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Corticosteroid therapy for corona virus disease 2019-related acute respiratory distress syndrome: a cohort study with propensity score analysis

Chaomin Wu
Qingpu Branch of Zhongshan Hospital Fudan University
Dongni Hou
Zhongshan Hospital Fudan University https://orcid.org/0000-0001-8332-7321
Chunling Du
Qingpu Branch of Zhongshan Hospital Fudan University
Yanping Cai
Wuhan Jin Yin-tan Hospital
Junhua Zheng
Shanghai General Hospital
Jie Xu
Fengxian Guhua Hospital
Xiaoyan Chen
Zhongshan Hospital Fudan University
Cuicui Chen
Zhongshan Hospital Fudan University
Xianglin Hu
Zhongshan Hospital Fudan University
Yuye Zhang
Zhongshan Hospital Fudan University
Juan Song
Zhongshan Hospital Fudan University
Lu Wang
Zhongshan Hospital Fudan University
Yen-cheng Chao
Zhongshan Hospital Fudan University
Yun Feng
Shanghai First People's Hospital
Weining Xiong
Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine
Dechang Chen

Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Ming Zhong
Zhongshan Hospital Fudan University
Jie Hu
Zhongshan Hospital Fudan University
Jinjun Jiang
Zhongshan Hospital Fudan University
Chunxue Bai
Zhongshan Hospital Fudan University
Xin Zhou
Shanghai First People's Hospital
Jinfu Xu
Tongji University Affiliated Shanghai Pulmonary Hospital
Fengyun Gong (gfy.yuyingzi@163.com)
Wuhan Jinyintan Hospital
Yuanlin Song (ylsong70_02@163.com)
Zhongshan Hospital, Fudan University

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Abstract

Background

The impact of corticosteroid therapy on outcomes of patients with Coronavirus disease-2019 (COVID-19) is highly controversial. We aimed to compare the risk of death between COVID-19-related ARDS patients with corticosteroid treatment and those without.

Methods

In this single-centre retrospective observational study, patients with ARDS caused by COVID-19 between 24 December 2019 and 24 February 2020 were enrolled. The primary outcome was 60-day in-hospital death. The exposure was prescribed systemic corticosteroids or not. Time-dependent Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for 60-day in-hospital mortality.

Results

A total of 382 patients including 226 (59.2%) patients who received systemic corticosteroids and 156 (40.8%) patients with standard treatment were analyzed. The maximum dose of corticosteroids was 80.0 (IQR 40.0–80.0) mg equivalent methylprednisolone per day, and duration of corticosteroid treatment was 7.0 (4.0–12.0) days in total. In Cox regression analysis using corticosteroid treatment as a time-varying variable, corticosteroid treatment was associated with a significant reduction in risk of in-hospital death within 60 days (HR, 0.48; 95% CI, 0.25, 0.93; $p = 0.0285$). The association remained significantly after adjusting for age, sex, Sequential Organ Failure Assessment score at hospital admission, propensity score of corticosteroid treatment, and comorbidities (HR: 0.51; CI: 0.27, 0.99; $p = 0.0471$). Corticosteroids were not associated with delayed viral RNA clearance in our cohort.

Conclusion

In this clinical practice setting, low-to-moderate dose corticosteroid treatment was associated with reduced risk of death in COVID-19 patients who developed ARDS.

Background

The World Health Organization (WHO) declared the outbreak of(SARS-CoV-2) constitutes a pandemic.[1] Since the first confirmed case on 22 January 2020, the virus has been emerged in 216 countries. More than 14,765,,000 laboratory-confirmed cases were reported, with an average mortality approaching 4.1% as of July 22 2020.[2] The spread of SARS-CoV-2 has led to serious socioeconomic consequences worldwide.

Currently, there is no specific treatment or vaccine for coronavirus disease-2019 (COVID-19), a clinical syndrome caused by SARS-CoV-2 infection. Corticosteroids has been widely used by clinicians among patients with COVID-19, especially those with critical illness,[3–5] albeit comprehensive controversy on its efficacy[6, 7]. Lymphopenia, neutrophilia, and higher levels of multiple cytokines and chemokines were found in COVID-19 patients and were associated with disease severity[8, 9], suggesting a role of dysregulated systemic inflammation leading to worse prognosis. Hyperinflammation lead to acute respiratory distress syndrome (ARDS) in 3–29% of the patients, [3, 4, 9] which was the main cause of death. Pathologically, interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, were reported in deceased patients[10, 11]. Suppression of inflammation by adjunctive corticosteroids may be theoretically beneficial.[12] However, evidence on corticosteroid treatment among COVID-19 patients is scarce, and results from previous studies investigating corticosteroids in other coronavirus infections were inconsistent and inconclusive. Previous observational studies reported that corticosteroid treatment was related to no reduction or even increase of mortality in patients with SARS-CoV-2, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome patients (MERS) [13, 14]. However, lower mortality was reported among the critically ill subgroup of SARS patients treated with corticosteroids in a retrospective study[15]. These findings suggests a heterogeneity in efficacy of corticosteroids among different phenotypes. Recently, we reported that methylprednisolone might associated with lower risk of death in COVID-19 patients who developed ARDS[5]. However, due to the limited sample size at early stage of COVID-19 pandemic, the above study did not include the key determinants or potential confounding effects of corticosteroids use on clinical outcome. In this study, we examined the use of corticosteroid treatment in relation to hospital mortality among COVID-19 patients who have developed ARDS.

Materials And Methods

Study design and patients

This single-centre, retrospective, cohort study was conducted at the Jin Yin-tan Hospital, Wuhan, China. We identified all adult patients with confirmed COVID-19 according to WHO interim guidance [16] and patients were admitted between December 24, 2019 and February 24, 2020. Then we identified those who developed ARDS according to the WHO definition for analysis.[16] To avoid the influence of early mortality before cortical steroid presenting treatment efficacy, patients who died or discharged within 2 days on hospital admission were excluded. Other exclusion criteria were: (1) participating in any double-blind clinical trial, (2) under long-term corticosteroid therapy, or (3) no valid medical history provided. The Jin Yin-tan Hospital Ethics Committee approved the study (No.KY-2020-44.01) and granted a waiver of informed consent from study participants.

Data collection

Administration of corticosteroids was defined as systemic use (oral or intravenous) of corticosteroids, including methylprednisolone, dexamethasone, hydrocortisone, and prednisone. The primary outcome

was 60-day in-hospital mortality. Patients were followed to death or discharge from hospital up to 60 days since hospital admission (last clinical outcome was observed on March 21, 2020). Data on demographics, medical history, laboratory findings, chest radiology, medication use, and clinical outcomes were extracted retrospectively from electronic medical records using a standardized data collection form. All data were checked independently by two physicians (DH and XC). To monitor the clearance of viral RNA, SARS-CoV-2 RNA were tested using polymerase chain reaction from throat-swab specimens for every other day after clinical remission of symptoms, including fever, cough, and dyspnea. [5] Viral clearance analysis was performed excluding patients who never cleared SARS-CoV-2 RNA before discharge or death. The definitions of ARDS and other diseases were described in **eMethods** (Additional file 1).

Statistical analysis

Baseline characteristics were compared between patients with and without corticosteroid treatment. Data were reported as percentage for categorical variables and as mean ± standard deviation (SD) or median with interquartile range (IQR, 25–75%) for continuous variables. Categorical variables were compared by Fisher exact test or Pearson chi-square test, as appropriate, and continuous variables were compared by Mann- Whitney U test or Student t test.

To reduce the effect of steroids treatment bias and potential confounding factors, we performed propensity score analysis[17] to adjust the differences in baseline characteristics. For each patient, a propensity score indicating the likelihood of receiving systemic corticosteroid treatment was calculated by a logistic regression model that included 10 pre-selected baseline variables: age; sex; SOFA score at admission; temperature, respiratory rate, heart rate, SpO_2/FiO_2 ratio, blood lymphocyte count, blood neutrophil count, and level of CRP at hospital admission. The outcome variable was whether or not the patient received corticosteroid therapy in current hospital stay. Goodness of fit was evaluated by the c-statistic and the Hosmer-Lemeshow test.

The effect of corticosteroid treatment on risk of 60-day in-hospital all-cause death were analyzed using a series of Cox proportional-hazard regression models. First, we constructed a univariable Cox regression models on hospital death by 60 days since admission with corticosteroid treatment treated as a time-varying covariate. Then we constructed a multivariable Cox model of 60-day hospital death with corticosteroid treatment as time-varying covariate and incorporated the individual propensity score into the model as a covariable to calculate the propensity adjusted hazard ratio (HR). In the final model, the effects of corticosteroids on 60-day in-hospital death were adjusted for propensity score of corticosteroid treatment, as well as the following pre-selected covariates: age, sex, Sequential Organ Failure Assessment (SOFA) score at hospital admission,, and comorbidities: diabetes, hypertension, chronic pulmonary disease, chronic renal or liver disease, solid malignant tumor, hematologic malignancy, and immunosuppressive status. [6]

Furthermore, we performed the same models described above in the subgroups stratified by days from ARDS onset to the initiation of corticosteroid treatment (≤ 1 day vs. > 1 day) and days from symptom

onset to the initiation of corticosteroid treatment (≤ 14 days vs. > 14 days). Several sensitivity analyses were performed to assess the robustness of our findings. To test whether the findings were influenced by the time point of baseline the time-dependent Cox regression analysis were repeated using the values of previously mentioned variables on the date of ARDS onset. To ensure that treatment-related survival differences were not confounded by prescription of lopinavir-ritonavir, which has been associated with shorter median time to clinical improvement in patients with COVID-19[18], the effects of corticosteroids were evaluated among patients without lopinavir-ritonavir treatment. To test whether the findings might be influenced by ARDS definition, we conducted survival analysis using the same model among patients diagnosed with ARDS by Berlin definition.

Results were analyzed with SAS (version 9.4, SAS Institute, Cary, NC). Unadjusted and adjusted hazard ratios and their 95% confidence intervals (CIs) were reported. Two-sided P values less than 0.05 were considered statistically significant.

Results

A total of 1147 patients with COVID-19 were screened for the study. 40 patients were excluded for participating in any double-blind clinical trial (n = 15), death or discharge from the hospital on the first day of admission (n = 21), underwent long-term corticosteroid therapy (n = 3), or no valid medical history provided (n = 1). From 1107 patients remained, 382 patients were identified as ARDS **(eFigure 1**, Additional file 1**)**. Among these patients, 84 have been described previously by Wu et al[5]. In addition, 91 patients with ARDS participated in the open-label trial of lopinavir - ritonavir.[18]

Baseline characteristics of the ARDS patients at hospital admission by receiving systemic corticosteroid treatment are shown in Table 1. In the entire cohort, the mean age was 60.7 ± 14.1 years, and 234 (61.3%) patients were male. 147 (38.5%) were treated with NIMV, 94 (24.6%) with IMV, and 11 (2.9%) with ECMO.

Table 1
Characteristics of patients with acute respiratory distress syndrome associated with coronavirus disease 2019

Characteristics	All	Corticosteroids	No corticosteroids	*P* value
N	382 (100.0)	226 (59.2)	156 (40.8)	…
Age, year	60.7 ± 14.1	59.1 ± 14.0	63.0 ± 14.0	0.0077
Male sex	234 (61.3)	150 (66.4)	84 (53.8)	0.0135
Smoking history	35 (9.2)	24 (10.6)	11 (7.1)	0.2347
Days from onset at admission	11.0 (8.0–15.0)	10.0 (7.0–14.0)	12.0 (9.0–16.5)	0.0029
Medical history				
Chronic pulmonary disease	20 (5.2)	12 (5.3)	8 (5.1)	0.9376
Hypertension	136 (35.6)	79 (35.0)	57 (36.5)	0.7508
Diabetes	67 (17.5)	36 (15.9)	31 (19.9)	0.3193
Chronic liver disease	15 (3.9)	11 (4.9)	4 (2.6)	0.2546
Chronic renal disease	6 (1.6)	2 (0.9)	4 (2.6)	0.1945
Cardiovascular disease	28 (7.3)	12 (5.3)	16 (10.3)	0.0682
Malignant tumor	12 (3.1)	7 (3.1)	5 (3.2)	0.9527
Hematological malignant tumor	2 (0.6)	1 (0.5)	1 (0.7)	0.8339
Immunosuppressive conditions	14 (3.7)	9 (4.0)	5 (3.2)	0.6911
SOFA score at admission	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.1383
Corticosteroid therapy before admission	40 (10.5)	28 (12.4)	12 (7.7)	0.1405
Temperature on admission, ℃	36.8 ± 0.7	36.9 ± 0.8	36.7 ± 0.5	0.0069
Heart rate, min^{-1}	90.9 ± 15.3	92.9 ± 16.3	88.0 ± 13.1	0.0018
Respiratory rate, min^{-1}	24.0 ± 6.3	24.5 ± 7.1	23.3 ± 5.0	0.0609
Laboratory findings at admission				
Blood leukocyte count, × 10^9/L	8.1 (5.2–11.3)	8.4 (5.1–11.7)	7.5 (5.4–10.0)	0.2593
Lymphocyte count, × 10^9/L	0.7 (0.5–1.0)	0.6 (0.5–0.8)	0.8 (0.6–1.1)	< .0001

Characteristics	All	Corticosteroids	No corticosteroids	*P* value
Neutrophil count, × 10^9/L	6.9 (4.0–10.2)	7.4 (4.2–10.7)	5.7 (4.0–8.7)	0.0508
SpO_2/FiO_2	229.3 (175.5–352.4)	218.6 (170.0–366.7)	241.5 (184.0–332.8)	0.2133
CRP, mg/L	89.0 (38.0–159.9)	96.7 (45.9–160.0)	68.7 (28.6–138.5)	0.0026
D-dimer, mg/L	1.5 (0.7–8.0)	1.5 (0.6–9.5)	1.5 (0.7–7.1)	0.9913
Lactate dehydrogenase, U/L	409.0 (304.0–545.0)	429.0 (320.0–569.0)	386.5 (277.0–509.5)	0.0124
Bilateral involvement	358 (93.7)	214 (94.7)	144 (92.3)	0.3455
Antivirus drugs				
Lopinavir	91 (24.0)	72 (31.9)	19 (12.4)	< .0001
Ganciclovir	32 (8.4)	19 (8.4)	13 (8.5)	0.9754
Interferon	103 (27.2)	65 (28.8)	38 (24.8)	0.3994
Oseltamivir	64 (16.9)	52 (23.0)	12 (7.8)	0.0001
Respiratory support				
High-frequency oscillation ventilation	146 (38.8)	100 (45.2)	46 (29.7)	0.0023
NIMV	147 (38.5)	104 (46.0)	43 (27.6)	0.0003
IMV	94 (24.6)	59 (26.1)	35 (22.4)	0.4130
ECMO	11 (2.9)	8 (3.5)	3 (1.9)	0.3530
Hyperglycemia	32 (8.4)	20 (8.8)	12 (7.7)	0.6882
In-hospital 60-day mortality	203 (53.1)	135 (59.7)	68 (43.6)	0.0019
In-hospital days for all patients	12.0 (7.0–18.0)	14.0 (9.0–21.0)	10.0 (6.0–13.0)	< .0001
In-hospital days for survivors	13.0 (10.0–19.0)	16.0 (11.0–24.0)	11.0 (8.5–15.0)	< .0001
Median survival time, days	18.0 (15.0–20.0)	19.0 (15.0–21.0)	15.0(12.0–23.0)	0.0239
Duration of viral shedding from symptom onset, days	18.0 (14.0–23.0)	19.0 (14.0–23.0)	18.0 (14.0–24.0)	0.7217

Note: Data are n (%), mean (SD), or median (IQR). For continuous variables, t-test or Mann-Whitney U test was used to calculate the P value unless otherwise noted. For categorical variables, chi-square test was used to calculate the P value unless otherwise noted.

Abbreviations: ARDS, acute respiratory distress syndrome; SOFA, sequential Organ Failure Assessment; CRP, c-reactive protein; MV, mechanical ventilation; NIMV, non-invasive mechanical ventilation; IMV, invasive mechanical ventilation; ECMO, extracorporeal membrane oxygenation; SpO2, pulse oxygen saturation; FIO2, fraction of inspired oxygen. ARDS was defined according to World Health Organization interim guidance.

A total of 226 (59.2%) ARDS patients had a prescription of systemic corticosteroids. Corticosteroids were more likely prescribed to the younger (p = 0.0077) and males (p = 0.0135). Corticosteroids group had lower lymphocyte count and higher levels of CRP and lactate dehydrogenase at admission than non-corticosteroids group, indicating a propensity in prescribing corticosteroids to patients with more severe immune dysfunction and inflammatory response (Table 1). The 60-day hospital death in patients who ever used corticosteroids were higher than the patients who did not use corticosteroids (135 [59.7%] vs. 68 [43.6%], p = 0.0019). However, the median survival duration were significantly longer in corticosteroid group (19.0 [IQR 15.0–21.0] vs. 15.0 [IQR 12.0–23.0], p = 0.0239).

Among patients prescribed corticosteroids, methylprednisolone was the most frequently administered corticosteroids (213, 94.2%) (Table 2). Corticosteroid treatment lasted for 7.0 (IQR 4.0–12.0) days in total. The maximum dose in methylprednisolone equivalent was 80.0 (IQR 40.0–80.0) mg per day and duration of maximum dose was 3.0 (IQR 2.0–5.0) days. Corticosteroids were initiated 13.0 (IQR 10.0–16.0) days after symptom onset. 82.3% (186/226) of the patients received corticosteroids started the therapy within 2 days after ARDS diagnosis. Survivors had shorter duration from symptom onset to corticosteroids (11.0 [9.0–14.0] vs. 14.00 [IQR 11.0–18.0], p = 0.0031) and had earlier initiation of corticosteroids with regard to the date of ARDS onset (0.0 [IQR − 1.0–1.0] vs. 1.00 [IQR 0.0–2.0], p = 0.0102) when compared with non-survivors. Clinical characteristics of survivors and non-survivors received corticosteroid were summarized in **eTable 1** (Additional file 1).

Table 2
Administration of corticosteroids, stratified by outcome

	All (n = 226)	Non-survivors (n = 135)	Survivors (n = 91)	*P*-value
Corticosteroid prescribed				
Methylprednisolone	213 (94.2)	132 (62.0)	83(38.0)	0.0004
Prednisolone	41 (18.1)	11 (73.2)	30 (26.8)	0.0007
Dexamethasone	5 (2.2)	4 (80.0)	1 (20.0)	0.4470
Maximum dose (methylprednisolone equivalent, mg)	80.0 (40.0–80.0)	80.0 (40.0–80.0)	80.0 (40.0–80.0)	0.0821
Days of corticosteroid treatment	7.0 (4.0–12.0)	6.0 (3.0–11.0)	9.0 (5.0–12.0)	0.0069
Days of maximum dose	3.0 (2.0–5.0)	3.0 (1.0–5.0)	4.0 (2.0–5.0)	0.0287
Days from symptom onset to corticosteroid treatment	13.0 (10.0–16.0)	14.0 (11.0–18.0)	11.0 (9.0–14.0)	0.0031
Days from admission to corticosteroid treatment	1.0 (0.0–3.0)	1.0 (0.0–4.0)	1.0 (0.0–2.0)	0.1892
Days from ARDS to corticosteroid treatment	0.0 (0.0–2.0)	1.0 (0.0–2.0)	0.0 (-1.0–1.0)	0.0102
Days from ventilation to corticosteroid treatment	-1.0 (-3.0–0.0)	-1.0 (-3.0–0.0)	-2.0 (-4.0–1.0)	0.7576

Note: Data are n (%) or medium (IQR). For continuous variables, t-test or Mann-Whitney U test was used to calculate the P value unless otherwise noted. For categorical variables, chi-square test was used to calculate the P value unless otherwise noted.

In the logistic regression model generating propensity score, the pre-selected variables most closely correlated with prescription of systemic corticosteroids included age, blood lymphocyte count, heart rate and CRP. (**eTable 2**, Additional file 1) The multivariable regression model of propensity for corticosteroid treatment had area under the receiver operating characteristic curve (ROC) of 0.71, indicating good discrimination.

In survival analysis, univariable time-dependent Cox regression model showed the prescription of corticosteroids was associated with a lower risk of death (HR: 0.48; CI: 0.25, 0.93; p = 0.0285) (Table 3). When adjusted for propensity score, the estimated HR was 0.49 (CI: 0.25, 0.93; p = 0.0298). In full model adjusted for age, sex, SOFA score, propensity score, and comorbidities, the association remained

significantly (HR: 0.51; CI: 0.27, 0.99 ; p = 0.0471) (Fig. 1). The association was found among patients treated within 1 day after ARDS onset (HR: 0.50; CI: 0.26, 0.98; p = 0.0439). The patients received corticosteroids 2 days after ARDS onset all survived, thus the estimated HR of this subgroups were not calculated. In patients treated within 14 days after symptom onset, corticosteroids group showed a trend of lower risk of death (HR: 0.47; CI: 0.22, 0.98; p = 0.0446).

Table 3
Estimated effects of corticosteroid treatment on sixty-day mortality in patients with ARDS associated with COVID-19

	No.	Hazard Ratio	95% CI	*P*-Value
All ARDS patients				
Univariate model	382	0.48	0.25, 0.93	0.0285
Propensity score[a] adjusted model	361	0.49	0.25, 0.93	0.0298
Full multivariate model[b]	325	0.51	0.27, 0.99	0.0471
Subgroup analysis[b]				
Initiated ≤ 1 days after ARDS onset vs. no corticosteroids (reference)	290	0.50	0.26, 0.98	0.0439
Initiated ≤ 14 days after symptom onset vs. no corticosteroids (reference)	243	0.47	0.22, 0.98	0.0446
Initiated > 14 days after symptom onset vs. no corticosteroids (reference)	220	0.54	0.13, 2.26	0.4007

Note: All of the models assessed the effects of corticosteroids as a time-varying covariate. All patients in the subgroup with corticosteroid treatment initiated > 1 days after ARDS onset were survived. So the HR of this subgroup was not reported.

Abbreviations: ARDS, acute respiratory distress syndrome; FIO_2, fraction of inspired oxygen; SOFA, sequential Organ Failure Assessment; SpO_2, pulse oxygen saturation.

[a] Propensity score was calculated by a non-parsimonious logistic regression model that included: age; sex; SOFA score at admission; temperature, respiratory rate, SpO_2/FiO_2 ratio, blood lymphocyte count, blood neutrophil count, and level of c-reactive protein at admission. [b]Adjusted for age, sex, SOFA score at admission, propensity score of corticosteroid treatment, and comorbidities : diabetes, hypertension, chronic pulmonary disease, chronic renal or liver disease, solid malignant tumor, hematologic malignancy, and immunosuppressive status.

In sensitivity analysis, narrowing to patients meet the Berlin definition of ARDS did not alter the association between corticosteroids and lower risk of death. The HR of corticosteroids on mortality were negative albeit insignificant when excluding patients treated with lopinavir or vital signs, laboratory findings and SOFA score on the ARDS onset date were used in time-dependent Cox regression analysis adjusting for the same confounders. (**eTable 3**, Additional file 1)

Viral shedding was observed in 9.2% (188/382) of the whole population, including 69.3% (124/179) of survivors and 31.5% (64/203) of the non-survivors. We found no difference in duration of viral shedding from symptom onset between corticosteroids treated group and the corresponding group (19.0 [IQR 14.0–23.0] vs. 18.0 [IQR 14.0–24.0], p = 0.7217) (Table 1) and between survivors and non-survivors (18.0 [IQR 14.0–23.0] vs. 18.0 [IQR 14.0–23.25], p = 0.9704) (**eTable 1**, Additional file 1).

CRP level decreased among corticosteroids group on the first 4 days after ARDS onset (Fig. 2), while an increase was found in non-corticosteroids group. CRP levels were significantly lower in corticosteroids treated group after 2 days of ARDS onset, indicating a suppression of inflammatory response due to corticosteroid treatment. The IL-6 level was comparable between the two groups(**eFigure 2**, Additional file 1).

Discussion

In this observational study, prescription of low-to-moderate dose systemic corticosteroids was significantly associated with lower risk of 60-day in-hospital death among of COVID-19 patients who have developed ARDS. Early corticosteroid treatment before or within 1 day after ARDS is related with lower mortality. Reduction of CRP, as the marker for systemic inflammation responses, was found in patients with corticosteroid treatment. No associations between corticosteroid treatment with viral shedding were found in our study.

The interim guidance of WHO recommend against the routine use of systemic corticosteroids for treatment of viral pneumonia.[16] The recommendation was based on previous studies reported no benefit or possible harms of corticosteroids therapy among SARS and MERS patients[14, 19–21]. However, the efficacy of corticosteroids on the patients developed ARDS after coronavirus infection was not clear. Our previous study on COVID-19-related ARDS patients with a small sample size showed that methylprednisolone was associated with lower risk of death.[5] In this study of a larger population, we reported the detailed regimens of corticosteroids therapy and used rigorous statistical method to control for indication and survival bias. We found that corticosteroids therapy was associated with a lower risk for death. At the same time, CRP levels decreased in patients receiving corticosteroid treatment, which indicated suppressed inflammatory responses and was compatible with previous the randomized trials[22, 23]. Our results were in line with several previous randomized controlled studies that showed

administration of corticosteroids was associated with a survival benefit in patients with established ARDS.[12, 22, 24, 25] Notably, the difference in mortality between groups was similar to the results reported in a recent randomized controlled study on moderate-to-severe ARDS[25]. These findings suggest that some patients with ARDS due to COVID-19 might benefit from appropriate corticosteroids therapy.

Survivors-treated bias is common in observational studies that assess exposure after the start of follow-up, where only patients survived long enough had an opportunity to receive the intervention. Therefore, the patients died early are more likely to be misclassified to the no-treatment group, leading to overestimation of the effectiveness of medicine[26]. This study was specifically designed to address survivors-treated bias of corticosteroid treatment, by using a time-dependent variable for corticosteroids initiation to define corticosteroids group and non-corticosteroids group.[27]In addition, there was a propensity of clinicians to give corticosteroids to patients who were critically ill in non-randomized clinical condition. The imbalance in baseline characteristics may introduce confounders in comparison of mortality between corticosteroids and non-corticosteroids group. In this cohort, lymphopenia and elevation of CRP and lactate dehydrogenase levels were more severe in patients who received corticosteroids therapy. Propensity score is a validated method to account for baseline confounding and control selection bias in this case.[28] We performed a rigorous propensity adjustment analysis in this study, and the results of time-varying Cox model was unchanged. These added to the strength of our results that found benefit of corticosteroids on mortality.

Timing, dosage, and duration of corticosteroids therapy were fundamental variables of corticosteroid treatment regimens. Benefit of early administration of corticosteroids has been reported by several randomized controlled trials in patients with ARDS.[22, 25] Most of the trials showed corticosteroids initiated in early ARDS was associated with better outcome.[24, 29] We also found survival benefit of corticosteroids therapy in the subgroup initiated within 1 day after ARDS onset, favoring administration of corticosteroids in the early phase of disease process. In addition, we found that administration of corticosteroids within 14 days after symptom onset were also related with better outcome. These results underlines early identification and intervention of ARDS in COVID-19 patients.

Low dose corticosteroid treatment (methylprednisolone of 1–2 mg/kg) was found to accelerates the resolution of ARDS, [25, 29, 30] while high dose treatment have risk of immune-suppression and corticosteroid-induced complications including diabetes, osteonecrosis, and psychosis in SARS.[19, 31, 32] The ranges of maximum dose of corticosteroids in this cohort were 40–160 mg of methylprednisolone equivalent, which was close to the recommended dose for ARDS patients.[30, 33] Our results show that low-to-moderate dose of corticosteroids may benefit COVID-19 patients who developed ARDS, without a significant increase of hyperglycemia.

In our study, the course of corticosteroid therapy was short, which was in agreement with most previous studies which suggested short-course corticosteroids of low-to-moderate dose was effective and safe among patients with ARDS[34, 35], sepsis[36], and H1N1 virus infection[37]. Tampering strategy were

performed as has been suggested by the guidelines for the ARDS -related corticosteroid insufficiency (CIRCI) to reduce deterioration from the development of a reconstituted inflammatory response and febrile response. More research is needed to determine the best duration of corticosteroid therapy. A recent individual patient data analysis of four trials including 322 patients showed prolonged corticosteroids therapy reduced mortality[29]. However, chronic side effects of corticosteroids including secondary infection and osteoporosis may occur in prolonged course of treatment.

Delayed virus clearance was reported in corticosteroid-treated patients with both SARS and MERS. [21, 38] In contrast, we found no difference in viral shedding duration from symptom onset between corticosteroid and non-corticosteroid groups from whom the data were available. Notably, positive SARS-CoV-2 test results has been reported after two consecutive negative results.[39] Unfortunately, viral tests of throat swabs were not monitored after two consecutive negative tests in our cohort, thus more evidence is needed for assessing the effects of corticosteroids on viral shedding.

Our study had some limitations. First, unlike randomized controlled trials, the selection bias and potential confounding effects might exist. We used propensity analysis rather than standard multivariable analysis to rigorously adjust for selection bias, and time-dependent model to avoid survivors-treated bias. Nonetheless, only measured factors were controlled for due to the nature of observational study design. Second, secondary infections was not monitored in this study, because microbiological culture results needed for definite diagnosis of secondary infection were possibly affected by antibiotic treatment the patients received simultaneously. To include the delayed effects of secondary infections on mortality, a longer the follow-up period of 60-day were used. Third, this study was single-centre and patients were sicker and transferred from other hospital, so might lacking of generality.

Conclusion

At present, several open-label randomized controlled trial investigating efficacy and safety of corticosteroids in COVID-19 are recruiting. Pending the results of the studies, our findings suggest administration of low-to-moderate dose of corticosteroids might reduce the risk of death in COVID-19 patients who developed ARDS.

Abbreviations List

ARDS, acute respiratory distress syndrome; CI, confidence intervals; COVID-19, coronavirus disease 2019; CRP, c-reactive protein; ECMO, extracorporeal membrane oxygenation; FIO2, fraction of inspired oxygen; HR, calculate hazard ratios; IMV, invasive mechanical ventilation; IQR, interquartile range; MERS, Middle East respiratory syndrome; MV, mechanical ventilation; NIMV, non-invasive mechanical ventilation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SOFA, sequential Organ Failure Assessment; SpO2, pulse oxygen saturation.

Declarations

Ethics approval and consent to participate

The Jin Yin-tan Hospital Ethics Committee approved the study (No.KY-2020-44.01) and granted a waiver of informed consent from study participants.

Consent for publication

Not applicable.

Availability of data and materials

The corresponding authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

The data are available from the corresponding authors upon reasonable request.

Competing interests

The authors declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Authors' contributions

Chaomin Wu, Chunling Du, Yanping Cai, Junhua Zheng contributed substantially to the study design, data collection and patient management. Dongni Hou contributed substantially to the study design, data collection, statistical analysis and interpretation, and the writing of the manuscript. Xiaoyan Chen contributed to statistical analysis and the writing of the manuscript. Jie Xu, Cuicui Chen, Xianglin Hu, Yuye Zhang, Juan Song, Lu Wang, Yen-cheng Chao contributed to the acquisition, analysis, or interpretation of data. Yun Feng, Weining Xiong, Dechang Chen, Ming Zhong, Jie Hu, Jinjun Jiang, Chunxue Bai, Xin Zhou contributed to critical revision of the manuscript for important intellectual content; Jinfu Xu, Fengyun Gong, Yuanlin Song contributed to administrative, technical, or material support.

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Supplementary Information

Additional file 1.pdf: Include eMethods, eTables and eFigures.

Figures

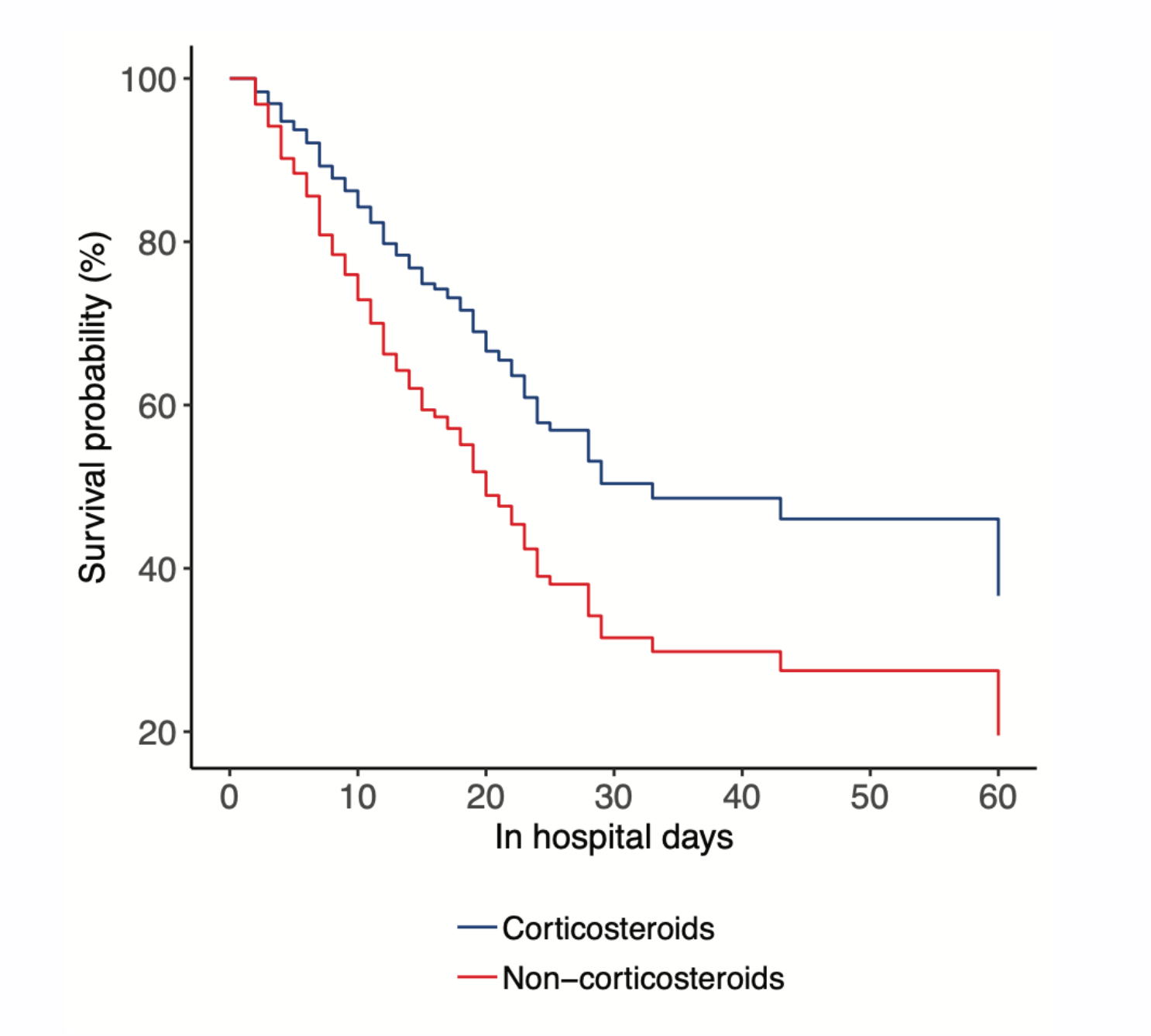

Figure 1

Estimated survival probability of multivariable Cox regression model with time-dependent corticosteroid treatment. Cox regression model with corticosteroid treatment was time-varying variable, adjusting for age, sex, SOFA score at admission, propensity score of corticosteroid treatment, and comorbidities : diabetes, hypertension, chronic pulmonary disease, chronic renal or liver disease, solid malignant tumor, hematologic malignancy, and immunosuppressive status. Propensity score was calculated by a non-parsimonious logistic regression model that included: age; sex; SOFA score at admission; temperature, respiratory rate, SpO2/FiO2 ratio, blood lymphocyte count, blood neutrophil count, and level of c-reactive protein at admission. ARDS, acute respiratory distress syndrome; SOFA, sequential Organ Failure Assessment.

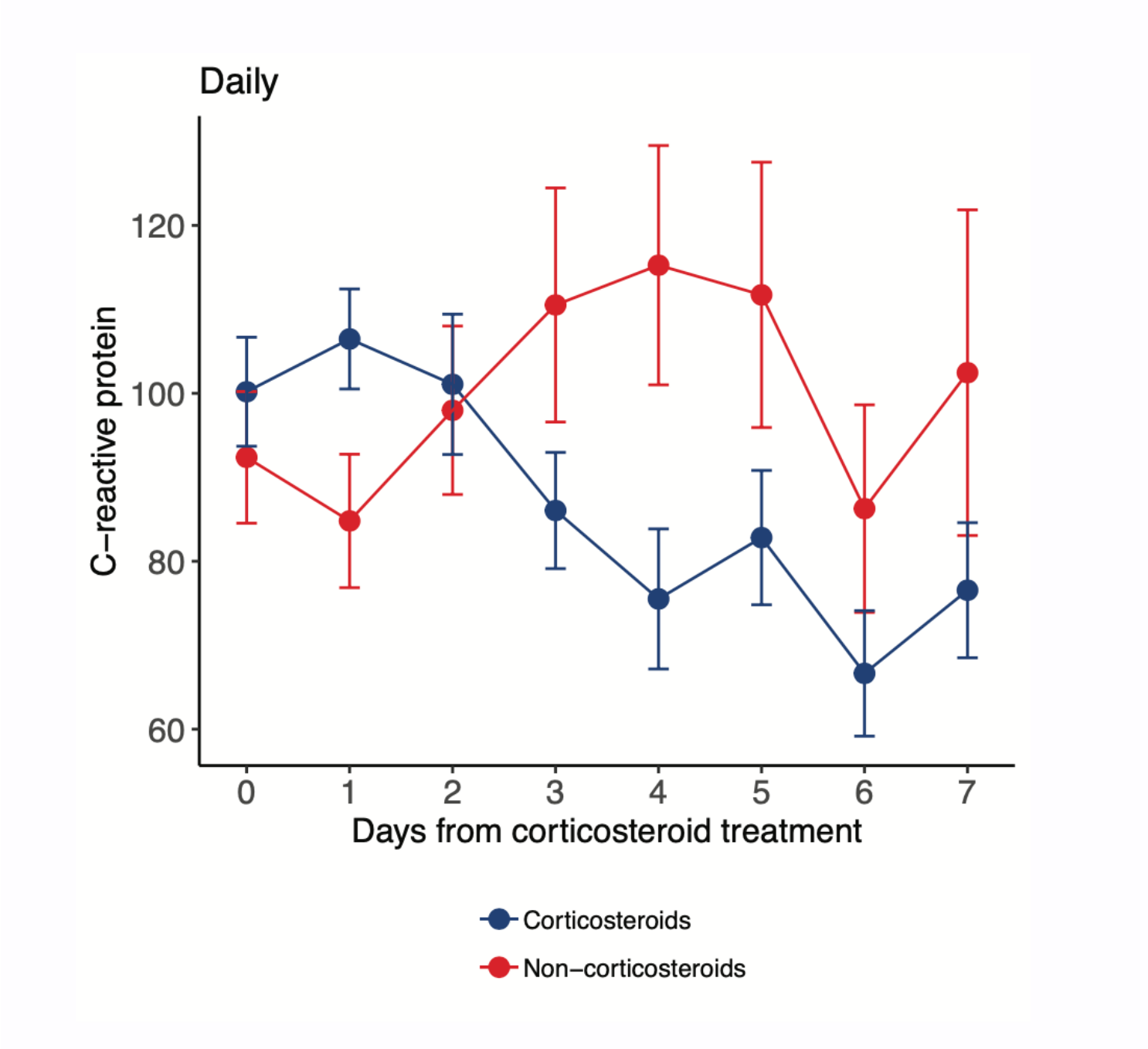

Figure 2

Changes in c-reactive protein in patients with ARDS associated with coronavirus disease 2019 ARDS, acute respiratory distress syndrome.

Supplementary Files

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