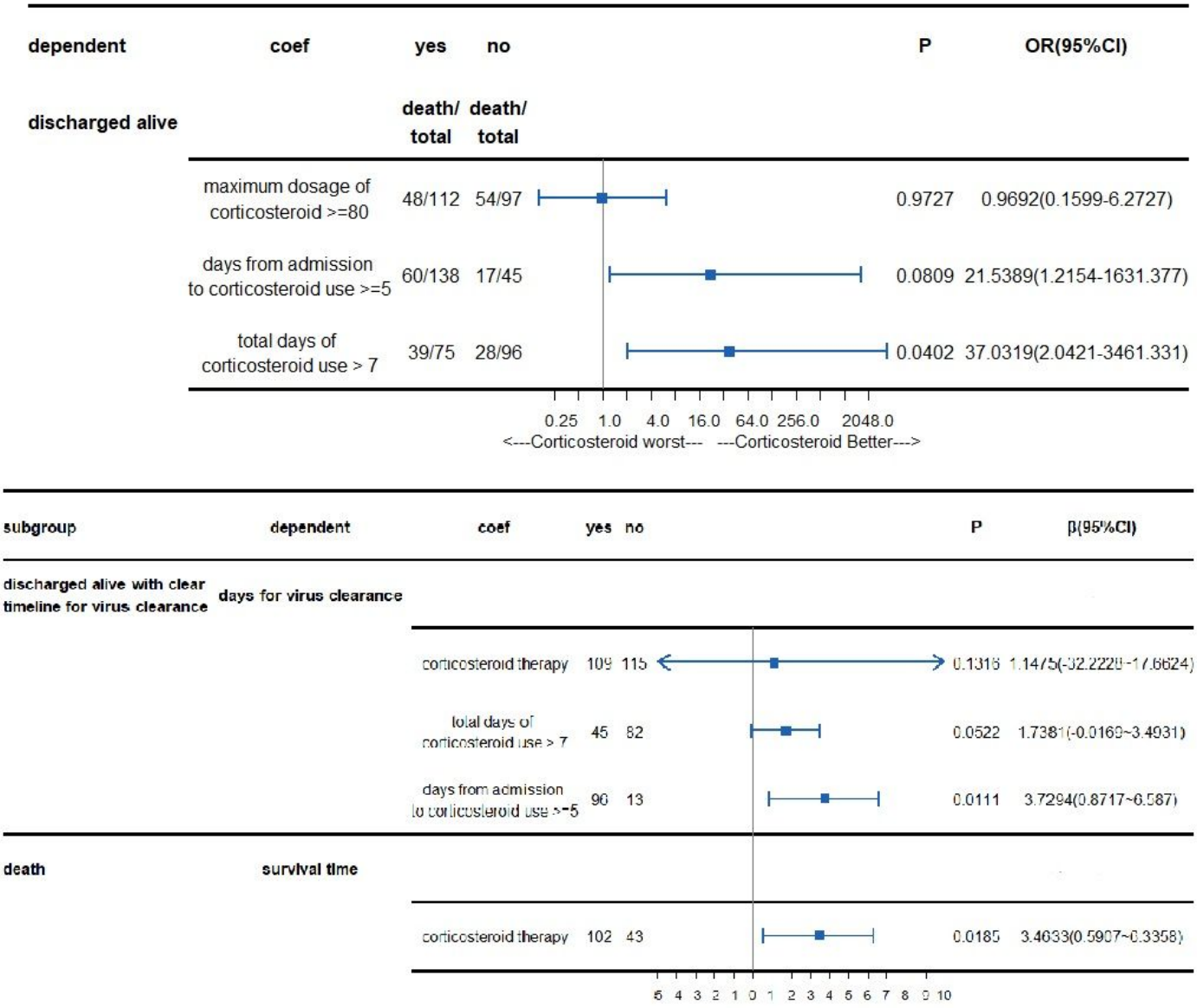

Figure 2

Subgroup logistic regression of different usage of corticosteroid affects survival rate. Subgroup linear regression of different usage of corticosteroid affects days for virus clearance or survival time.

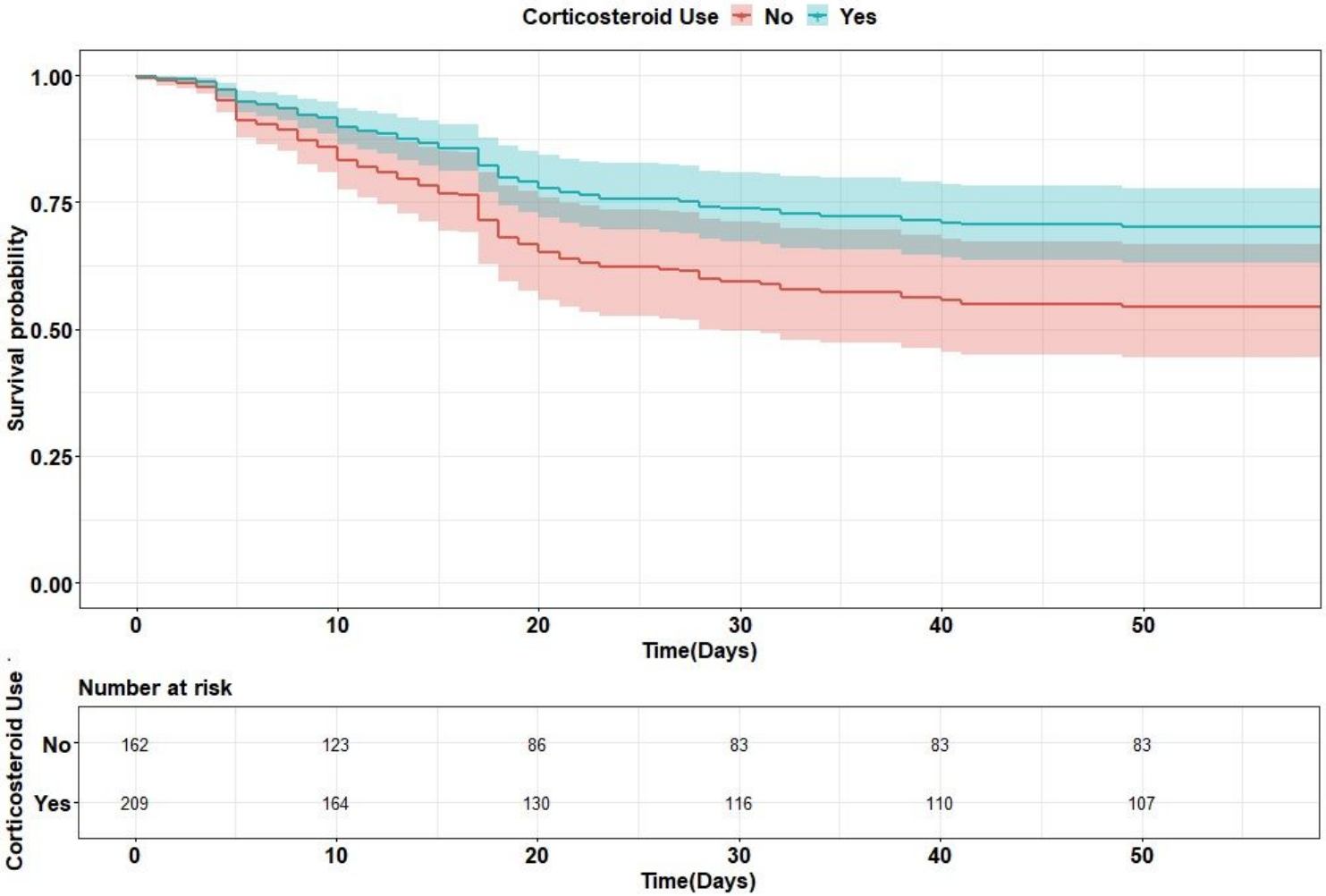

Figure 3

Cox regression survival plot according to corticosteroid treatment use.