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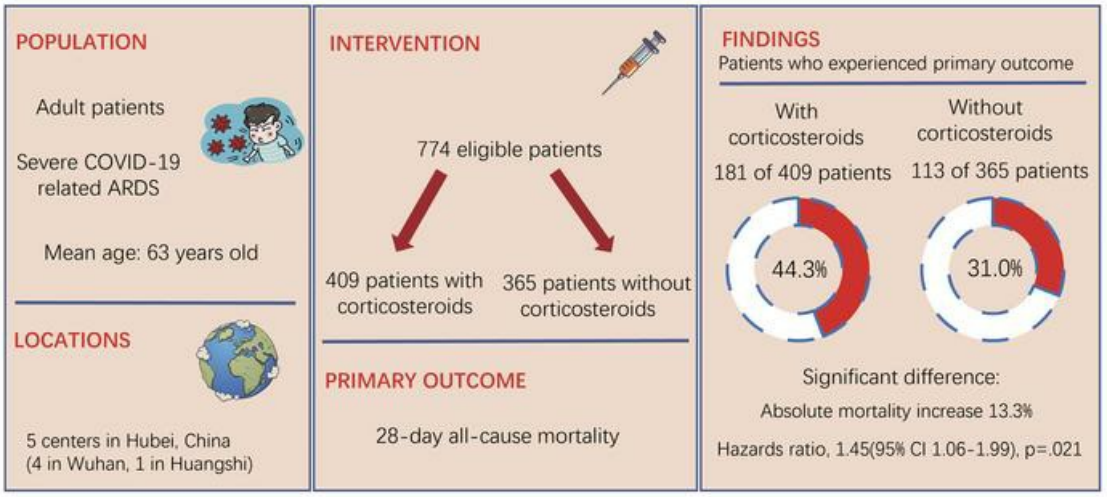
Graphical abstract



Corticosteroid treatment in severe COVID-19 patients with acute respiratory distress syndrome

Jiao Liu,[1,2] Sheng Zhang,[1] Xuan Dong,[3] Zhongyi Li,[4] Qianghong Xu,[5] Huibin Feng,[6] Jing Cai,[7] Sisi Huang,[2] Jun Guo,[8] Lidi Zhang,[2] Yizhu Chen,[2] Wei Zhu,[9] Hangxiang Du,[1] Yongan Liu,[1] Tao Wang,[1] Limin Chen,[1] Zhenliang Wen,[2] Djillali Annane,[10] Jieming Qu,[11] and Dechang Chen[1,2]

[1]Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. [2]Department of Critical Care Medicine, Ruijin Hospital North, Shanghai Jiao Tong University School of Medicine, Shanghai, China. [3]Tuberculosis and Respiratory Department, Wuhan Jinyin-tan Hospital, Wuhan, China. [4]Department of Critical Care Medicine, Wuhan No. 9 Hospital, Wuhan, China. [5]Department of Critical Care Medicine, Zhejiang Hospital, Hangzhou, China. [6]Intensive Care Unit, Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, Edong Healthcare Group, Huangshi, China. [7]Department of Critical Care Medicine, Second Affiliated Hospital of Zhejiang University Medical College, Hangzhou, China. [8]Intensive Care Unit, Huazhong University of Science and Technology Union Jiangbei Hospital, Wuhan, China. [9]Intensive Care Unit, Tianyou Hospital Affiliated to Wuhan University of Science and Technology, Wuhan, China. [10]FHU SEPSIS (Saclay and Paris Seine Nord Endeavour to PerSonalize Interventions for Sepsis), RHU RECORDS (Rapi'd rEcognition of CORticosteroiD resistant or sensitive Sepsis), Department of Intensive Care, Hôpital Raymond Poincaré (APHP), Laboratory of Infection and Inflammation — U1173, School of Medicine Simone Veil, University Versailles Saint Quentin — University Paris Saclay, INSERM, Garches, France. [11]Department of Pulmonary and Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

BACKGROUND. Corticosteroids are widely used in patients with COVID 19, although their benefit-to-risk ratio remains controversial.

METHODS. Patients with severe COVID-19–related acute respiratory distress syndrome (ARDS) were included from December 29, 2019 to March 16, 2020 in 5 tertiary Chinese hospitals. Cox proportional hazards and competing risks analyses were conducted to analyze the impact of corticosteroids on mortality and SARS–CoV-2 RNA clearance, respectively. We performed a propensity score (PS) matching analysis to control confounding factors.

RESULTS. Of 774 eligible patients, 409 patients received corticosteroids, with a median time from hospitalization to starting corticosteroids of 1.0 day (IQR 0.0–3.0 days) . As compared with usual care, treatment with corticosteroids was associated with increased rate of myocardial (15.6% vs. 10.4%, $P = 0.041$) and liver injury (18.3% vs. 9.9%, $P = 0.001$), of shock (22.0% vs. 12.6%, $P < 0.001$), of need for mechanical ventilation (38.1% vs. 19.5%, $P < 0.001$), and increased rate of 28-day all-cause mortality (44.3% vs. 31.0%, $P < 0.001$). After PS matching, corticosteroid therapy was associated with 28-day mortality (adjusted HR 1.46, 95% CI 1.01–2.13, $P = 0.045$). High dose (>200 mg) and early initiation (≤3 days from hospitalization) of corticosteroid therapy were associated with a higher 28-day mortality rate. Corticosteroid use was also associated with a delay in SARS–CoV-2 coronavirus RNA clearance in the competing risk analysis (subhazard ratio 1.59, 95% CI 1.17–2.15, $P = 0.003$).

CONCLUSION. Administration of corticosteroids in severe COVID-19–related ARDS is associated with increased 28-day mortality and delayed SARS–CoV-2 coronavirus RNA clearance after adjustment for time-varying confounders.

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Introduction

SARS–CoV-2 has spread worldwide (1). As of July 17, there were more than 13 million cases and 585,727 deaths worldwide, including over 4000 reported deaths in China (1). There is still no specific treatment for COVID-19, and patient management relies on supportive care (2).

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Approximately 31%–41.8% of hospitalized COVID-19 patients rapidly develop acute respiratory distress syndrome (ARDS), with subsequent increased risk of death (3, 4), and patient deterioration is likely related to dysregulated systemic inflammation (5), as highlighted by increases in serum levels of inflammatory cytokines (6). Corticosteroids downregulate systemic inflammation by nongenomic and genomic effects (7).

Corticosteroids have been widely used to treat severe pneumonia due to influenza A (H5N1) and SARS-CoV (8, 9). However, the benefits of corticosteroid treatment in patients with respiratory infection due to coronavirus has remained controversial. In a systematic review including 29 studies with corticosteroid therapy for SARS infection, 25 studies were inconclusive and 4 studies indicated harmful results (10). In a retrospective cohort study of 309 critically ill adults with Middle East respiratory syndrome

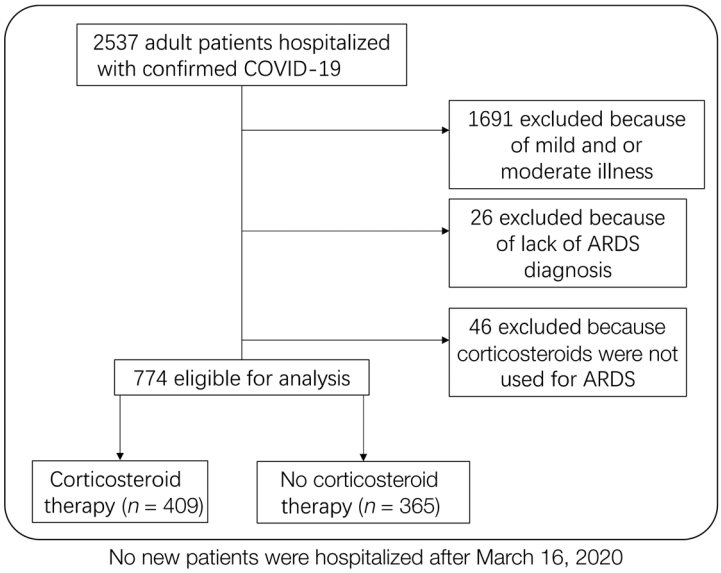

Figure 1. Flow chart of the present study.

(MERS), corticosteroid therapy did not significantly change mortality and was associated with delayed viral clearance (11). An observational cohort of COVID-19 patients with ARDS suggested that treatment with methylprednisolone may decrease the risk of death (3). We conducted a retrospective multicenter study to explore the effects of corticosteroids on mortality from COVID-19 with ARDS. We also explored the effects of corticosteroids on the clearance of SARS–CoV-2 RNA. We aimed to explore the roles of corticosteroids and their influence on clinical outcomes in confirmed severe COVID-19–related ARDS.

Results

Description of the cohort. Of 2537 patients with confirmed COVID-19 admitted to 5 tertiary hospitals from December 29, 2019 to March 16, 2020, 820 had ARDS and 774 were eligible (Figure 1). The median age was 64 years (IQR 54–73 years) (Table 1) and 452 (58.0%) were male, 322 (42%) were female. A total of 596 patients (77%) had one or more comorbidities. The median acute physiology and chronic health evaluation (APACHE) II score was 11 (IQR 9–13). A total of 409 out of 774 (52.8%) received corticosteroids and 365 (47.2%) did not. The median PaO_2/FiO_2 was 168 (IQR 99–237) before treatment in the whole cohort. On admission, 693 of 774 (89.5%) patients received nasal cannula oxygen treatment, 43 of 774 (5.6%) high-flow oxygen, 27 of 774 (3.5%) noninvasive mechanical ventilation, and 11 of 774 (1.4%) invasive mechanical ventilation. There was no significant difference in respiratory support between groups ($P = 0.143$). The crude 28-day all-cause mortality was 38.0% (294 of 774). Admission characteristics of ARDS patients are shown in Supplemental Table 1 (supplemental material available online with this article; https://doi.org/10.1172/JCI140617DS1).

Corticosteroid therapy. Methylprednisolone was the most frequently used corticosteroid (396 of 409 [96.8%] patients) followed by prednisolone (32 of 409 [7.8%] patients) (Table 2). The median length from admission to initiation of corticosteroid therapy was 1.0 day (IQR 0.0–3.0 days) (Supplemental Figure 1), with a maximum daily hydrocortisone-equivalent median dose of 200 mg (IQR 200–400 mg). The median duration of corticosteroid therapy was 6.0 days (IQR 4.0–10.0 days). Before corticosteroid administration, the median PaO_2/FiO_2 was 122 mmHg (IQR 98–217 mmHg).

Mortality. At 28 days, there were 181 of 409 (44.3%) deaths in the corticosteroid group and 113 of 365 (31.0%) in the control group (OR 1.77, 95% CI 1.32–2.38, $P < 0.001$). A total of 185 out of 409 (45.2%) corticosteroid-treated patients died during hospitalization, compared with 115 of 365 (31.5%) controls (OR 1.79, 95% CI 1.34–2.41, $P < 0.001$). The cumulative 28-day survival rate was significantly different between the 2 groups ($P = 0.00061$, log-rank test; Figure 2A). Multivariate logistic regression analysis suggested increased 28-day mortality with corticosteroids (adjusted OR 2.17, 95% CI 1.36–3.53, $P = 0.001$). Other independent risk factors for increased 28-day mortality included age, APACHE II score, diabetes, leukocytosis, and human immunoglobulin use (Table 3). Likewise, Cox's proportional hazards regression model also suggested increased mortality with corticosteroid therapy (adjusted HR 1.45, 95% CI 1.06–1.99, $P = 0.021$; Table 3). The association between corticosteroid use and mortality was more evident when treating corticosteroid as a time-varying exposure variable in the extended Cox regression model (adjusted HR 6.69, 95% CI 4.53–9.87, $P < 0.001$; Table 3). The increase risk of death at 28 days associated with exposure to corticosteroids was consistent across subgroups except for patients with APACHE II scores of 11 or higher who had shock or received mechanical ventilation (Figure 3). Among patients with shock, low-dose glucocorticoid therapy (≤200 mg equivalent hydrocortisone per day) did not significantly decrease the risk of death (OR 0.41, 95% CI 0.12–1.33, $P = 0.14$).

Finally, to determine the effect of corticosteroid therapy on 28-day mortality, we conducted a propensity score (PS) matching analysis. After applying PS matching, 182 control and 182 case patients were matched. The summaries of balance for unmatched and matched data are shown in Table 4 and Figure 4. Corticosteroid therapy was significantly associated with increased 28-day mortality in multiple analyses, including Kaplan-Meier survival plot (Figure 2B), multivariable logistic regression model (adjusted OR 1.64, 95% CI 1.05–2.57, $P = 0.032$; Table 5), and extended multivariable Cox regression model which treated corticosteroid as a time-varying exposure variable (adjusted HR 1.46, 95% CI 1.01–2.13, $P = 0.045$; Table 5). In subgroup analyses, high dose (>200 mg) and early initiation (≤3 days from hospitalization) of corticosteroid therapy were associated with a higher 28-day mortality rate. In addition, even short course (≤6 days) exposure to corticosteroids increased the risk of death (Table 5).

SARS–CoV-2 RNA clearance. Corticosteroid therapy was associated with delayed SARS–CoV-2 RNA clearance among survivors by log-rank test ($P = 0.00017$; Figure 5A). Likewise in the whole cohort, the viral clearance was delayed with corticosteroid therapy (subhazard ratio [sHR] 1.59, 95% CI 1.17–2.15, $P = 0.003$; Figure 5B). The relationship between corticosteroid use and viral clear-

Table 1. Baseline characteristics and physiological parameters on admission of severe COVID-19 patients with ARDS in the corticosteroid-therapy and no-corticosteroid-therapy groups

Variables	All patients (*n* = 774)	Glucocorticoid (*n* = 409)	No Glucocorticoid (*n* = 365)	*P* value
Age (yr), median (IQR)	64 (54–73)	65 (55–74)	63 (54–72)	0.480
Sex, male, *n* (%)	452 (58.4)	249 (60.9)	203 (55.6)	0.159
Smoking, *n* (%)	28 (3.6)	9 (2.2)	19 (5.2)	0.041
Drinking, *n* (%)	25 (3.2)	9 (2.2)	16 (4.4)	0.131
Exposure history, *n* (%)				
Wuhan exposure	750 (96.9)	398 (97.3)	352 (96.4)	0.623
Out of Wuhan City	24 (3.1)	11 (2.7)	13 (3.6)	
Household clustered				<0.001
No	458 (59.2)	210 (51.3)	248 (67.9)	
Yes	55 (7.1)	22 (5.4)	33 (9)	
Unknown	261 (33.7)	177 (43.3)	84 (23)	
Any comorbidity, *n* (%)				
Chronic obstructive pulmonary disease	25 (3.2)	11 (2.7)	14 (3.8)	0.486
Diabetes	118 (15.2)	50 (12.2)	68 (18.6)	0.018
Hypertension	248 (32)	126 (30.8)	122 (33.4)	0.483
Chronic cardiac disease	91 (11.8)	36 (8.8)	55 (15.1)	0.010
Chronic kidney disease	22 (2.8)	7 (1.7)	15 (4.1)	0.074
Chronic liver disease	24 (3.1)	10 (2.4)	14 (3.8)	0.365
Stroke	43 (5.6)	18 (4.4)	25 (6.8)	0.184
Malignancy	26 (3.4)	16 (3.9)	10 (2.7)	0.482
Immunosuppressive agents	26 (3.4)	14 (3.4)	12 (3.3)	>0.999
Signs and symptoms at admission				
Fever, *n* (%)	589 (76.1)	300 (73.3)	289 (79.2)	0.070
Highest temperature (°C), median (IQR)	38.6 (38–39)	38.75 (38–39)	38.5 (38–39)	0.036
Cyanosis, *n* (%)	91 (11.8)	62 (15.2)	29 (7.9)	0.003
Systolic pressure (mmHg), median (IQR)	130 (119–140)	130 (120–144)	126 (116–138)	<0.001
Heart rate (bpm), median (IQR)	88 (80–100)	88 (79–100)	89 (80–99)	0.646
Respiratory rate (bpm), median (IQR)	21 (20–25)	22 (19–27)	21 (20–25)	0.355
SOFA score (IQR)	7 (6–9)	7 (6–8)	7 (6–9)	0.549
APACHE II score (IQR)	11 (9–13)	12 (9–14)	10 (8–12)	0.001
Respiratory support, *n* (%)				0.148
Nasal cannula	693 (89.5)	357 (87.3)	336 (92.1)	
High-flow nasal cannula	43 (5.6)	26 (6.4)	17 (4.7)	
Noninvasive mechanical ventilation	27 (3.5)	18 (4.4)	9 (2.5)	
Invasive mechanical ventilation	11 (1.4)	8 (2)	3 (0.8)	
Physiologic parameters				
Platelets ($\times 10^9$/L), median (IQR)	174 (128–232)	165 (122–213)	190 (138–260)	<0.001
Lymphocytes ($\times 10^9$/L), median (IQR)	0.7 (0.5–1.1)	0.6 (0.4–1.0)	0.8 (0.5–1.1)	<0.001
PT (seconds), median (IQR)	11.7 (10.9–13.1)	12.0 (11.1–13.7)	11.5 (10.8–12.5)	<0.001
D-dimer (μg/mL), median (IQR)	0.8 (0.5–2.1)	0.9 (0.5–2.1)	0.8 (0.5–2.1)	0.794
TBil (μmol/L), median (IQR)	13 (9.7–16.9)	13.5 (10.0–17.4)	12.3 (9.4–15.9)	0.015
Scr (μmol/L), median (IQR)	73.7 (60.0–92.3)	78 (62.0–97.8)	69.6 (57.4–89.0)	<0.001
LDH (U/L), median (IQR)	355 (269–508)	407 (307–578)	308 (241–433)	<0.001
Procalcitonin (ng/mL), median (IQR)	0.14 (0.06–0.65)	0.22 (0.09–1.01)	0.10 (0.05–0.25)	<0.001
IL-6 (pg/mL), median (IQR)	9.4 (7.2–12.6)	9.2 (7.3–12.5)	9.6 (6.9–12.7)	0.992
hsCRP (mg/L), median (IQR)	52.8 (25.1–97.2)	62.4 (30.2–117.8)	44.5 (19.9–77.8)	<0.001
Hemoglobin (g/L), median (IQR)	124 (112–135)	126 (113–135)	123 (112–134)	0.362
WBC ($\times 10^9$/L), median (IQR)	7.0 (4.6–10.9)	7.9 (5.0–11.9)	6.3 (4.5–9.5)	<0.001

PT, partial thromboplastin time; TBil, total bilirubin; Scr, serum creatinine; LDH, lactate dehydrogenase; IL-6, interleukin-6; hsCRP, high sensitivity C-reactive protein.

Table 2. Corticosteroid therapy among severe COVID-19 patients with ARDS (*n* = 409)

Medication variable	Result
Dexamethasone, *n* (%)	12 (2.9)[A]
Hydrocortisone, *n* (%)	2 (0.5)[A]
Methylprednisolone, *n* (%)	396 (96.8)[A]
Prednisolone, *n* (%)	32 (7.8)[A]
Duration of corticosteroids, days (IQR)	
All patients	6 (4 to 10)
Survivors	7 (4 to 11)
Nonsurvivors	5 (3 to 9)
Dose, hydrocortisone equivalent/day, mg (IQR)	
All patients	200 (200 to 400)
Survivors	200 (200 to 400)
Nonsurvivors	400 (200 to 400)
Duration between onset of illness and corticosteroid initiation, days (IQR)	10 (7 to 14)
Duration between hospital admission and corticosteroid initiation, days (IQR)	1 (0 to 3)
Duration between ARDS onset and corticosteroid initiation, days (IQR)	0 (–1 to 1)
Duration between ICU admission and corticosteroid initiation, days (IQR)	0 (–2 to 0)
Duration between onset of non-invasive ventilation and corticosteroid initiation, days (IQR)	0 (–2 to 0)
Duration between onset of invasive ventilation and corticosteroid initiation, days (IQR)	–3 (–8 to –1)

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit. Data presented as *n* (%) or median (Q1 to Q3). [A]Percentages add up to more than 100% because some patients received more than one formulation of corticosteroids during ICU stay.

ance did not change significantly in patients with early initiation of corticosteroid therapy (sHR 1.39, 95% CI 1.02–1.89, $P = 0.039$) and those with late initiation of corticosteroid therapy (sHR 2.79, 95% CI 1.72–4.54, $P < 0.001$).

Other secondary outcomes. During hospitalization, as compared with controls, corticosteroid-treated patients were more likely to develop myocardial injury (15.6% vs. 10.4%, $P = 0.041$), acute liver injury (18.3% vs. 9.9%, $P = 0.001$), and shock (22.0% vs. 12.6%, $P < 0.001$). They were more likely to receive treatment with ganciclovir (29.3% vs. 20.0%, $P = 0.004$), ribavirin (43.0% vs. 21.6%, $P < 0.001$), antibiotics (98.3% vs. 76.7%, $P < 0.001$), antifungal drugs (10.5% vs. 1.1%, $P < 0.001$), high-flow oxygen therapy (33.5% vs. 16.2%, $P < 0.001$), noninvasive mechanical ventilation (25.9% vs. 14.0%, $P < 0.001$), invasive mechanical ventilation (19.8% vs. 10.4%, $P < 0.001$), and prone-position ventilation (4.6% vs. 1.4%, $P = 0.016$) (Table 6 and Supplemental Table 2). As compared with controls, corticosteroid-treated patients were more likely to require ICU admission (47.7% vs. 22.5%, $P < 0.001$), had longer duration of stay in the hospital (median 15 days, IQR 9–21 days; compared with 13 days, IQR 8–18 days; $P < 0.001$), and longer time in the ICU (median 5 days, IQR 1–11 days; compared with 2 days, IQR 0–7 days; $P < 0.001$) (Table 6). There was no significant difference between groups in the rate of occurrence of bacterial (5.8% vs. 3.4%, $P = 0.336$) and fungal (8.0% vs. 8.3%, $P > 0.99$) lower respiratory tract infections (Supplemental Table 3).

Discussion

This multicenter cohort study suggested that, in severe COVID-19–related ARDS patients, corticosteroids increased the risk of death at 28 days and during hospitalization, and delayed SARS–CoV-2 clearance from the airway. The increase in mortality was consistent across subgroups with early initiation (≤3 days from hospitalization), high dose (>200 mg), and independent of duration of corticosteroid treatment.

SARS–CoV-2–related ARDS is characterized by poor outcome, with 35%–40% of patients who have died in the short term (12). The mechanisms by which SARS–CoV-2 induces ARDS and eventually causes death remain uncertain. Similar to SARS-CoV infection, SARS–CoV-2 infection is associated with excessive lung and systemic inflammation (13) that contributes to the severity of illness (14) and the development of multiple organ failure (12). Corticosteroids are potent immunomodulatory drugs that downregulate inflammation by nongenomic and genomic effects (7). Therefore, they have been broadly used in adults with ARDS with variable results (15, 16). A meta-analysis from 4 trials suggested that in patients with SARS corticosteroids might have detrimental effects (10). Although corticosteroids were not recommended during the 2003 SARS epidemic (17, 18), these drugs were broadly used by physicians. About half of critically ill adults with MERS received corticosteroids and were more likely to require mechanical ventilation, vasopressors, and renal replacement therapy during hospitalization (11). There was no evidence for any effect of corticosteroids on short-term mortality in these patients (11), independent of dose, duration, and initiation time.

During the COVID-19 pandemic, the indication for steroid use was mentioned in the New Coronavirus Pneumonia Diagnosis and Treatment Plan in China (http://www.cac.gov.cn/2020-03/04/c_1584872634644633.htm), which suggested low dose (1–2 mg/kg/d) and short duration (3–5 days) of methylprednisolone use in COVID-19 patients who had rapid PaO_2/FiO_2-ratio and pulmonary-imaging deterioration after hospitalization. However, the decision to treat a patient with corticosteroid was left at the discretion of his/her primary physician. Fadel et al. found that hospitalized patients with moderate to severe COVID-19 who received an early short course of methylprednisolone had a reduced rate of mortality and mechanical ventilation (19). The RECOVERY trial, a platform open-label trial aimed at assessing multiple treatments for COVID-19 in hospitalized patients in the United Kingdom, found an age-adjusted rate ratio (aRR) of 28-day all-cause mortality of 0.83 (95% CI 0.75–0.93) in favor of 6 mg dexamethasone daily for 10 days (20). Nevertheless, in this trial, reduction in mortality with dexamethasone was seen only in patients who required supplemental oxygen with or without invasive mechanical ventilation. In patients who did not require supplemental oxygen, the aRR was 1.19 (95% CI 0.91–1.55). A recent meta-analysis with a sample size of 5270 patients

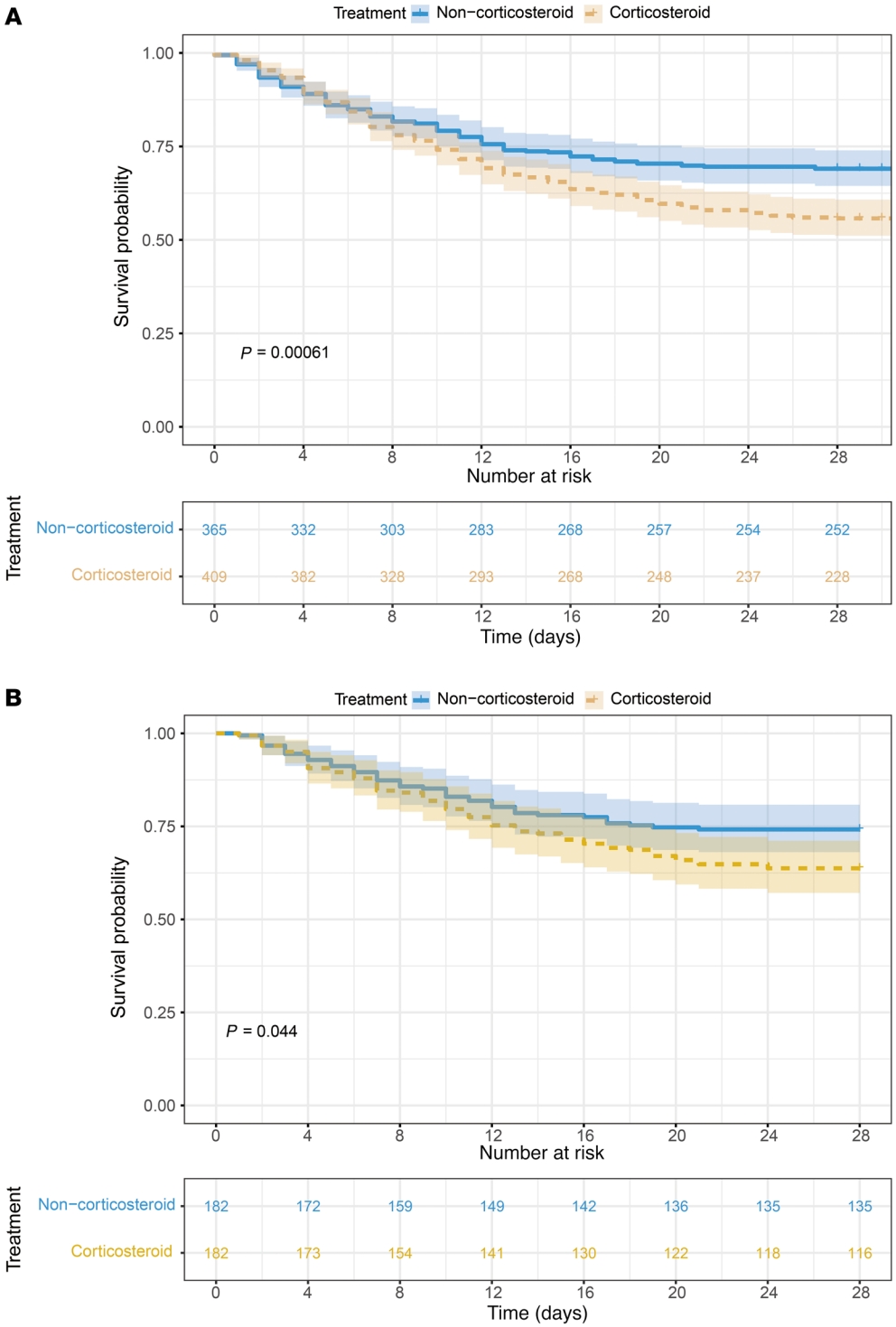

Figure 2. Survival curve during hospitalization according to corticosteroid therapy. Kaplan-Meier survival curves before (**A**) and after propensity score matching (**B**).

suggested that treatment with corticosteroids was associated with increased mortality and prolonged hospital stays in patients with coronavirus pneumonia (21). The increase in mortality was consistent across subgroups with early initiation (≤3 days from hospitalization) and high dose (>200 mg). The discrepancy in the findings from the current study and the RECOVERY trial may be related to differences in corticosteroid regimen and study populations. In the current study, most of the patients received methylprednisolone versus dexamethasone in the RECOVERY trial. Pharmacological differences between methylprednisolone and dexamethasone include differences in mineralocorticoid activity (some versus none, respectively) and in plasma half-life (3 hours versus 72 hours, respectively). There were also differences in dose and duration of treatment with corticosteroids between the 2 studies with lower daily doses (150 versus 200 to 400 mg of hydrocortisone equivalent, respectively) and longer duration (10 versus 6 days, respectively). Therefore, the inconsistent findings between the present study and previous studies (19, 20) may

Table 3. Risk factors associated with 28-day mortality in severe COVID-19 patients with ARDS identified by logistic regression model, traditional Cox proportional hazards regression model, and extended Cox regression model

	Logistic regression model			Traditional Cox model			Extended Cox model[A]		
Variables	aOR	95% CI	*P* value	aHR	95% CI	*P* value	aHR	95% CI	*P* value
Age	1.04	1.03–1.06	<0.001	1.03	1.02–1.05	<0.001	1.04	1.02–1.05	<0.001
Sex	0.99	0.64–1.56	0.981	0.82	0.61–1.11	0.202	0.82	0.58–1.15	0.244
APACHE II score	1.17	1.11–1.25	<0.001	1.11	1.08–1.15	<0.001	1.08	1.04–1.12	<0.001
COPD	1.92	0.66–5.77	0.233	1.50	0.77–2.90	0.232	1.31	0.67–2.58	0.432
Diabetes	2.28	1.26–4.14	0.007	1.58	1.12–2.25	0.010	1.46	1.02–2.09	0.040
Hypertension	0.69	0.40–1.16	0.167	0.86	0.61–1.21	0.389	0.93	0.65–1.34	0.696
Chronic cardiac disease	1.12	0.55–2.24	0.755	1.11	0.73–1.70	0.617	1.12	0.68–1.84	0.647
Chronic kidney disease	1.24	0.22–6.69	0.803	1.3	0.47–3.58	0.607	0.85	0.20–3.38	0.832
Chronic liver disease	0.49	0.13–1.59	0.252	0.56	0.23–1.36	0.203	0.62	0.23–1.65	0.338
Stroke	1.56	0.63–3.90	0.334	0.99	0.58–1.70	0.972	0.78	0.40–1.52	0.461
Malignancy	0.92	0.28–2.93	0.890	1.14	0.54–2.41	0.738	1.59	0.71–3.57	0.259
Immunosuppression	0.69	0.17–2.70	0.596	0.52	0.21–1.25	0.142	0.56	0.23–1.36	0.198
Fever at admission	1.67	0.95–2.99	0.078	1.26	0.87–1.84	0.228	1.31	0.87–1.96	0.195
Systolic pressure at admission	1.00	0.99–1.01	0.881	1.00	0.99–1.01	0.978	1.00	0.99–1.00	0.496
Leukocytes	1.09	1.04–1.15	0.001	1.08	1.04–1.11	<0.001	1.07	1.03–1.10	<0.001
Hemoglobin	1.00	0.99–1.02	0.596	1.01	1.00–1.01	0.272	1.00	0.99–1.02	0.335
Platelets	1.00	0.99–1.00	0.117	1.00	1.00–1.00	0.034	1.00	1.00–1.00	0.226
Lymphocytes	0.91	0.66–1.24	0.576	0.94	0.74–1.19	0.616	1.01	0.79–1.29	0.931
D-dimer	1.02	1.00–1.04	0.034	1.02	1.01–1.02	<0.001	1.02	1.01–1.03	<0.001
TBil	1.03	1.00–1.06	0.034	1.02	1.00–1.03	0.025	1.02	1.01–1.04	0.004
sCr	1.00	1.00–1.00	0.679	1.00	1.00–1.00	0.225	1.00	1.00–1.00	0.615
Procalcitonin	1.04	1.00–1.11	0.161	1.01	1.00–1.03	0.078	1.01	1.00–1.02	0.210
Corticosteroids	2.17	1.36–3.53	0.001	1.45	1.06–1.99	0.021	6.69	4.53–9.87	<0.001
Antiviral	0.30	0.17–0.50	<0.001	0.43	0.32–0.60	<0.001	0.42	0.30–0.60	<0.001
Human immunoglobulin	1.79	1.05–3.08	0.035	1.55	1.09–2.22	0.016	0.91	0.60–1.37	0.643

[A]Extended Cox model treating corticosteroid exposure as a time-varying exposure variable. COPD, chronic obstructive pulmonary disease; TBil, total bilirubin; sCr, serum creatinine; aHR, adjusted HR; aOR, adjusted OR.

be related to differences in the targeted population, mainly differences in severity and stage of the disease, as well as different practical modalities for corticosteroid treatment, i.e., different dose, timing, and duration. In the subset of patients with shock, the direction of the point estimate (OR = 0.41) suggested potential benefits in this subset of patients with shock. However, the sample size was too limited, resulting in some imprecision in the result that precluded any definite conclusions. We also found that the use of corticosteroids in SARS–CoV-2–related ARDS was associated with higher prevalence of myocardial and hepatic injury, higher need for respiratory support, and subsequently increased risk of death.

Our findings of delayed SARS–CoV-2 RNA clearance in corticosteroid-treated patients are in line with previous reports in patients with SARS-CoV (22) and MERS-CoV (11) infections. The altered viral clearance may be related to corticosteroid effects on T cell responses and on interferon pathways (23). However, the persistence of the virus does not necessarily correlate with organ damage, as presence of SARS–CoV-2 RNA does not directly indicate shedding of live virus. A large retrospective cohort study demonstrated that viral RNA positivity persisted up to death, suggesting a possible correlation between viral persistence and poor prognosis (4).

To our knowledge, this is first large, multicenter observational study that addressed the effects of corticosteroids in severe COVID-19 patients with ARDS. The main strength of this study included a well-defined population, large size, and focus on corticosteroid therapy for ARDS and not for other reasons. Therefore, with a homogeneous group of patients with severe disease, and after careful minimization of confounding biases through a PS matching analysis and competing risks analysis, we offer strong evidence to support the association between corticosteroid therapy and increased mortality as well as delayed SARS–CoV-2 RNA clearance. However, there are still some limitations. The main limitations include the retrospective design and some heterogeneity in the population partly related to critically ill patients treated outside the ICU due to shortages in ICU beds. Some laboratory parameters (such as LDH, ferritin, and CRP) were missing for some patients on admission, which may have introduced some biases, although we did use multiple analytical strategies to increase the robustness of our estimates. In addition, the lack of a statistically significant increase in secondary infections related to corticosteroids may have resulted from insufficient power and should be taken with caution. We did not record practical modalities for lung-protective ventilation. Finally, there was no long-term follow-up.

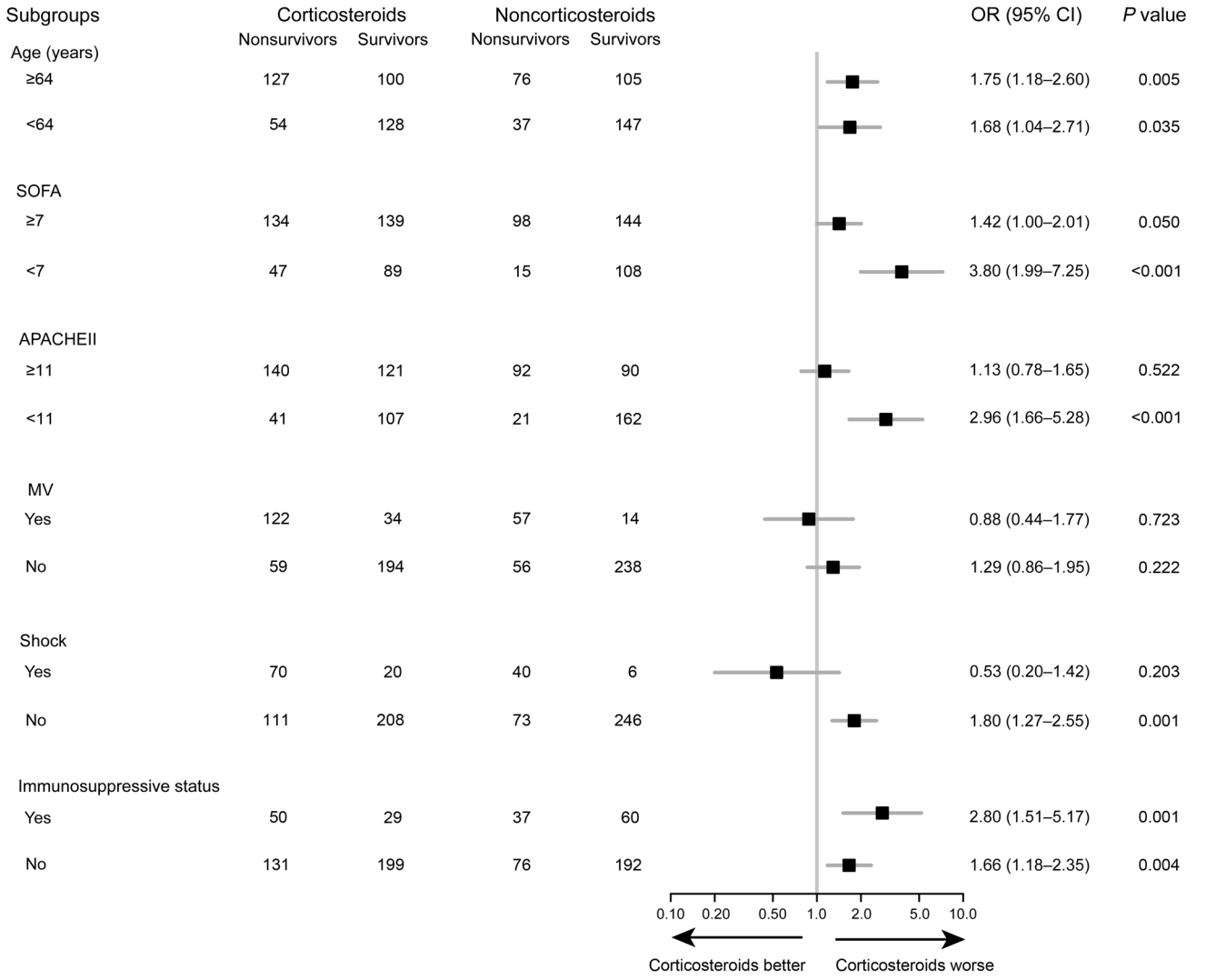

Figure 3. Subgroup analysis of 28-day mortality according to corticosteroid treatment in the whole cohort. APACHE II, acute physiology and chronic health evaluation II score; MV, mechanical ventilation; SOFA, sequential organ failure assessment.

Methods

Study design

This multicenter retrospective observational study was conducted in 5 tertiary hospitals (median hospital size, 578 beds [IQR 469–687]) from December 29, 2019 to March 16, 2020. The first part of the present study was to determine eligible patients who received corticosteroids and those who did not. To determine if the effect of corticosteroid therapy on 28-day mortality was different in subgroups, we examined the logistic regression analysis in the following subgroups: age ≥ 64 years vs. age < 64 years; APACHE II ≥ 11 vs. APACHE II < 11; with shock vs. without shock; sequential organ failure assessment (SOFA) ≥ 7 vs. SOFA < 7; with immunosuppressive status vs. without immunosuppressive status.

The second part of the study was to match patients who were exposed to corticosteroids at a 1:1 ratio with patients who were not exposed to corticosteroids. Matching was based on a multivariable logistic regression–generated PS for each patient without replacement.

Study population

We retrospectively collected medical records of adult patients with confirmed severe COVID-19–related ARDS who were admitted to 1 of the 5 participating tertiary hospitals, and who received corticosteroids for ARDS. We excluded patients who were already on long-term corticosteroid therapy and those who received corticosteroid therapy for other reasons, e.g., asthma, chronic obstructive pulmonary disease, etc.

Intervention

Patients with severe COVID-19–related ARDS were treated according to the Chinese national guidelines for the diagnosis and treatment of COVID-19. It was suggested that patients with severe COVID-19–related ARDS should receive comprehensive treatments, including suitable respiratory support (lung-protective ventilation if necessary), antiviral therapy (lopinavir/ritonavir 100 mg, bid; Arbidol, 200 mg, tid, etc.), organ support, etc.

The intervention of interest for this cohort study was administration of corticosteroids for SARS-CoV-2–related ARDS, regardless

Table 4. Standard mean difference after propensity score matching

Variables	Matched sample		
	No Glucocorticoid (*n* = 182)	Glucocorticoid (*n* = 182)	SMD
Age (yr), mean (±SD)	62.85 ± 12.75	63.42 ± 14.35	0.042
COPD, *n* (%)	4 (2.2)	6 (3.3)	0.067
Diabetes, *n* (%)	28 (15.4)	28 (15.4)	<0.001
Hypertension, *n* (%)	57 (31.3)	54 (29.7)	0.036
CCD, *n* (%)	20 (11.0)	20 (11.0)	<0.001
CKD, *n* (%)	4 (2.2)	3 (1.6)	0.040
CLD, *n* (%)	6 (3.3)	4 (2.2)	0.067
Stroke, *n* (%)	7 (3.8)	8 (4.4)	0.028
Malignancy, *n* (%)	5 (2.7)	8 (4.4)	0.089
Immunosuppression, *n* (%)	6 (3.3)	6 (3.3)	<0.001
Fever on admission, *n* (%)	137 (75.3)	130 (71.4)	0.087
Respiratory support on admission, *n* (%)			0.026
Nasal cannula, *n* (%)	166 (91.2)	167 (91.8)	
High-flow nasal cannula, *n* (%)	9 (4.9)	8 (4.4)	
Noninvasive mechanical ventilation, *n* (%)	5 (2.7)	5 (2.7)	
Invasive mechanical ventilation, *n* (%)	2 (1.1)	2 (1.1)	
Male sex, *n* (%)	106 (58.2)	98 (53.8)	0.089
Systolic pressure on admission, *n* (%)	129.49 ± 20.15	130.18 ± 21.66	0.033
Antiviral therapy, *n* (%)	143 (78.6)	150 (82.4)	0.097
Immunoglobulin therapy, *n* (%)	91 (50.0)	89 (48.9)	0.022
APACHE II score on admission, mean (±SD)	11.54 ± 4.61	11.45 ± 3.76	0.022
Leukocytes ($\times10^9$/L), mean (±SD)	7.74 ± 5.01	7.91 ± 3.78	0.037
Hemoglobin (g/L), mean (±SD)	123.71 ± 15.53	122.87 ± 16.80	0.052
Platelets ($\times10^9$/L), mean (±SD)	171.87 ± 74.05	177.81 ± 59.50	0.088
Lymphocytes ($\times10^9$/L), mean (±SD)	0.87 ± 0.62	0.89 ± 0.69	0.037
D-dimer (μg/mL), mean (±SD)	5.01 ± 13.20	4.56 ± 12.86	0.034
TBil (μmol/L), mean (±SD)	13.95 ± 7.42	13.64 ± 5.57	0.046
Scr (μmol/L), mean (±SD)	86.24 ± 81.94	92.32 ± 85.24	0.073
Procalcitonin (ng/mL), mean (±SD)	0.95 ± 3.90	0.93 ± 2.32	0.003

SMD, standard mean difference; COPD, chronic obstructive pulmonary disease; CCD, chronic cardiac disease; CKD, chronic kidney disease; CLD, chronic liver disease; TBil, total bilirubin; Scr, serum creatinine.

of the type of molecule, the dose, and the duration of treatment. The dose of corticosteroids is expressed as the hydrocortisone equivalent (methylprednisolone 1:5, dexamethasone 1:25, prednisolone 1:4). The control intervention was usual care.

Definitions

COVID-19 diagnosis was made according to WHO interim guidance (22). Nasal and pharyngeal swab specimens from patients with history of epidemiology and characteristics of viral pneumonia in chest CT or x-ray were obtained. The time interval between 2 specimens was at least 24 hours. Detection of SARS–CoV-2 nucleic acid was performed as previously described (https://www.who.int/publications/i/item/10665-331501). Patients with at least 2 consecutive positive results from high-throughput sequencing or real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swab specimens were confirmed as having COVID-19.

Severe patients were defined according to the *Diagnosis and treatment of COVID-19 guidelines* (sixth version) published by the National Health Commission of China (24). Patients who met one of the conditions listed below were diagnosed as having severe illness: (i) respiratory distress, respiratory rate ≥ 30 per minute; (ii) oxygen saturation at room air at rest ≤ 93%; or (iii) oxygen index less than 300 mmHg. We used the standard Berlin definition for ARDS (25–26), with noninvasive SpO_2/FiO_2 as a surrogate of $PaO2/FiO_2$, which was allowed for patients without PaO_2 (27–29). An immunosuppressive status was defined as patients who had an underlying disease, such as human malignancy, liver cirrhosis, or chronic renal failure, diabetes, or receiving immunosuppressive therapy. Diagnosis of acute kidney injury (AKI) was according to the KDIGO clinical practice guidelines (30).

Data collection

We extracted the following from the medical records: (i) demographic data including age, sex, comorbidities, exposure history of coronavirus; (ii) clinical data: the course of SARS–CoV-2 infection, blood-chemical test, blood-gas analysis; (iii) severity of illness based on APACHE II score (31) and SOFA score (32), presence of shock; (iv) corticosteroid use: type of drug, initial and maximum daily dosage (converted to equivalent hydrocortisone dose), duration of treatment, time from initiation of mechanical ventilation; and (v) respiratory support, including oxygen therapy, noninvasive mechanical ventilation, invasive mechanical ventilation, prone-position ventilation, and extracorporeal membrane oxygenation (ECMO).

Endpoints

The primary endpoint was 28-day all-cause mortality. The key secondary endpoint was length from symptom onset to SARS–CoV-2 RNA clearance in respiratory secretions. Other secondary outcomes included in-hospital mortality; length of ICU and hospital stay; ICU admission; development of ARDS, disseminated intravascular coagulation (DIC), myocardial injury, acute hepatic injury (AHI), shock, AKI, respiratory support, prone-position ventilation, continuous renal replacement therapy (CRRT), ECMO, and presence of secondary infection.

Statistical analysis

There was no formal computation of sample size. We compared baseline characteristics, interventions, and outcomes in patients who received corticosteroid therapy with those in patients who did not. Continuous variables are expressed as the mean (± standard deviation), or as median (IQR 25%–75%), and compared using 2-tailed Student's *t* test or Mann-Whitney *U* test. Discrete variables are expressed

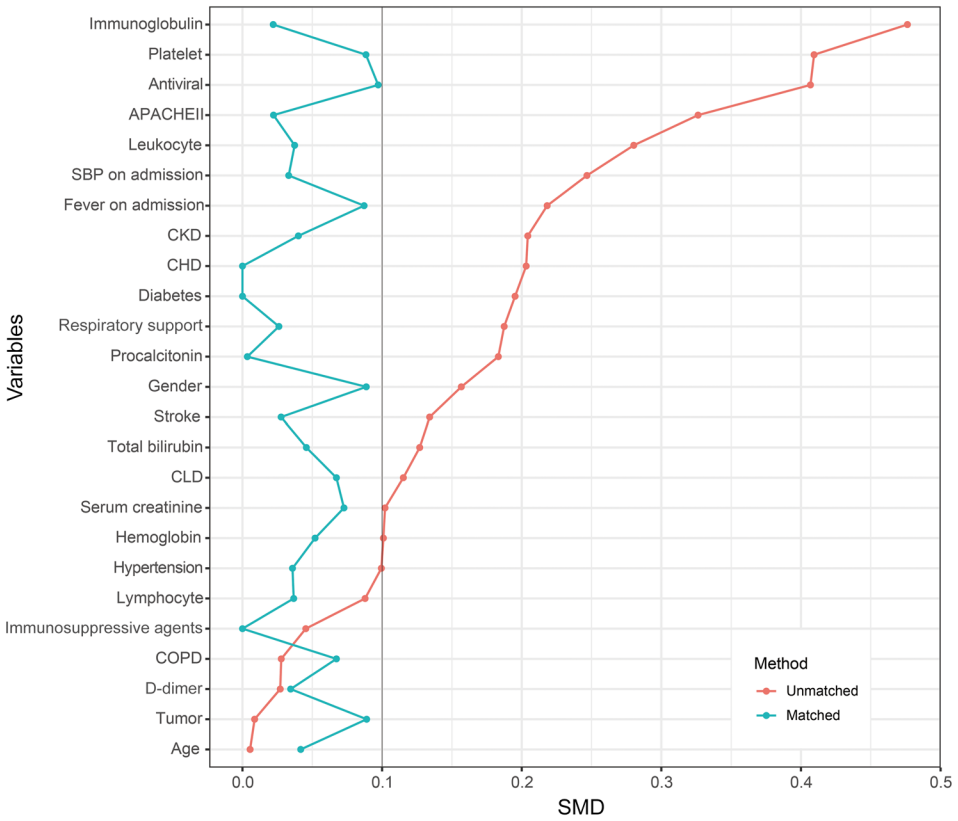

Figure 4. Summaries of the balance of variables before and after propensity score matching. SBP, systolic blood pressure; CKD, chronic kidney disease; CHD, chronic heart disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; SMD, standard mean difference.

as number (percentage), and compared using χ^2 test or Fisher's exact test, as appropriate.

Association of corticosteroid therapy and 28-day mortality

Logistic regression analysis. The effects of corticosteroids on 28-day all-cause mortality were explored by a multivariable logistic regression model. The model was adjusted on a priori–decided baseline variables of clinical interest and on those with a *P* value of less than 0.05 in the univariate analysis. The included variables were age, sex, day 1 APACHE II score, COPD, chronic cardiac disease, chronic kidney disease, chronic liver disease, stroke, malignancy, diabetes with chronic complications, fever and systolic blood pressure at admission, leukocytes, platelets, lymphocytes, D-dimer, total bilirubin, creatinine, procalcitonin, therapy including immunoglobulin, and antiviral drugs. We chose respiratory support rather than PaO_2/FiO_2 to reflect respiratory status, as this variable was well documented for all patients. We excluded the variables SOFA score, diastolic blood pressure at admission, neutrophil count, prothrombin time, levels of C-reactive protein and LDH, and ferritin, owing to colinearity or to an unacceptable rate of missing data.

The effects of corticosteroids therapy on 28-day all-cause mortality were also explored in the following subgroups: age ≥ 64 years vs. age < 64 years; APACHE II ≥ 11 vs. APACHE II < 11; with shock vs. without shock; SOFA ≥ 7 vs. SOFA < 7; and with vs. without immunosuppressive status. The cutoff value for continuous variables in each subgroup was determined according to the median value of our population.

Cox's proportional hazards regression. To estimate the association between corticosteroid use and mortality as a time to event, we used the multivariable Cox regression model. An initial multivariable Cox regression model incorporated corticosteroid therapy as a categorical variable with adjustment for the same above-mentioned variables used in the logistic regression model. In addition, to account for the time-varying exposure of corticosteroids, we fitted an extended Cox's regression model by considering the corticosteroids as a time-varying exposure variable with adjustment for the same above-mentioned variables.

Association of corticosteroid therapy and SARS-CoV-2 RNA clearance

Kaplan-Meier plot and log-rank test. We used the Kaplan-Meier plot and log-rank test to analyze the time to SARS–CoV-2 RNA clearance. For this purpose, we only selected patients if they survived during hospitalization and had complete timelines of SARS–CoV-2 RNA clearance. We computed cumulative rates of SARS–CoV-2 RNA clearance over time for patients who received or did not receive corticosteroid therapy.

Competing risks analysis. Because a proportion of patients did not have SARS–CoV-2 RNA clearance until death, the Cox hazards model is not satisfactory for describing SARS–CoV-2 RNA clearance over time. We therefore performed a competing risk analysis using the Fine and Gray model, which considered events of interest (SARS–CoV-2 RNA clearance) and competing events (death) in the same model. In addition, we explored whether early initiation (≤3 days of hospitalization) or late initiation (>3 days of hospitalization) of corticosteroid therapy would affect SARS–CoV-2 RNA clearance. The association between each variable and the outcome was estimated by the sHR with 95% CI.

In both the Kaplan-Meier survival plot and competing risks analysis, we only included patients who initiated corticosteroid therapy before SARS–CoV-2 RNA clearance to ensure a causal relationship.

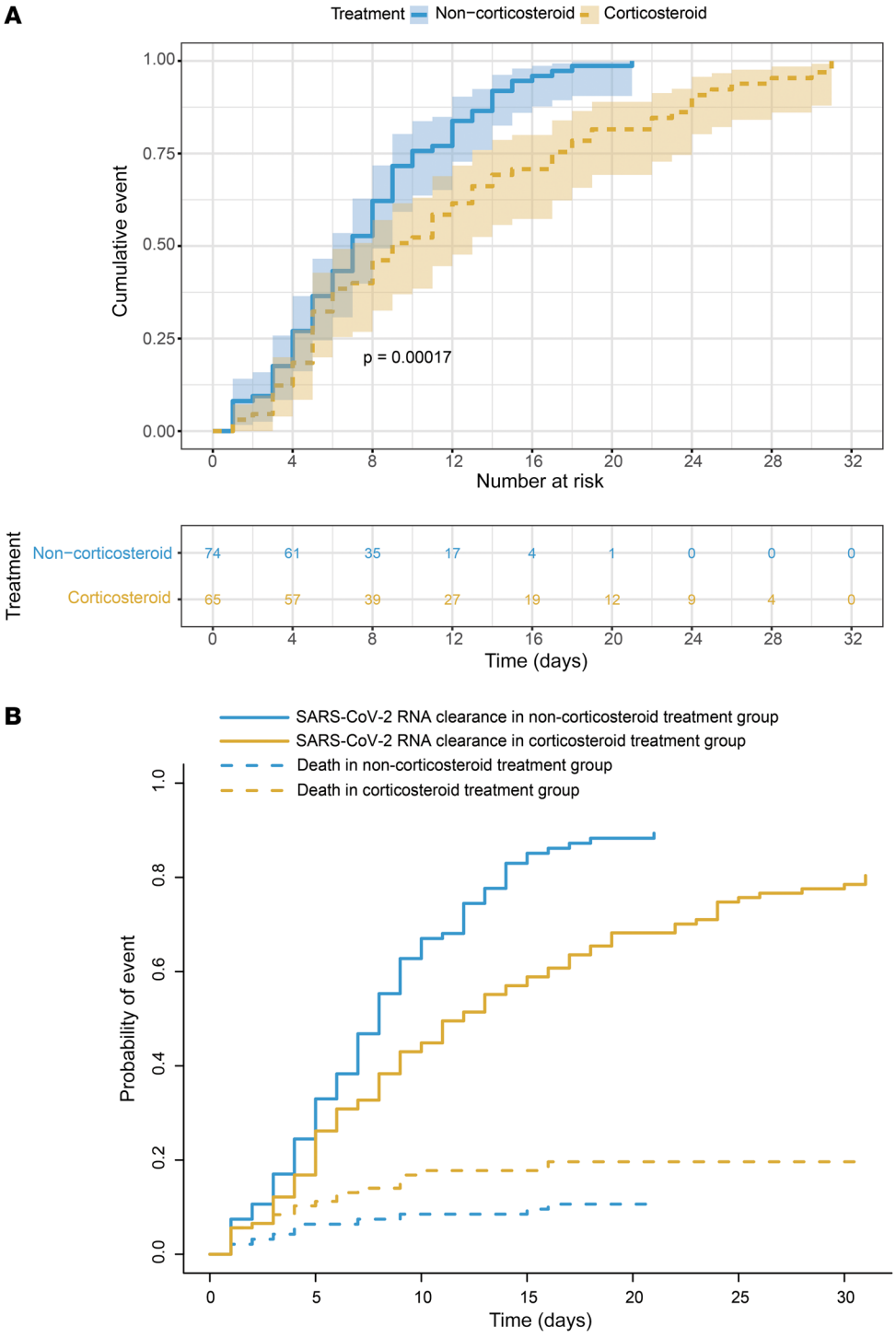

Figure 5. Cumulative incidence of SARS-CoV-2 RNA clearance according to corticosteroid therapy. (**A**) Cumulative incidence of SARS-CoV-2 RNA clearance according to corticosteroid therapy by Kaplan-Meier plot. (**B**) Cumulative incidence of SARS-CoV-2 RNA clearance and 28-day mortality by competing risks analysis.

Full-matching PS analysis. We performed a one-to-one PS matching analysis to account for potential confounding factors. This would allow us to compare outcomes between 2 cohorts of patients who had similar baseline characteristics except for treatment variable (receiving or not receiving corticosteroid therapy). PS was calculated for each patient based on a logistic-regression model that included the same variables used in the above-mentioned logistic regression model and Cox regression model. Matching was based on the logit of the PS using nearest-neighbor matching (greedy-type matching) with a caliper width of 0.2. Standardized mean differences for all covariates before and after matching were estimated and a difference of 10% or greater was considered to be indicative of imbalance. After matching, Kaplan-Meier curves were used to track the 28-day mortality for patients receiving or not receiving corticosteroid therapy. In addition, an extended Cox regression model that treated corticosteroids as a time-varying exposure variable was used to assess the effect of corticosteroid therapy on 28-day mortality.

Subgroup analysis after PS matching. To examine whether the effects of corticosteroid therapy on 28-day all-cause mortality were modified by varied dose, duration, and timing of initiation, we

Table 5. Twenty-eight–day mortality of severe COVID-19 patients with ARDS using various adjustment methodologies (after propensity score matching)

		Logistic regression model			Extended Cox regression model[A]		
Variables	*n*	OR	95% CI	*P* value	HR	95% CI	*P* value
All patients treated with corticosteroids vs. not treated with corticosteroids	182 vs. 182	1.64	1.05–2.57	0.032	1.46	1.01–2.13	0.045
Patients treated with corticosteroids >200 mg vs. not treated with corticosteroids	97 vs. 182	2.13	1.26–3.60	0.005	1.76	1.15–2.67	0.008
Patients treated with corticosteroids ≤200 mg vs. not treated with corticosteroids	85 vs. 182	1.16	0.65–2.06	0.611	1.13	0.69–1.84	0.623
Patients treated with corticosteroids ≤6 days vs. not treated with corticosteroids	102 vs. 182	1.77	1.05–2.98	0.031	1.64	1.07–2.51	0.022
Patients treated with corticosteroids >6 days vs. not treated with corticosteroids who survived >6 days	80 vs. 163	2.54	1.36–4.76	0.003	2.14	1.26–3.64	0.005
Corticosteroid initiation >3 days vs. not treated with corticosteroids	38 vs. 182	1.67	0.78–3.47	0.174	1.40	0.77–2.54	0.272
Corticosteroid initiation ≤3 days vs. not treated with corticosteroids	144 vs. 182	1.63	1.01–2.63	0.045	1.48	1.00–2.19	0.050

[A]Extended Cox model treating corticosteroid exposure as a time-varying exposure variable. OR, odds ratio; HR, hazard ratio; CI, confidence interval.

Table 6. Clinical course and outcomes among severe COVID-19 patients with ARDS in the corticosteroid-therapy and no-corticosteroid-therapy groups

Medication Variable	Glucocorticoid (*n* = 409)	No Glucocorticoid (*n* = 365)	*P* value
In-hospital mortality, *n* (%)	185 (45.2)	115 (31.5)	<0.001
28-day mortality, *n* (%)	181 (44.3)	113 (31.0)	<0.001
Length of hospitalization (days), median (IQR)	15 (9–21)	13 (8–18)	<0.001
Length of ICU stay (days), median (IQR)	5 (1–11)	2 (0–7)	<0.001
Duration between COVID-19 onset and hospital admission (days), median (IQR)	9.0 (6.0–12.0)	9.0 (6.0–14.0)	0.054
Duration between COVID-19 onset and ICU admission (days), median (IQR)	11.0 (7.0–15.0)	12.0 (8.0–16.0)	0.569
ICU admission, *n* (%)	195 (47.7)	82 (22.5)	<0.001
Duration between COVID-19 onset and ARDS onset (days), median (IQR)	11.0 (7.0–15.0)	10.0 (3.0–15.0)	0.160
ARDS, *n* (%)	409 (100)	365 (100)	1.000
Duration between COVID-19 onset and DIC onset (days), median (IQR)	18.0 (14.0–23.0)	19.0 (14.0–20.5)	0.781
DIC, *n* (%)	13 (3.2)	7 (1.9)	0.381
Duration between COVID-19 onset and myocardial injury onset (days), median (IQR)	16.0 (11.0–21.0)	17.0 (10.3–23.0)	0.970
Myocardial injury, *n* (%)	64 (15.6)	38 (10.4)	0.041
Duration between COVID-19 onset and AHI onset (days), median (IQR)	15.0 (10.0–21.0)	15.5 (11.0–21.0)	0.975
AHI, *n* (%)	75 (18.3)	36 (9.9)	0.001
Duration between COVID-19 onset and shock onset (days), median (IQR)	17.0 (13.0–22.8)	18.0 (13.0–22.8)	0.934
Shock, *n* (%)	90 (22.0)	46 (12.6)	<0.001
Duration between COVID-19 onset and AKI (days), median (IQR)	19.0 (13.0–23.0)	15.5 (11.0–20.3)	0.148
AKI, *n* (%)	41 (10.0)	30 (8.2)	0.457
Duration between COVID-19 onset and high-flow oxygen therapy (days), median (IQR)	12.0 (8.0–17.0)	12.0 (9.0–16.5)	>0.99
High-flow oxygen therapy, *n* (%)	137 (33.5)	59 (16.2)	<0.001
Duration between COVID-19 onset and noninvasive mechanical ventilation (days), median (IQR)	12.0 (9.0–16.8)	13.0 (8.5–19.5)	0.632
Noninvasive mechanical ventilation, *n* (%)	106 (25.9)	51 (14.0)	<0.001
Duration between COVID-19 onset and invasive mechanical ventilation (days), median (IQR)	15.0 (11.0–20.0)	16.5 (11.0–23.5)	0.410
Invasive mechanical ventilation, *n* (%)	81 (19.8)	38 (10.4)	<0.001
Duration between COVID-19 onset and prone-position ventilation (days), median (IQR)	16.0 (11.0–20.0)	24.0 (21.0–24.0)	0.042
Prone-position ventilation, *n* (%)	19 (4.6)	5 (1.4)	0.016
Duration between COVID-19 onset and CRRT (days), median (IQR)	20.5 (18.8–23.0)	22.0 (19.0–25.0)	0.682
CRRT, *n* (%)	12 (2.9)	13 (3.6)	0.806
Duration between COVID-19 onset and ECMO (days), median (IQR)	22.0 (20.5–24.5)	23.5 (19.8–25.0)	>0.99
ECMO, *n* (%)	3 (0.7)	4 (1.1)	0.713

ICU, intensive care unit; ARDS, acute respiratory distress syndrome; DIC, diffuse intravascular coagulation; AHI, acute hepatic injury; AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

explored treatment effects in the following subgroups: high (>200 mg hydrocortisone equivalent per day) and low dose (≤200 mg of hydrocortisone equivalent); long (≥6 days) and short (<6 days) course; early (≤3 days of hospitalization) and late (>3 days of hospitalization) initiation versus no corticosteroid treatment. All subgroup analyses were performed in the matched samples using 2 approaches: first, a logistic regression model that treated corticosteroid therapy as a category variable and was adjusted by PS; second, an extended Cox regression

model that treated corticosteroids as a time-varying exposure variable and was adjusted by PS.

Data were analyzed using SPSS software (version 22.0) and R software (version 3.6.2). A *P* value less than 0.05 was considered significant.

Study approval

This study was approved by the Medicine Institutional Review Board of Wuhan Jinyin-tan Hospital (KY-2020-03.01).

Author contributions

JL wrote this manuscript and organized tables and figures. SZ was responsible for statistical analysis and figures construction. XD, ZL, QX, and HF were responsible for clinical data collection. JC, SH, JG, LZ, YC, WZ, HD, YL, TW, LC, and ZW were responsible for data extraction and verification. DC and JQ designed and guided this study. DA revised the raw manuscript. JL, SZ, XD, ZL, QX, and HF contributed equally and shared first authorship.

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Address correspondence to: Dechang Chen or Jieming Qu, no. 197, Ruijin 2nd Road, Shanghai 200025, China. Email: chendechangsh@hotmail.com (DC) or jmqu0906@163.com (JQ). Or to: Djillali Annane, Department of Intensive Care, Hôpital Raymond Poincaré (APHP), Laboratory of Infection & Inflammation — U1173, School of Medicine Simone Veil, University Versailles Saint Quentin — University Paris Saclay, INSERM, Garches 92380, France. Email: djillali.annane@aphp.fr.

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