Research Article

Therapeutic Effect of Corticosteroids for Critical COVID-19 Patients

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Received: April 06, 2022; **Accepted:** May 04, 2022; **Published:** May 11, 2022

Abstract

The rapid spread of severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) infection has resulted in an unprecedented public health, economic, and social crisis worldwide. As therapeutics that can effectively clear the virus and terminate transmission are not available, supportive therapeutics are the main clinical methods for Corona Virus Disease (COVID-19) including corticosteroids, respiratory support, and extracorporeal membrane oxygenation for salvage therapy, while subsequent agents and vaccine candidates are still under investigation. COVID-19 is a two-phase disease: in the early phase, the pathology of the virus dominates; in the later phase, Immunopathology drives the disease. Low-dose dexamethasone treatment suppresses COVID-19-related Immunopathology by complementing endogenous cortisol activity, while avoiding the adverse effects of high-dose glucocorticoids therapy. Corticosteroids, as one of the main means of anti-inflammatory adjuvant, are controversial about its role in the treatment of COVID-19. Here, we retrospectively evaluate the therapeutic effect of corticosteroids by comparing the clinical data of patients with or without corticosteroids therapy at different severity level.

Methods: This retrospective, observational study included 3337 patients with SARS-CoV-2 pneumonia who were admitted to the Tongji Hospital, Wuhan, China, between January, 2020 and April, 2020. Demographic data, medical record, laboratory test, comorbidities, treatments, and clinical outcomes were all collected. Laboratory test includes blood routine, biochemical assay, coagulation assay, and blood gas analysis. Multivariate clinical data were statistically compared between patients with corticosteroids therapy and without corticosteroids therapy. Kaplan-Meier curves analyze survival times when not all the subjects continue in the study for severe and critical patients after hospital admission. The Cox proportional-hazards model evaluates the association between the survival time of patients and one or more predictor variables.

Findings: Of 3337 patients admitted, 2243 severe and 800 critical COVID-19 pneumonia were included in the study. In the severe group, the mortality between patients with and without corticosteroids therapy has no significant difference whereas the therapeutic effect was negative in the critical group. Patients with corticosteroids therapy have lower Basophil Percentage (Baso%) and Basophil Count (Baso#) in severe group. For the patients in the critical group, males receiving corticosteroids therapy show slightly higher risk of death, while hypertension and trauma history reduce the Hazard Ratio (HR). Patients with corticosteroids therapy show higher White Blood Cell Count (WBC#), Lactate Dehydrogenase (LDH), Neutrophil Count (Neut#), Neutrophil Percentage (Neut%) and lower Uric Acid (UA), Albumin (ALB), Total Protein (TP), Lymphocytes Percentage (Lymph%).

Interpretation: The mortality of critically ill patients with SARS-CoV-2 pneumonia is higher than that of severe group. Therapy with whatever types of corticosteroids increases the risk of death in patients with critical COVID-19 pneumonia.

Introduction

COVID-19 is caused by SARS-CoV-2, which is responsible for the global public health emergency. Despite World Health Organization (WHO) and many countries provide guidelines for COVID-19 at different clinical stages, no pharmaceutical products or measures have yet been shown to be safe and effective for treatment of COVID-19. Supportive treatment is the surrogate before the emergence of specific therapeutics [1]. Most patients have mild illness, but older persons and those with underlining comorbidities may develop severe disease necessitating hospitalization and care in the Intensive Care Unit (ICU) [2]. The pathological progression in severe COVID-19 includes host inflammatory cytokine storm resulting in immunopathological lung injury, diffuse alveolar damage with the development of Acute Respiratory Distress Syndrome (ARDS), and death [3].

Cytokine storm, along with viral evasion of cellular immune responses, play an equally important role in disease progression [4]. Thus, tackling the immune response with Immunomodulatory agents may be as important as addressing viral replication to prevent the progression to multiorgan dysfunction [5]. Among the drugs that received early attention were corticosteroids because of their well-known broad-spectrum anti-inflammatory and Immunomodulatory effects via both the innate and adaptive immune system [6]. Corticosteroid monotherapy was reported for treating SARS-CoV-2 with underlining illness such as renal transplantation [7]. Corticosteroids improve the dysregulated immune response caused by ARDS and sepsis. However, its adverse effects are partly due to the suppression of normal host immune responses and impeded viral clearance [8]. High corticosteroid doses are closely associated with adverse events such as secondary infections, inhibition of glucose uptake, delayed viral clearance, and emergence of viral resistance [9,10]. Thus, the debate regarding the use of corticosteroids in COVID-19 patients is controversial [11].

Observational studies in patients with SARS and MERS demonstrated corticosteroid therapy delayed viral clearance and increased high risk of complications including hyperglycemia, psychosis, and a vascular necrosis [12]. Patients with moderate-to-severe COVID-19 pneumonia likely benefit from moderate-dose corticosteroid treatment relatively late in the disease course, especially when patients require mechanical ventilation. Early treatment in milder disease seems harmful harmed [13]. Low-dose corticosteroid therapy or pulse corticosteroid therapy appears to have a beneficial role in the management of severely ill COVID-19 patients. The WHO recommends systemic corticosteroids for the treatment of patients with severe and critical COVID-19, and recommends short courses of corticosteroids at low-to-moderate dose, used prudently, for critically ill patients with COVID-19 pneumonia [14].

More recently, systemic corticosteroids, in the form of dexamethasone, have been shown to reduce mortality in patients with severe COVID-19 requiring oxygen therapy or on mechanical ventilator [15]. Nonetheless, more studies are needed to replicate the outcome shown in RECOVERY trial for a substantial conclusion [16]. Intravenous methylprednisolone (1-2 mg/kg/day) is recommended for 3-5 days, but not for long-term use [17]. Methylprednisolone (dose and regimen were not reported) reduced the risk of death in patients with COVID-19-associated ARDS [18]. However, it is also reported that corticosteroids in severe COVID-19-related Acute Respiratory Distress Syndrome (ARDS) were associated with increased mortality and delayed viral clearance. There are potential deleterious and beneficial effects of corticosteroids at different stages of infection, lung injury, and ARDS. Corticosteroid use was not associated with beneficial effect in reducing in-hospital mortality for severe or critical cases in Wuhan [19]. Here, we aimed to estimate the effects of corticosteroid use on mortality with a large cohort of COVID-19 with severe or critical ill conditions.

Methods

Study design and participants

This retrospective study was based on the clinical data collected from January, 2020 and April, 2020 at Tongji Hospital, Wuhan, China. All subjects had been diagnosed with COVID pneumonia according to WHO interim guidance. Patients were risk stratified by severity of symptoms on presentation to the hospital as mild, moderate, or severe COVID-19. Patients without hypoxia or exertional dyspnea were considered to have mild COVID-19. Patients with mild COVID-19 were treated with symptom relief only and not admitted to the hospital. Patients who presented with infiltrates on chest radiography and required supplemental oxygen by nasal cannula or High Flow Nasal Cannula (HFNC) were classified as having moderate COVID-19. Patients who had respiratory failure requiring mechanical ventilation were classified as having severe COVID-19.

Data collection

Data were ascertained from hospital's electronic medical record and recorded in a standardized electronic case report form. Demographic data, information on clinical symptoms or signs at presentation, and laboratory and radiological examinations during admission were collected for all COVID-19 patients. Patients with multiple admissions are included. All laboratory tests and radiologic assessments, including plain chest radiography and computed tomography of the chest, were performed at the discretion of the treating physician. We collected demographic data (gender, birth date, age, ancestral home, death time, visit date, discharge date, length and times of in-hospital), present illness history, past disease history (infectious disease, allergic history, blood transfusion history, past surgery, hypertension, coronary, diabetes, COPD (Chronic Obstructive Pulmonary Diseases), malignancy, cerebrovascular disease, hepatitis, tuberculosis, trauma history, cardiovascular), physical exam, specialist exam, chest X-ray exam, chest CT exam, blood routine, biochemical exam, coagulation exam, blood gas analysis, and treatment (ventilator, intubate, oxygen therapy, hemodialysis, ECMO, CRRT, gamma globulin therapy, traditional Chinese medicine, corticosteroids therapy, immunotherapy, antiviral therapy, and antibacterial therapy). The primary evaluation parameter was mortality of severe and critical patients after hospital admission.

Inclusion and exclusion criteria

We excluded cases missing clinical information and mild symptoms. The statistical model estimates the association between corticosteroid use in COVID-19 patients and one of the following outcomes: (1) in-hospital mortality, (2) mechanical ventilation, (3) ICU admission, (4) viral shedding and (5) composite outcomes if reported. The parameters used in Univariate and multivariable Cox regression are laboratory test values including blood routine, biochemical exam, coagulation exam, blood gas analysis.

Statistical analysis

We aimed to evaluate the therapeutic effect of corticosteroids for patients with or without corticosteroids therapy in different severity category. We divide all patients into four groups (mild, moderate, severe, critical) according to their severity. Survival analysis is the analysis of time-to-event data, which describe the length of time from a time origin to an endpoint of interest. Kaplan-Meier curves analysis is a Univariate analysis, which is used when the predictor variable is categorical. Therefore, we did a Kaplan-Meier curves analysis for patients with and without corticosteroid therapy for patients in both severe and critical groups, which starts from the date of visit until the date of discharge or death.

Table 1: Characteristic distribution for collected COVID-19 patients.

n	Level	Total	Mild	Moderate	Severe	Critical	P
		3337	2	262	2243	800	
Gender (%)	male	1664 (49.9)	1 (50.0)	132 (50.4)	1037 (46.2)	477 (59.6)	<0.001
	female	1673 (50.1)	1 (50.0)	130 (49.6)	1206 (53.8)	323 (40.4)	
Age (mean (SD))		58.39 (16.12)	59.00 (25.46)	49.33 (14.68)	57.22 (15.07)	64.95 (16.66)	<0.001
BMI (mean (SD))		23.89 (8.89)	NaN (NA)	25.52 (23.44)	23.78 (4.02)	23.25 (3.39)	0.038
Corticosteroids therapy (%)	no	1784 (53.4)	2 (100.0)	219 (83.6)	1386 (61.8)	155 (19.4)	<0.001
	yes	1553 (46.5)	0 (0.0)	43 (16.4)	857 (38.2)	645 (80.6)	
Past disease (%)	no	1468 (44.0)	1 (50.0)	146 (55.7)	1077 (48.0)	237 (29.6)	<0.001
	yes	1845 (55.3)	1 (50.0)	112 (2.7)	1155 (51.5)	556 (69.5)	
Infectious disease (%)	no	3225 (96.6)	2 (100.0)	250 (95.4)	2175 (97.0)	769 (96.1)	0.614
	yes	112 (3.4)	0 (0.0)	12 (4.6)	68 (3.0)	31 (3.9)	
Allergic history (%)	no	3070 (92.0)	2 (100.0)	244 (93.1)	2043 (91.1)	751 (93.9)	0.047
	yes	267 (8.0)	0 (0.0)	18 (6.9)	200 (8.9)	49 (6.1)	
Blood transfusion history (%)	no	3307 (99.1)	2 (100.0)	262 (100.0)	2224 (99.2)	790 (98.8)	0.234
	yes	30 (0.9)	0 (0.0)	0 (0.0)	19 (0.8)	10 (1.2)	
Past surgery (%)	no	2759 (82.7)	2 (100.0)	217 (82.8)	1870 (83.4)	644 (80.5)	0.385
	yes	578 (17.3)	0 (0.0)	45 (17.2)	373 (16.6)	156 (19.5)	
Hypertension (%)	no	2338 (70.1)	1 (50.0)	221 (84.4)	1638 (73.0)	459 (57.4)	<0.001
	yes	999 (29.9)	1 (50.0)	41 (15.6)	605 (27.0)	341 (42.6)	
Coronary (%)	no	3100 (92.9)	1 (50.0)	256 (97.7)	2098 (93.5)	716 (89.5)	<0.001
	yes	237 (7.1)	1 (50.0)	6 (2.3)	145 (6.5)	84 (10.5)	
Diabetes (%)	no	2881 (86.3)	1 (50.0)	241 (92.0)	1951 (87.0)	662 (82.8)	0.001
	yes	456 (13.7)	1 (50.0)	21 (8.0)	292 (13.0)	138 (17.2)	
COPD (%)	no	3292 (98.7)	2 (100.0)	261 (99.6)	2222 (99.1)	777 (97.1)	0.001
	yes	45 (1.3)	0 (0.0)	1 (0.4)	21 (0.9)	23 (2.9)	
Malignoncy(%)	no	3243 (97.2)	2 (100.0)	258 (98.5)	2191 (97.7)	763 (95.4)	0.01
	yes	94 (2.8)	0 (0.0)	4 (1.5)	52 (2.3)	37 (4.6)	
Cerebrovascular disease (%)	no	3220 (96.5)	2 (100.0)	257 (98.1)	2197 (97.9)	736 (92.0)	<0.001
	yes	117 (3.5)	0 (0.0)	5 (1.9)	46 (2.1)	64 (8.0)	
Hepatitis (%)	no	3278 (98.2)	2 (100.0)	254 (96.9)	2208 (98.4)	784 (98.0)	0.423
	yes	59 (1.8)	0 (0.0)	8 (3.1)	35 (1.6)	16 (2.0)	
Tuberculosis (%)	no	3275 (98.1)	2 (100.0)	257 (98.1)	2206 (98.4)	781 (97.6)	0.716
	yes	62 (1.9)	0 (0.0)	5 (1.9)	37 (1.6)	19 (2.4)	
Trauma history (%)	no	3263 (97.8)	2 (100.0)	261 (99.6)	2197 (97.9)	773 (96.6)	0.04
	yes	74 (2.2)	0 (0.0)	1 (0.4)	46 (2.1)	27 (3.4)	
Cardiovascular (%)	no	2185 (65.5)	1 (50.0)	210 (80.2)	1545 (68.9)	410 (51.2)	<0.001
	yes	1152 (34.5)	1 (50.0)	52 (19.8)	698 (31.1)	390 (48.8)	

The calculated parameters are n (%) or mean (SD). SD: Standard Deviation; NA: Not Applicable; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Diseases; P values are from Chi-square test for categorical variables and Analysis of variance (ANOVA) for continuous variables.

The Kaplan-Meier curves analysis describes the survival rate according to one factor under investigation, but ignores the impact of other factors. The Cox model is a choice which extends survival analysis methods to assess simultaneously the effect of several risk factors on survival time. Cox model is a survival analysis regression model, which investigates the association between the patients' survival time or mortality and multiple predictor variables in medical field. The survival time used in Cox regression is the time from hospital admission (usually coinciding with the start of the first treatment administered) to the last visit. Cox model works for both quantitative predictor variables and for categorical variables. We did Univariate Cox regression to find individual factor that is significantly related to mortality. Multivariable Cox regression model was used to describe how the factors jointly impact on survival time.
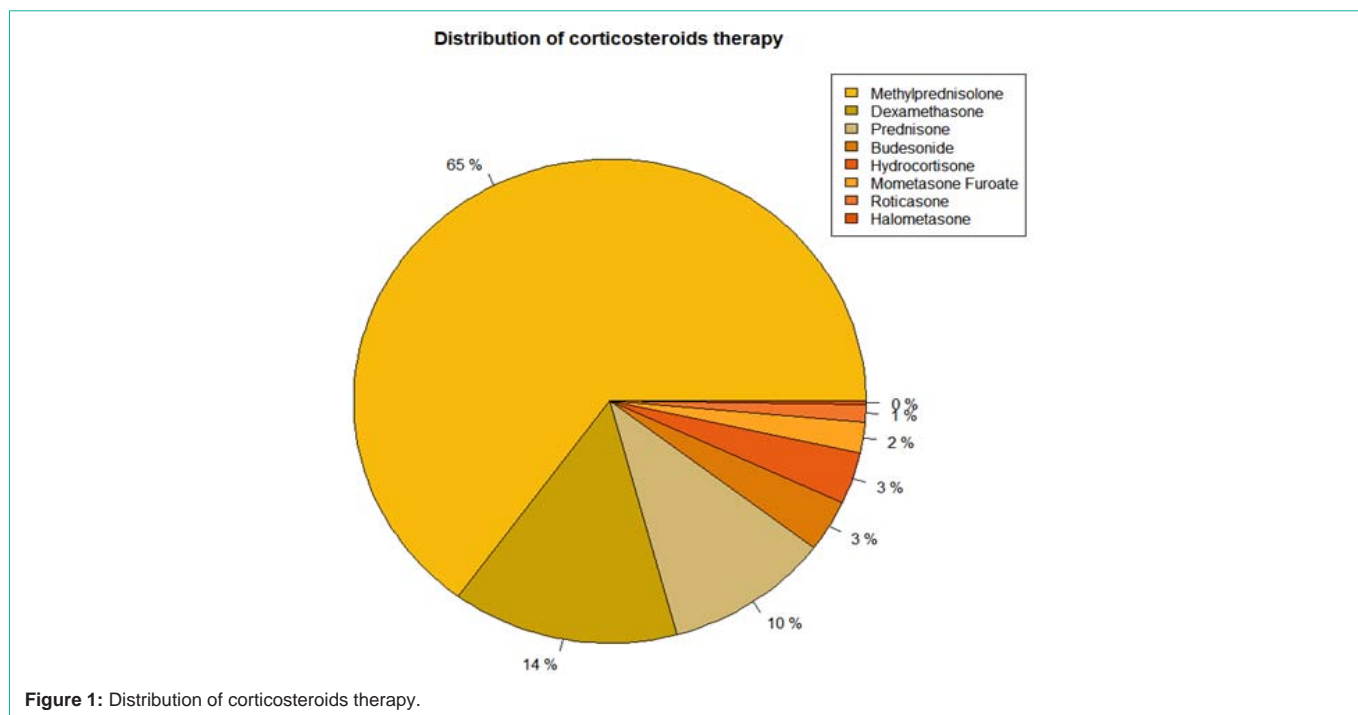
Figure 1: Distribution of corticosteroids therapy.

In multivariable Cox proportional hazard model, only variables with a p < 0.05 in univariable analysis or a presumptive association with the event were included to avoid over fitting. All variables with significance < 0.05 in the Univariate study plus age and gender were included in the multivariate study [20]. We compared the baseline characteristics of the participants with and without corticosteroids therapy, including blood routine, biochemical exam, coagulation exam, cytokines, vital signs and so on. Descriptive data were presented as mean with standard deviation. Categorical variables were presented as percentages. All statistical analyses were conducted using the R Studio.

Results

Characteristic and K-M survival curves

By April, 2020, 3337 patients had been admitted to Tongji Hospital. We classify all patients into four groups (mild, moderate, severe, critical) according to the severity of COVID-19 except 30 of them had no accurate diagnosis (Table 1). 49.9% patients are male, which is slight less than the female cases. For critical ill cases, 59.6% cases are male, which indicates that male is more susceptible to COVID-19. Patients with mean age of 58.39 years (Standard Deviation (SD) = 16.12), and the critical group have highest mean age (64.95, SD =16.66). Older individuals have defective immune response. Ageing is associated with endothelial dysfunction, which contributes to vascular pathologies and cardiovascular diseases in old individuals. Systematic use of corticosteroid treatment is higher in critically ill patients with COVID-19, as many as 80.6% of these patients receiving it. Patients with underlincing commodities have less percentage of corticosteroid therapy. 65% of patients receiving corticosteroids therapy used methylprednisolone and 14% used dexamethasone (Figure 1).

Of 3337 patients admitted to the hospital, we exclude 294 patients

Table 2: Univariate Cox regression of severe patients.

|	Beta	HR(95% CI)	Wald test	p value
Age	0.04	1 (1-1.1)	3.8	0.052
Gender	1.2	3.2 (1-10)	4	0.045
Corticosteroids therapy	0.57	1.8 (0.64-4.9)	1.2	0.27
Past disease	1.2	3.4 (0.95-12)	3.5	0.061
Infectious disease	1.6	5.1 (1.1-22)	4.6	0.033
Allergic history	-17	3.6e-08 (0-Inf)	0	1
Blood transfusion history	-15	3e-07 (0-Inf)	0	1
Past surgery	0.6	1.8 (0.58-5.7)	1	0.31
Hypertension	1.1	3.1 (1.1-8.4)	4.6	0.031
Coronary	0.024	1 (0.13-7.8)	0	0.98
Diabetes	0.019	1 (0.23-4.5)	0	0.98
COPD	2	7.6 (1-58)	3.8	0.05
Malignoncy	1.1	3 (0.39-23)	1.1	0.29
Cerebrovascular disease	1.2	3.4 (0.45-26)	1.4	0.24
Hepatitis	1.6	4.7 (0.62-36)	2.2	0.13
Tuberculosis	1.4	4.2 (0.56-32)	1.9	0.16
Trauma history	1.2	3.4 (0.45-26)	1.4	0.24
Cardiovascular	1.2	3.3 (1.2-9.2)	5.1	0.024

HR: Hazard Ratios; CI: Confidence Interval.

in mild and moderate groups and cases without accurate diagnosis. 2243 (67%) severe pneumonia patients and 800 (24%) critical pneumonia patients were included in our analysis (Figure 2). The cases with various complications are also listed, which might perturb the therapeutic effect of corticosteroids. In the severe group, 1037 (46%) of the patients were male, 857 (38%) received corticosteroids therapy, with an average age of 57 years. In the critical group, 477 (60%) of the

Table 3: Multivariable Cox regression of severe patients.

	Coef	Exp(coef)	Lower 95%	Upper 95%	Se(coef)	Z	Pr(>|z|)	
Gender = male	1.0989	3.001	0.9489	9.49	0.5874	1.871	0.0614	
Infectious disease = yes	1.5683	4.799	1.0683	21.56	0.7665	2.046	0.0407	*
Hypertension =yes	0.2367	1.267	0.1582	10.15	1.0614	0.223	0.8236	-
Cardiovascular = yes	1.0218	2.778	0.3345	23.08	1.0801	0.946	0.3441	-
Concordance= 0.749 (se = 0.059)								
Likelihood ratio test = 12.74 on 4 df, p=0.01								
Wald test = 13.5 on 4 df, p=0.009								
Score (logrank) test = 15.76 on 4 df, p=0.003								

*P-values between 0.01 and 0.05. **P-values between 0.001 and 0.01. ***P-values less than 0.001. coef: Coefficient; coef > 0 means higher hazard and worse prognosis. Exp (coef): Exponential Coefficients, known as hazard ratios, give the effect size of covariates. Exp (coef) > 1 means higher hazard. se(coef): Standard Error of coefficients; z: Wald statistic value. Z = coef / se (coef).
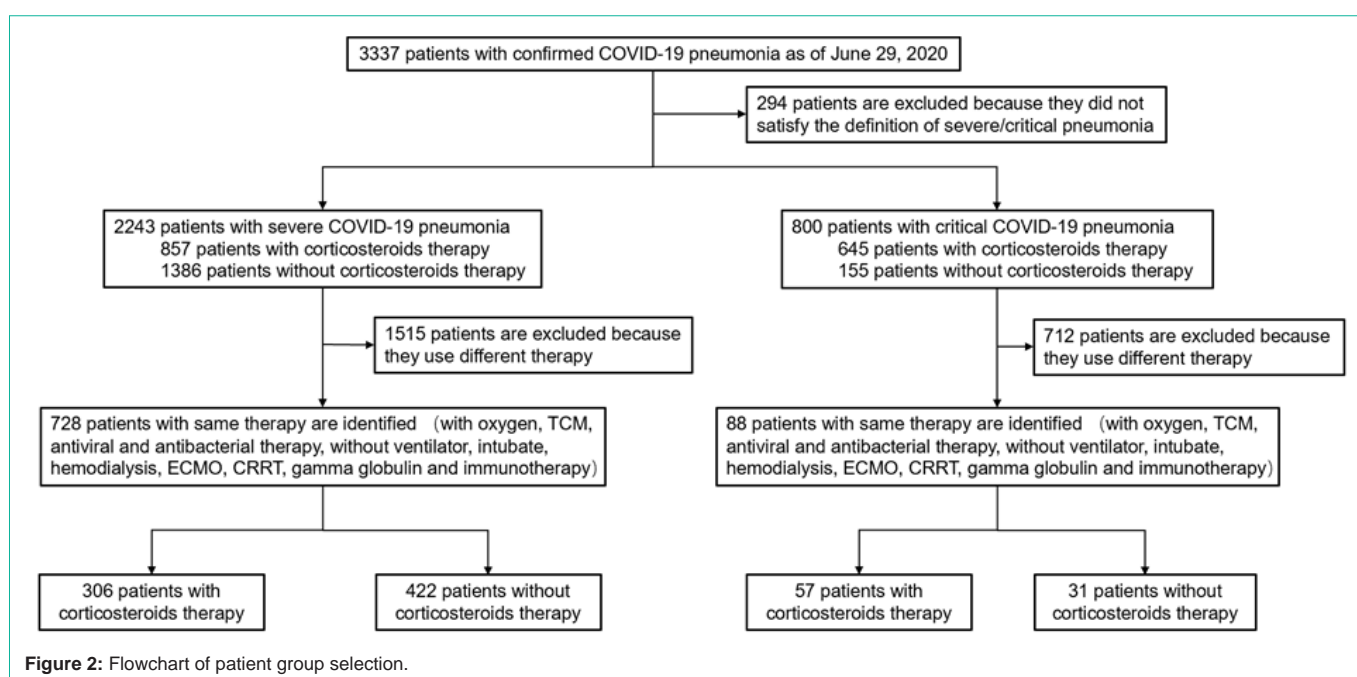
Figure 2: Flowchart of patient group selection.

participants were male, 645 (81%) received corticosteroids therapy, with an average age of 65 years. We did a survival analysis for two groups of participants starting from the date of entry into hospital until discharge or death. We perform survival analysis for severe (2243) and critical (800) group including Kaplan–Meier survival curves and Cox regression. Kaplan–Meier survival curves showed the beneficial effect of therapy with control therapy compared with corticosteroids and methylprednisolone therapy in critical groups and no obviously difference between the corticosteroids therapy group and control group without corticosteroids therapy in severe group (Figure 3 and 4). Patients using dexamethasone therapy has no significant difference compared with control group in both severe group and critical group (Figure 5). We control the therapy variables except corticosteroids therapy, and compare the laboratory test values of patients with and without corticosteroids therapy in severe (728) and critical (88) group.

Previous analysis has small sample, and the patients included in their study were relatively young (median age, 39 years) and had mild disease, limiting the generalisability of their findings to patients

without ARDS, the main threat and challenge in clinical practice. The observational nature means that many confounders may have influenced our results [21]. For the patients in severe group, the result of the Univariate Cox regression showed that gender (p < 0.05), infectious disease (p < 0.05), hypertension (p < 0.05) and cardiovascular history (p < 0.05) are significantly related to mortality. COVID-19 patients have diverse complications, where different complication contributes differently to the survival time. COPD influence the mortality greater than other complications.

Univariate and multivariable Cox regression

A Univariate Cox proportional hazards model was used to estimate the association between medical history and in-hospital mortality. Administration of corticosteroids in severe COVID-19–related ARDS is not associated with increased 78-day mortality and delayed SARS–CoV-2 corona virus RNA clearance (Table 2). However, corticosteroids in critical ill COVID-19 are associated with increased 78-day mortality (Table 4 and 5). Having infectious diseases will increase the hazard ratio of death according to the multivariable Cox regression result in the severe group (Table 3). Corticosteroid is
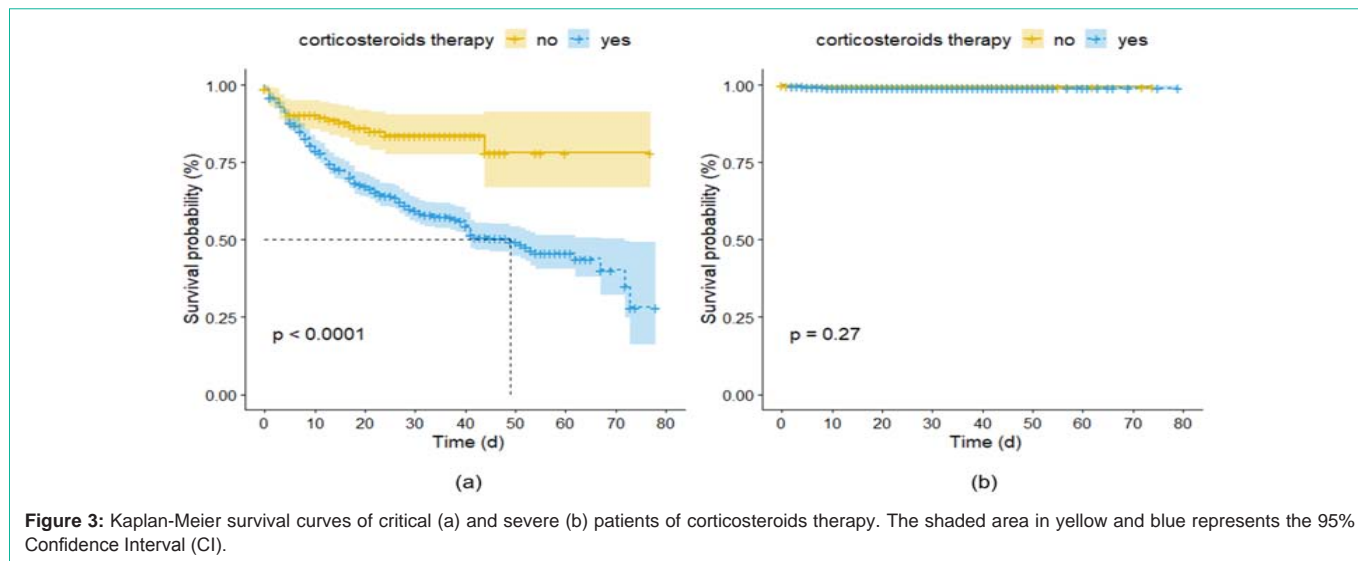
Figure 3: Kaplan-Meier survival curves of critical (a) and severe (b) patients of corticosteroids therapy. The shaded area in yellow and blue represents the 95% Confidence Interval (CI).
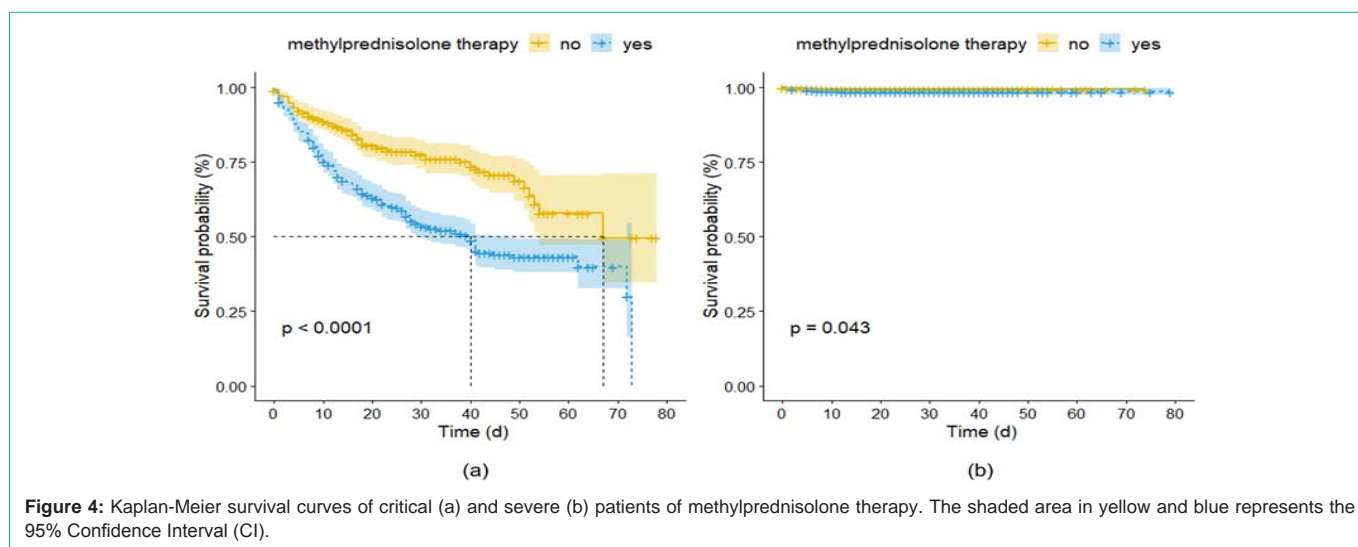

Figure 4: Kaplan-Meier survival curves of critical (a) and severe (b) patients of methylprednisolone therapy. The shaded area in yellow and blue represents the 95% Confidence Interval (CI).
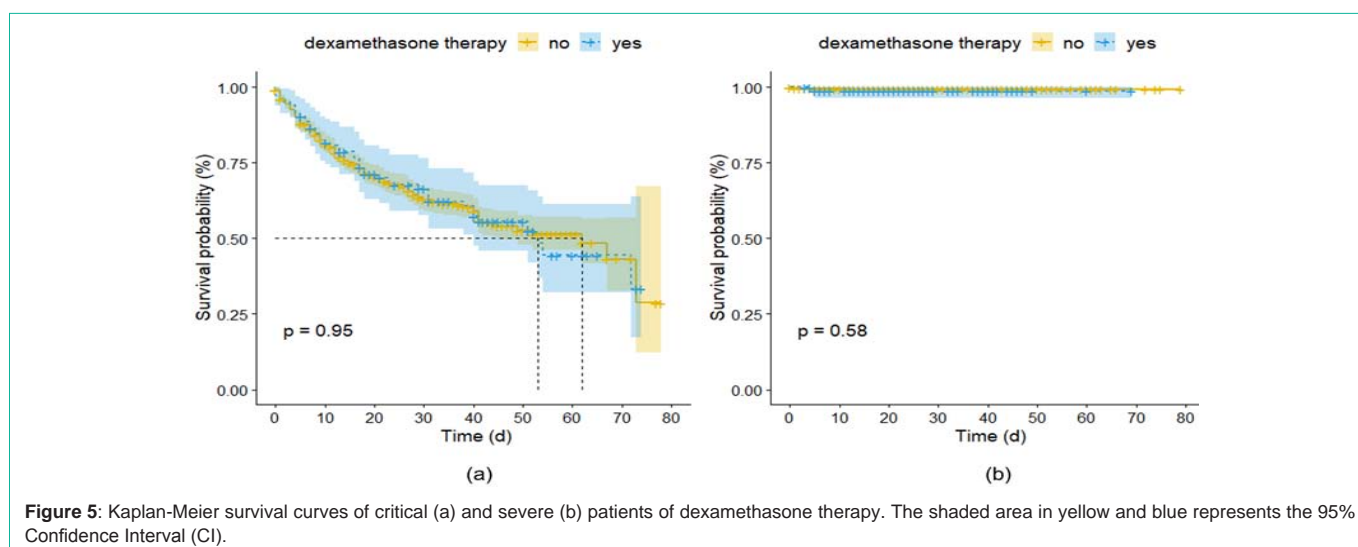

Figure 5: Kaplan-Meier survival curves of critical (a) and severe (b) patients of dexamethasone therapy. The shaded area in yellow and blue represents the 95% Confidence Interval (CI).

Table 4: Univariate Cox regression of critical patients.

	Beta	HR(95% CI)	Wald test	p value
Age	0.018	1 (1-1)	18	1.70E-05
Gender	0.42	1.5 (1.2-1.9)	12	0.00053
Corticosteroids therapy	1	2.7 (1.8-4.2)	21	4.00E-06
Past disease	-0.2	0.82 (0.64-1)	2.7	0.1
Infectious disease	0.34	1.4 (0.82-2.4)	1.5	0.22
Allergic history	0.028	1 (0.64-1.7)	0.01	0.91
Blood transfusion history	0.72	2.1 (0.97-4.3)	3.5	0.061
Past surgery	-0.2	0.82 (0.61-1.1)	1.8	0.18
Hypertension	-0.28	0.75 (0.6-0.95)	5.8	0.016
Coronary	0.17	1.2 (0.84-1.7)	0.93	0.33
Diabetes	-0.29	0.75 (0.55-1)	3.2	0.072
COPD	-0.047	0.95 (0.47-1.9)	0.02	0.9
Malignoncy	0.32	1.4 (0.88-2.2)	2	0.16
Cerebrovascular disease	-0.16	0.85 (0.56-1.3)	0.56	0.45
Hepatitis	-0.064	0.94 (0.39-2.3)	0.02	0.89
Tuberculosis	0.063	1.1 (0.53-2.1)	0.03	0.86
Trauma history	-1	0.35	4.3	0.039
Cardiovascular	-0.2	0.82 (0.66-1)	3	0.081

HR: Hazard Ratios; CI: Confidence Interval.

Table 5: Multivariable Cox regression of critical patients.

	Coef	Exp(coef)	Lower 95%	Upper 95%	Se(coef)	z	Pr(>|z|)	
Age	0.02377	1.0241	1.015	1.0332	0.00452	5.264	1.41E-07	***
Gender = male	0.42608	1.5312	1.2073	1.9421	0.12127	3.513	4.42E-04	***
Corticosteroids therapy = yes	0.99776	2.7122	1.7701	4.1557	0.21771	4.583	4.58E-06	***
Hypertension = yes	-0.4006	0.6699	0.5317	0.844	0.11789	-3.398	6.78E-04	***
Trauma history = yes	-1.0057	0.3658	0.1363	0.9815	0.50358	-1.997	0.04582	*
Concordance = 0.642 (se = 0.017)								
Likelihood ratio test = 81.55 on 5 df, p=4e-16								
Wald test = 69.86 on 5 df, p=1e-13								
Score (logrank) test = 71.34 on 5 df, p=5e-14								

*P-values between 0.01 and 0.05. **P-values between 0.001 and 0.01. ***P-values less than 0.001. coef: Coefficient; coef > 0 means higher hazard and worse prognosis. Exp (coef): Exponentiated coefficients, known as hazard ratios, give the effect size of covariates. Exp (coef) > 1 means higher hazard. Se (coef): Standard error of coefficients; Z: Wald statistic value; Z = coef / se (coef).

hazardous during recovery since the virus will not only persist, but the body will be prevented from generating protective antibodies. Previous report demonstrates the beneficial effect of corticosteroid to critically ill COVID-19 patients [21]. Compared to non-corticosteroid group, systemic corticosteroid use was not associated with beneficial effect in reducing in-hospital mortality in both severe cases (HR = 1.8, 95% CI: 0.64-4.9, p = 0.27), and critical cases (HR = 2.7, 95% CI: 1.8-4.2, p < 0.001).

For the patients in critical group, the result of the Univariate Cox regression showed that age (p < 0.001), gender (p < 0.001), corticosteroids therapy (p < 0.001), hypertension (p < 0.05) and trauma history (p < 0.05) are significantly related to mortality. Hypertension is the common factor contributing mortality rate for both severe and critical COVID-1 groups. Males have higher risk of death and the corticosteroids therapy increase the hazard. Trauma history reduces the hazard ratio of death according to the multivariable Cox regression result. Corticosteroid increases the mortality in critical ill COVID-19, which is different from previous report.

Differences in physiological indicators

Further, we controlled other therapy variables since the treatment is always tailored to individual patients and the combination of different treatment is really diverse. We chose the patients who had accepted the following treatments including oxygen therapy,
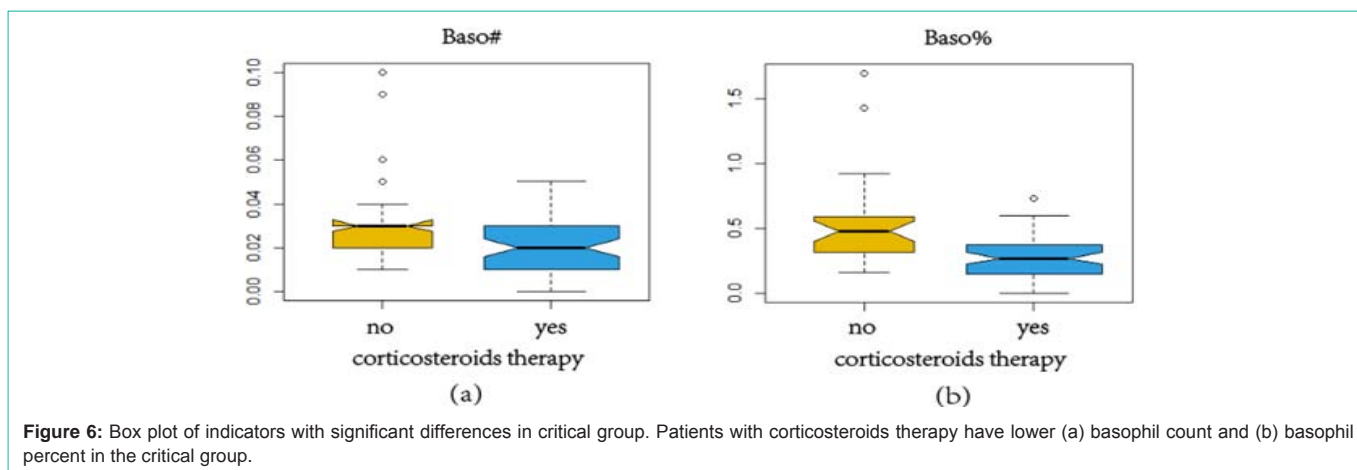

Figure 6: Box plot of indicators with significant differences in critical group. Patients with corticosteroids therapy have lower (a) basophil count and (b) basophil percent in the critical group.

Table 6: Descriptive statistics for parameters in severe patients group.

n	level	Overall	No corticosteroids therapy	Corticosteroids therapy	p
		728	422	306	
Gender (%)	Male	353 (48.5)	207 (49.1)	146 (47.7)	0.778
	Female	375 (51.5)	215 (50.9)	160 (52.3)	
WBC #(mean (SD))		6.06 (1.75)	5.80 (1.53)	6.41 (1.96)	<0.001
RBC #(mean (SD))		4.10 (0.53)	4.12 (0.51)	4.08 (0.55)	0.444
MCV (mean (SD))		89.81 (4.72)	89.85 (4.65)	89.75 (4.82)	0.777
MCHC (mean (SD))		342.42 (12.59)	342.99 (10.87)	341.63 (14.61)	0.152
MCH (mean (SD))		30.76 (2.11)	30.82 (1.89)	30.68 (2.38)	0.378
RDW-CV (mean (SD))		12.80 (1.52)	12.67 (1.49)	12.99 (1.53)	0.005
RDW-SD (mean (SD))		41.38 (3.93)	40.97 (3.73)	41.95 (4.12)	0.001
Lymph % (mean (SD))		26.62 (8.01)	28.27 (7.97)	24.33 (7.51)	<0.001
Lymph # (mean (SD))		1.52 (0.50)	1.57 (0.48)	1.46 (0.51)	0.003
Mono % (mean (SD))		9.27 (2.30)	9.35 (2.24)	9.16 (2.38)	0.278
Mono # (mean (SD))		0.54 (0.17)	0.53 (0.15)	0.56 (0.18)	0.003
Neut % (mean (SD))		61.63 (9.01)	59.72 (8.72)	64.25 (8.76)	<0.001
Neut # (mean (SD))		3.85 (1.53)	3.56 (1.32)	4.25 (1.69)	<0.001
Hct (mean (SD))		36.70 (4.03)	36.85 (4.03)	36.49 (4.02)	0.235
Eos % (mean (SD))		1.71 (1.30)	1.78 (1.27)	1.57 (1.36)	0.528
Baso % (mean (SD))		0.45 (0.24)	0.49 (0.24)	0.40 (0.23)	<0.001
Eos # (mean (SD))		0.12 (0.09)	0.12 (0.08)	0.11 (0.10)	0.081
Baso # (mean (SD))		0.03 (0.01)	0.03 (0.01)	0.02 (0.01)	0.002
Hb (mean (SD))		125.60 (14.75)	126.44 (14.82)	124.44 (14.61)	0.072
PLT # (mean (SD))		243.99 (70.08)	246.07 (70.08)	241.11 (70.10)	0.348
MPV (mean (SD))		10.53 (0.81)	10.50 (0.82)	10.56 (0.80)	0.375
PDW (mean (SD))		12.12 (1.84)	12.09 (1.89)	12.16 (1.77)	0.635
PCT (mean (SD))		0.25 (0.07)	0.26 (0.07)	0.25 (0.07)	0.216
P-LCR (mean (SD))		28.83 (6.61)	28.66 (6.74)	29.06 (6.44)	0.432
ALT (mean (SD))		30.22 (21.12)	28.63 (20.02)	32.41 (22.40)	0.017
AST (mean (SD))		25.20 (11.65)	24.29 (10.41)	26.44 (13.09)	0.014
GGT (mean (SD))		41.77 (37.14)	38.80 (34.41)	45.85 (40.31)	0.012
TBIL (mean (SD))		9.57 (5.49)	9.56 (4.89)	9.57 (6.23)	0.979
DBIL (mean (SD))		4.09 (3.97)	3.98 (2.98)	4.25 (5.02)	0.36
IBIL (mean (SD))		5.54 (2.60)	5.64 (2.76)	5.40 (2.36)	0.226
ALB (mean (SD))		37.12 (3.89)	37.77 (4.02)	36.23 (3.53)	<0.001
GLO (mean (SD))		30.42 (4.07)	30.32 (4.27)	30.56 (3.79)	0.435
TP (mean (SD))		67.54 (4.47)	68.09 (4.44)	66.78 (4.40)	<0.001
ALB/GLO (mean (SD))		1.26 (0.25)	1.29 (0.27)	1.22 (0.23)	0.001
PA (mean (SD))		239.71 (61.70)	244.05 (56.80)	234.17 (67.22)	0.143
TBA (mean (SD))		5.31 (11.50)	4.93 (8.19)	5.78 (14.62)	0.491
Crea (mean (SD)		70.49 (19.04)	70.52 (18.47)	70.45 (19.82)	0.965
Urea (mean (SD))		4.48 (1.43)	4.44 (1.32)	4.54 (1.57)	0.323
UA (mean (SD))		275.14 (79.31)	285.96 (78.73)	260.23 (77.78)	<0.001
TC (mean (SD))		4.14 (0.87)	4.11 (0.87)	4.17 (0.86)	0.373
TG (mean (SD))		1.66 (0.95)	1.64 (1.00)	1.67 (0.89)	0.759
HDL-C (mean (SD))		1.04 (0.28)	1.04 (0.27)	1.03 (0.28)	0.739

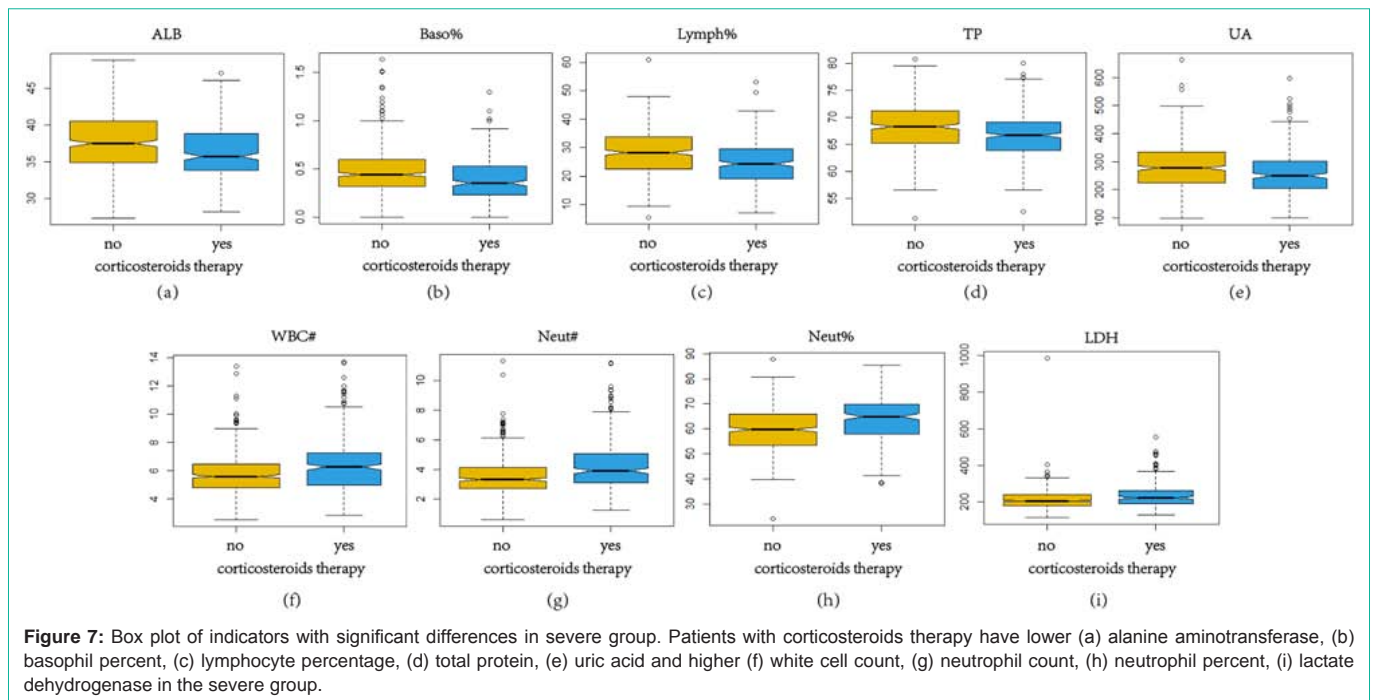|				
LDL-C (mean (SD))	2.61 (0.78)	2.61 (0.78)	2.60 (0.77)	0.921
K$^+$ (mean (SD))	4.25 (0.37)	4.25 (0.37)	4.25 (0.37)	0.904
Na$^+$ (mean (SD))	140.03 (2.33)	140.23 (2.30)	139.76 (2.34)	0.007
Cl$^-$ (mean (SD))	101.43 (2.56)	101.63 (2.41)	101.15 (2.73)	0.013
Ca (mean (SD))	2.18 (0.10)	2.19 (0.10)	2.17 (0.10)	0.006
P (mean (SD))	1.09 (0.17)	1.10 (0.17)	1.08 (0.17)	0.273
Mg^{2+} (mean (SD))	0.86 (0.07)	0.86 (0.06)	0.85 (0.08)	0.062
Glu (mean (SD))	6.31 (2.26)	6.08 (1.87)	6.63 (2.69)	0.001
LDH (mean (SD))	221.87 (61.19)	213.85 (59.91)	232.91 (61.30)	<0.001
ALP (mean (SD))	72.11 (25.86)	70.35 (24.58)	74.52 (27.37)	0.032
ChE (mean (SD))	7246.98 (1831.97)	7407.12 (1959.45)	7048.08 (1644.60)	0.068
AFU (mean (SD))	24.68 (8.37)	24.07 (6.16)	25.43 (10.46)	0.13
Cys-C (mean (SD)	1.06 (0.32)	1.06 (0.30)	1.07 (0.33)	0.796
Amy (mean (SD))	67.81 (33.12)	64.86 (21.47)	71.67 (43.71)	0.07
CKD-EPI (mean (SD))	91.86 (17.20)	92.20 (17.06)	91.40 (17.40)	0.534
TT (mean (SD))	16.66 (1.25)	16.68 (1.25)	16.65 (1.26)	0.749
PT (mean (SD))	13.70 (0.97)	13.68 (1.07)	13.72 (0.82)	0.542
APTT (mean (SD))	38.94 (4.63)	39.03 (4.45)	38.82 (4.88)	0.568
AT:A (mean (SD))	93.65 (12.17)	93.76 (11.90)	93.47 (12.64)	0.783
PT-INR (mean (SD))	1.05 (0.10)	1.05 (0.11)	1.05 (0.08)	0.921
D-Dimer (mean (SD))	1.04 (1.25)	0.99 (1.40)	1.10 (1.00)	0.273
FDP (mean (SD))	6.45 (7.73)	6.46 (7.62)	6.43 (7.91)	0.975
Fbg (mean (SD))	4.36 (1.16)	4.24 (1.17)	4.53 (1.13)	0.001
PTA (mean (SD))	93.79 (10.00)	93.91 (9.90)	93.64 (10.16)	0.729
IL-6 (mean (SD))	12.17 (20.86)	9.68 (15.28)	14.97 (25.47)	0.005
IL-10 (mean (SD))	8.79 (5.18)	8.77 (5.18)	8.81 (5.22)	0.969
IL-8 (mean (SD))	18.27 (30.76)	18.10 (35.29)	18.45 (24.82)	0.9
TNF-α (mean (SD))	8.35 (3.91)	8.34 (4.23)	8.37 (3.50)	0.928
IL-1β (mean (SD))	11.31 (10.62)	13.10 (14.27)	9.62 (4.87)	0.101
IL-2R (mean (SD))	532.05 (330.07)	496.89 (311.32)	575.53 (347.59)	0.004
IgA (mean (SD))	2.43 (0.99)	2.38 (0.89)	2.48 (1.07)	0.511
IgG (mean (SD))	11.44 (2.45)	11.46 (2.17)	11.42 (2.68)	0.921
IgM (mean (SD))	1.08 (0.46)	1.13 (0.49)	1.04 (0.44)	0.232
C3 (mean (SD))	0.86 (0.16)	0.85 (0.14)	0.86 (0.18)	0.549
C4 (mean (SD))	0.23 (0.08)	0.23 (0.07)	0.23 (0.09)	0.999
Temperature (mean (SD))	36.85 (8.30)	36.43 (1.98)	37.41 (12.55)	0.118
Breathe (mean (SD))	19.79 (1.63)	19.75 (1.92)	19.84 (1.10)	0.431
Diastolic (mean (SD))	76.61 (11.41)	76.54 (9.12)	76.70 (13.90)	0.849
Systolic (mean (SD))	125.39 (13.53)	125.52 (13.25)	125.22 (13.92)	0.772
Pulse-rate (mean (SD))	80.42 (8.93)	80.20 (9.51)	80.73 (8.08)	0.434
SpO$_2$ (mean (SD))	97.12 (5.51)	97.11 (6.13)	97.13 (4.54)	0.958

WBC#: White Blood Cell Count; RBC: Red Blood Cell Count; MCV: Mean Red Blood Cell Volume; MCHC: Mean Red Blood Cell Hemoglobin Concentration; MCH: Average Red Blood Cell Hemoglobin; RDW: Red Blood Cell Volume Distribution Width; Lymph %: Lymphocyte Percentage; Lymph #: Lymphocytes Count; Mono%: Monocyte Percentage; Mono#: Monocyte Count; Neut%: Neutrophil Percentage; Neut#: Neutrophil Count; Hct: hematocrit; Eos%: eosinophils percentage; Eos#: Eosinophils Count; Baso%: Basophils Percentage; Baso#: Basophils Count; Hb: Hemoglobin; PLT#: Platelet Count; MPV: Mean Platelet Volume; PDW: Platelet Distribution Width; PCT: Platelet Hematocrit; P-LCR: Percentage Of Large platelets; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase; TBIL: Total Bilirubin; DBIL: Direct Bilirubin; IBIL: Indirect Bilirubin; ALB: Albumin; GLO: Globulin; TP: Total Protein; PA: Prealbumin; TBA: Total Bile Acid; UA: Uric Acid; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; Glu: Glucose; LDH: Lactate Dehydrogenase; ALP: Alkaline Phosphatase; ChE: Cholinesterase; AFU: α-L-Fucosidase; Cys-C: Cystatin; Amy: Amylase; TT: Thrombin Time; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; AT:A: Antithrombin Activity; FDP: Fibrinogen Degradation Products; Fbg: Fibrinogen; PTA: Prothrombin Time Activity; IL: Interleukin; TNF: Tumor Necrosis Factor; Ig: Immunoglobulin; SpO$_2$: SpO$_2$ Oxygen Saturation.

Table 7: Descriptive statistics for parameters in critical patients group.

n	level	Overall	No corticosteroids therapy	Corticosteroids therapy	p
		88	31	57	
Gender (%)	Male	40 (45.5)	13 (41.9)	27 (47.4)	0.791
	Female	48 (54.5)	18 (58.1)	30 (52.6)	
WBC #(mean (SD))		7.34 (2.69)	6.62 (2.03)	7.73 (2.93)	0.063
RBC #(mean (SD))		3.90 (0.57)	3.84 (0.58)	3.93 (0.57)	0.471
MCV (mean (SD))		89.49 (5.40)	89.08 (6.74)	89.71 (4.56)	0.604
MCHC (mean (SD))		338.87(12.08)	339.83 (13.83)	338.34 (11.10)	0.585
MCH (mean (SD))		30.35 (2.40)	30.31 (3.05)	30.37 (2.00)	0.909
RDW-CV (mean (SD))		13.40 (1.51)	13.25 (1.46)	13.49 (1.54)	0.491
RDW-SD (mean (SD))		43.09 (5.05)	42.55 (5.47)	43.39 (4.84)	0.46
Lymph % (mean (SD))		19.79 (8.27)	21.65 (7.04)	18.78 (8.75)	0.12
Lymph # (mean (SD))		1.26 (0.59)	1.38 (0.81)	1.20 (0.41)	0.183
Mono % (mean (SD))		8.49 (2.72)	9.71 (2.88)	7.82 (2.41)	0.002
Mono # (mean (SD))		0.57 (0.20)	0.61 (0.18)	0.56 (0.21)	0.244
Neut % (mean (SD))		69.48 (10.31)	65.39 (8.10)	71.70 (10.76)	0.005
Neut # (mean (SD))		5.37 (2.60)	4.44 (1.55)	5.87 (2.91)	0.013
Hct (mean (SD))		34.72 (4.74)	33.90 (4.08)	35.16 (5.05)	0.238
Eos % (mean (SD))		2.31 (1.23)	2.13 (0.85)	2.48 (1.65)	0.727
Baso % (mean (SD)		0.37 (0.26)	0.53 (0.34)	0.28 (0.16)	<0.001
Eos # (mean (SD))		0.12 (0.13)	0.17 (0.17)	0.09 (0.08)	0.003
Baso # (mean (SD))		0.02 (0.02)	0.03 (0.02)	0.02 (0.01)	<0.001
Hb (mean (SD))		117.20(17.65)	115.17 (14.91)	118.30 (19.01)	0.43
PLT # (mean (SD))		234.50(75.56)	223.80 (72.08)	240.32 (77.38)	0.33
MPV (mean (SD))		10.83 (0.94)	11.11 (0.94)	10.69 (0.92)	0.047
PDW (mean (SD))		12.77 (2.14)	13.33 (2.11)	12.47 (2.12)	0.075
PCT (mean (SD))		0.25 (0.06)	0.25 (0.06)	0.25 (0.07)	0.638
P-LCR (mean (SD))		31.18 (7.45)	33.43 (7.60)	29.99 (7.16)	0.04
ALT (mean (SD))		36.48(86.20)	23.25 (21.56)	43.68 (105.56)	0.291
AST (mean (SD))		32.30(47.35)	28.90 (17.56)	34.15 (57.52)	0.622
GGT (mean (SD))		45.35(35.40)	32.09 (22.01)	52.56 (39.20)	0.009
TBIL (mean (SD))		10.90 (8.85)	12.38 (13.54)	10.10 (4.65)	0.25
DBIL (mean (SD))		5.30 (6.73)	6.27 (10.56)	4.78 (3.14)	0.324
IBIL (mean (SD))		5.66 (2.78)	6.13 (3.85)	5.40 (1.96)	0.245
ALB (mean (SD))		34.64 (3.57)	35.01 (3.88)	34.44 (3.40)	0.481
GLO (mean (SD))		31.67 (5.17)	32.15 (5.85)	31.41 (4.79)	0.523
TP (mean (SD))		66.27 (4.75)	67.16 (5.67)	65.78 (4.14)	0.194
ALB/GLO (mean (SD))		1.15 (0.26)	1.14 (0.27)	1.15 (0.25)	0.875
PA (mean (SD))		221.13(69.33)	225.86 (84.86)	218.68 (61.34)	0.749
TBA (mean (SD))		5.78 (8.53)	8.17 (13.95)	4.52 (2.72)	0.143
Crea (mean (SD))		72.01(29.72)	75.11 (33.43)	70.33 (27.67)	0.474
Urea (mean (SD))		6.10 (3.52)	6.30 (3.30)	6.00 (3.65)	0.705
UA (mean (SD))		248.85(78.71)	262.74 (78.17)	241.30 (78.66)	0.224
TC (mean (SD))		4.01 (0.91)	3.80 (0.86)	4.13 (0.92)	0.106
TG (mean (SD))		1.54 (0.77)	1.43 (0.70)	1.61 (0.81)	0.382
HDL-C (mean (SD))		0.99 (0.35)	1.04 (0.45)	0.96 (0.28)	0.392
LDL-C (mean (SD))		2.41 (0.72)	2.32 (0.78)	2.47 (0.69)	0.461

K+ (mean (SD))	4.31 (0.42)	4.31 (0.47)	4.31 (0.40)	0.983
Na+ (mean (SD))	139.88 (3.13)	139.94 (2.98)	139.86 (3.24)	0.909
Cl- (mean (SD))	101.14 (3.67)	101.70 (3.71)	100.84 (3.64)	0.295
Ca (mean (SD))	2.16 (0.11)	2.19 (0.12)	2.14 (0.10)	0.052
P (mean (SD))	1.04 (0.21)	1.03 (0.26)	1.04 (0.17)	0.863
Mg2+ (mean (SD))	0.83 (0.10)	0.81 (0.08)	0.84 (0.11)	0.251
Glu (mean (SD))	7.00 (2.13)	6.79 (2.48)	7.12 (1.92)	0.491
LDH (mean (SD))	294.41(212.48)	251.62 (73.04)	317.68 (256.36)	0.165
ALP (mean (SD))	72.94 (23.15)	70.67 (25.78)	74.17 (21.73)	0.501
ChE (mean (SD))	6027.11(1742.86)	6235.45 (2075.83)	5916.80 (1561.53)	0.536
AFU (mean (SD))	24.06 (7.64)	23.54 (6.93)	24.34 (8.08)	0.724
Cys-C (mean (SD))	1.28 (0.61)	1.44 (0.73)	1.19 (0.51)	0.152
Amy (mean (SD))	70.58 (28.27)	77.22 (22.26)	66.59 (31.00)	0.211
CKD-EPI (mean (SD))	87.83 (21.83)	80.76 (22.30)	91.67 (20.77)	0.024
TT (mean (SD))	16.73 (1.72)	16.81 (1.34)	16.68 (1.91)	0.734
PT (mean (SD))	14.37 (1.91)	14.69 (2.37)	14.20 (1.60)	0.253
APTT (mean (SD))	40.01 (5.67)	41.49 (6.46)	39.15 (5.03)	0.068
AT:A (mean (SD))	91.09 (14.46)	90.86 (15.10)	91.21 (14.28)	0.923
PT-INR (mean (SD))	1.12 (0.20)	1.15 (0.24)	1.10 (0.17)	0.22
D-Dimer (mean (SD))	1.81 (1.62)	1.84 (1.47)	1.80 (1.72)	0.915
FDP (mean (SD))	8.35 (7.60)	9.03 (5.73)	7.97 (8.52)	0.605
Fbg (mean (SD))	4.65 (1.23)	4.72 (1.37)	4.61 (1.15)	0.686
PTA (mean (SD))	88.58 (14.72)	85.24 (15.99)	90.40 (13.79)	0.117
IL-6 (mean (SD))	42.59 (140.08)	30.29 (40.50)	50.13 (175.50)	0.566
IL-10 (mean (SD))	15.14 (22.57)	21.50 (38.96)	12.25 (8.57)	0.29
IL-8 (mean (SD))	21.92 (23.02)	25.26 (29.54)	20.02 (18.46)	0.368
TNF-α (mean (SD))	10.41 (5.52)	11.54 (6.96)	9.73 (4.37)	0.173
IL-1β (mean (SD))	16.35 (17.99)	12.67 (9.51)	19.79 (23.17)	0.295
IL-2R (mean (SD))	732.42 (495.55)	748.50 (541.31)	722.15 (469.81)	0.822
IgA (mean (SD))	2.37 (1.10)	2.74 (1.40)	2.20 (0.92)	0.163
IgG (mean (SD))	13.18 (4.78)	11.90 (3.06)	13.78 (5.34)	0.265
IgM (mean (SD))	1.11 (0.58)	0.96 (0.42)	1.18 (0.64)	0.282
C3 (mean (SD))	0.87 (0.19)	0.94 (0.24)	0.85 (0.16)	0.188
C4 (mean (SD))	0.23 (0.09)	0.24 (0.10)	0.23 (0.08)	0.796
Temperature (mean (SD))	36.31 (2.26)	36.79 (1.31)	36.05 (2.61)	0.144
Breathe (mean (SD))	20.37 (2.23)	19.70 (1.19)	20.73 (2.56)	0.037
Diastolic (mean (SD)	150.19 (714.27)	73.35 (7.10)	191.98 (887.43)	0.46
Systolic (mean (SD))	126.30 (12.93)	127.43 (12.74)	125.68 (13.10)	0.547
Pulse-rate (mean (SD))	81.46 (8.40)	81.60 (7.15)	81.39 (9.07)	0.913
SpO2 (mean (SD))	96.10 (5.87)	97.69 (2.14)	95.24 (6.99)	0.061

WBC#: White Blood Cell Count; RBC: Red Blood Cell Count; MCV: Mean Red Blood Cell Volume; MCHC: Mean Red Blood Cell Hemoglobin Concentration; MCH: Average Red Blood Cell Hemoglobin; RDW: Red Blood Cell Volume Distribution Width; Lymph %: Lymphocyte Percentage; Lymph #: Lymphocytes Count; Mono%: Monocyte Percentage; Mono#: Monocyte Count; Neut%: Neutrophil Percentage; Neut#: Neutrophil Count; Hct: hematocrit; Eos%: eosinophils percentage; Eos#: Eosinophils Count; Baso%: Basophils Percentage; Baso#: Basophils Count; Hb: Hemoglobin; PLT#: Platelet Count; MPV: Mean Platelet Volume; PDW: Platelet Distribution Width; PCT: Platelet Hematocrit; P-LCR: Percentage Of Large platelets; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase; TBIL: Total Bilirubin; DBIL: Direct Bilirubin; IBIL: Indirect Bilirubin; ALB: Albumin; GLO: Globulin; TP: Total Protein; PA: Prealbumin; TBA: Total Bile Acid; UA: Uric Acid; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; Glu: Glucose; LDH: Lactate Dehydrogenase; ALP: Alkaline Phosphatase; ChE: Cholinesterase; AFU: α-L-Fucosidase; Cys-C: Cystatin; Amy: Amylase; TT: Thrombin Time; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; AT:A: Antithrombin Activity; FDP: Fibrinogen Degradation Products; Fbg: Fibrinogen; PTA: Prothrombin Time Activity; IL: Interleukin; TNF: Tumor Necrosis Factor; Ig: Immunoglobulin; SpO2: SpO2 Oxygen Saturation.

Figure 7: Box plot of indicators with significant differences in severe group. Patients with corticosteroids therapy have lower (a) alanine aminotransferase, (b) basophil percent, (c) lymphocyte percentage, (d) total protein, (e) uric acid and higher (f) white cell count, (g) neutrophil count, (h) neutrophil percent, (i) lactate dehydrogenase in the severe group.

Traditional Chinese Medicine (TCM), antiviral therapy, antibacterial therapy and did not take ventilator, intubate hemodialysis, ECMO, CRRT, gamma globulin therapy, and immunotherapy. 728 patients in the severe group and 88 patients in the critical group met the above conditions. We compared the all available indicators for patients with and without corticosteroids therapy in both two groups and found numerous differences, including lower Baso% in two groups and lower Baso# in the critical group. Box plot shows the different of Baso% and Baso# between corticosteroids therapy and control group (Figure 3). For the severe patients, the result showed that patients with corticosteroids therapy had higher WBC#, LDH, Neut#, Neut% and lower UA, ALB, TP, Lymph% (p < 0.001) (Table 6,7 and Figure 4).

Discussion

Corticosteroids influence the inflammatory component of the inflammation–thrombosis–hypoxia interaction, which is beneficial when mechanical ventilation is required and less effective once thrombi have developed [22]. Corticosteroid is recommended in cases of sudden hearing loss of more than 60 dB, either in the form of intratympanic injections or a week's course of oral medication. Systemic or local corticosteroid therapy is not indicated for bacterial ENT infections [23]. Corticosteroids treatment should balance the potential small reduction in mortality with potential effects of prolonged corona virus shedding [24], and time of corticosteroid treatment should not be limited to 14 days [25].

Previous report performed survival analysis for 28 days and we extended the mortality analysis to 78 days. In this prospective analysis, we collected and screened clinical data for 2243 severe patients and 800 critical cases out of 3337 COVID-19 patients. The survival analysis demonstrates that a therapy with corticosteroids was no associated with a significant reduction in mortality among both severe and critical patients. Corticosteroids should be considered in

severe critically ill patients with COVID-19 but must be discouraged in patients not requiring oxygen therapy [26]. Absence of the beneficial effect in our study in contrast to that was observed in the RECOVERY clinical trial may be due to biases in observational and indication data, differences in clinical characteristics of patients, choice of corticosteroid, dosage of administration, concomitant antiviral or anti-inflammatory drugs, initiation timing and duration of treatment [18].

In order to address this controversy, efforts have been made to clarify the effectiveness of corticosteroids in ARDS through large-scale multi-centered randomized controlled trials [27]. The characterization of immune activation pattern in COVID-19 patients should provide additional insights into the timing and therapeutic effects of corticosteroids and help determine which COVID-19 patients will benefit or be harmed [13].

Limitations

This study has several limitations. First, sample size is big. However, many variables are involved in such as dosage, types of corticosteroids, initiation and duration of treatment, other accompanying treatments, undersing commodities, and demographic factors. The absence of stratification and incomplete information about some factors associated with outcome may have resulted in imbalance between the treated and control groups. Second, the study is retrospective in nature using real-world observational data, outside the context of random controlled trial. Third, because of the emergency situation, small variations to the standard clinical management of patients with COVID-19 may not be totally ruled out as a result of hospital reorganization and resource availability, which involves a wide spectrum of departments and physician specialists. Data in the studies were too sparse to draw any firm conclusions; there might be a signal of delayed viral clearance and an increase in secondary infections [28]. Finally, the daily evolution of inflammatory parameters throughout

the first days after corticosteroid administration was registered in a limited number of included patients, which is not firm enough to draw conclusions [29,30].

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