Original Article

Efficacy of low-dose corticosteroids in patients with acute respiratory distress syndrome: a prospective observational study

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Background: There is still no agreement on whether corticosteroids can reduce mortality in patients with acute respiratory distress syndrome (ARDS). The aim of this study was to investigate the efficacy of low-dose corticosteroid administration in patients with ARDS.

Methods: A prospective observational study of patients with ARDS in 17 hospitals in China was performed between March 2016 and February 2018. Propensity score matching was performed to adjust for differences in baseline characteristics between different groups. The effects of corticosteroids were assessed by using the Kaplan-Meier method and a multivariate Cox regression.

Results: A total of 527 ARDS patients were enrolled in the study. Sixty-five patients (12.3%) were administered low-dose (methylprednisolone ≤1 $mg \cdot kg^{-1} \cdot d^{-1}$) corticosteroids. The median dose was equivalent to 0.67 (0.57–0.81) mg/kg methylprednisolone for a median duration of 10 days. The control group included 224 patients (42.5%) who had never receive corticosteroids. In the matched sample, the hospital mortality rates in the low-dose (n=40) and control groups (n=80) were 27.5% and 42.5% (P=0.110), respectively. The length of hospital stay was significantly longer in the low-dose corticosteroid group than in the control group (24.0 *vs.* 17.0, P=0.002), and the multivariate Cox regression analysis suggested that the low-dose group had a significantly lower risk of death than the control group (HR: 0.48; 95% CI: 0.24–0.97; P=0.040).

Conclusions: The administration of low-dose corticosteroids may reduce mortality in patients with ARDS.

Keywords: Acute respiratory distress syndrome (ARDS); corticosteroid; mortality

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Introduction

Acute respiratory distress syndrome (ARDS) is a severe clinical syndrome characterized by refractory hypoxemia that is caused by intrapulmonary and/or extrapulmonary factors (1). Despite progress in ARDS treatment, the mortality of ARDS patients is still high; thus, more effective treatments are needed (2).

Acute inflammatory responses are observed in early ARDS, and they cause an increase in vascular permeability, extravasation of plasma, and the recruitment and activation of immune cells to further induce severe refractory respiratory failure (3). Due to their significant inflammatory response inhibition and immune regulation activity, corticosteroids have been considered as potential drugs for the treatment of ARDS (4).

However, whether ARDS patients can benefit from corticosteroids remains controversial (5-7). Previous studies have determined the effects of different doses of corticosteroids on ARDS patients. Evidence from previous clinical trials has unanimously shown that a high dose of corticosteroids significantly increases the mortality of ARDS patients (8-10). Therefore, in recent years, more studies have aimed to address the effects of low-dose corticosteroids. However, the results of those studies are contradictory. Some randomized clinical trials have suggested that low-dose corticosteroids can reduce mortality or improve pulmonary function; thus, corticosteroids have been recommended for the treatment of ARDS patients (11,12). Conversely, other studies have shown that low-dose corticosteroids do not improve patient outcomes and can cause additional side effects (13,14). In general, more studies are needed to evaluate the effects and indications of low-dose corticosteroids in ARDS patients.

The CHARDS study is a real-world study with the aim of elucidating clinical practice for respiratory support and adjunctive measures for ARDS patients in intensive care units (ICUs) in China. The aim of the present study was to analyse the impact of low-dose corticosteroids on mortality in patients with ARDS based on data from the CHARDS study. Herein, we present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-890/rc).

Methods

Patients

This was a multicentre, prospective, observational study. In this study, we included all patients with ARDS who were admitted to the medical intensive care units/respiratory intensive care units (MICUs/RICUs) of 17 hospitals in mainland China between March 2016 and February 2018. All of the enrolled patients and their family members fully understood and agreed to participate in the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committees of all of the participating study centers (No. 2015-77) and informed consent was taken from all the patients. The clinical study registration number is NCT02975908.

Inclusion and exclusion criteria

All the patients met the Berlin definition of ARDS when they were enrolled in the study (1). The patients were managed with noninvasive or invasive ventilation with positive end-expiratory pressure (PEEP) or continuous positive airway control (CPAP) ≥5 cmH_2O. The arterial blood gas analysis was repeated 15 min after ventilation and confirmed the PaO_2/FiO_2 (P/F). Subsequently, the investigators diagnosed the ARDS when the patients met the above criteria and signed consent forms; afterwards, the investigators completed the case report forms. The exclusion criteria were as follows: (I) patients younger than 18 years of age; (II) patients who had structural lung diseases, including moderate-to-severe chronic obstructive pulmonary disease (COPD), bronchiectasis, and pulmonary interstitial fibrosis; (III) patients who died on the day of inclusion; or (IV) informed consent was not received from patients or family members.

Data collection and quality control

All of the patients were evaluated on days 0–14, 21, and 28 after the diagnosis of ARDS. D0 was defined as the day when patients were diagnosed with ARDS. Data were recorded as close to 8 AM as possible on each day.

Patient outcomes included ICU and hospital mortality, lengths of stay in the ICU and hospital, and intubation rate. Nosocomial infections included hospital-acquired pneumonia (HAP), catheter-related bloodstream infection and urinary, abdominal and other infections that occurred after 48 h of admission. Any organ failure during an ICU stay was documented.

All of the data entry was double-checked. The completeness and accuracy of the data were checked during and after entry. Two inspectors supervised the quality of the data and provided feedback to the investigators. Missing or poor-quality data were removed before the data analysis was conducted.

Definition of corticosteroid doses

The daily dose of methylprednisolone or an equivalent treatment within 14 days after diagnosis was recorded. For a further description and analysis of corticosteroid usage, we grouped the patients as follows: (I) low-dose group—administration within seven days after ARDS diagnosis, daily dose of methylprednisolone equivalent to within 0.5–1 $mg \cdot kg^{-1} \cdot d^{-1}$ for more than five consecutive days; (II) high-dose group—administration within seven days after ARDS diagnosis, daily dose of methylprednisolone equivalent to >1 $mg \cdot kg^{-1} \cdot d^{-1}$ for more than five consecutive days but <500 mg/d methylprednisolone equivalent; and (III) corticosteroid pulse group—dose of methylprednisolone equivalent within 500–1,000 mg/d for five consecutive days, regardless of a dose reduction. Apart from the previously described conditions, other corticosteroid administrations were not discussed further.

Statistical analysis

Discrete variables are expressed as counts (percentages), and continuous variables are expressed as the means with standard deviations (SDs) or medians [interquartile ranges (IQRs)]. Proportions were compared by using a χ^2 test or Fisher's exact test. Continuous variables were compared via a *t*-test or Wilcoxon rank-sum test. Normality was tested by using histograms and the Kolmogorov-Smirnov normality test. Moreover, 1:2 propensity score matching was performed to adjust for differences in baseline characteristics between the low-dose corticosteroid and control groups. A survival analysis was conducted, and survival curves were plotted via a Kaplan-Meier analysis. A multivariate analysis was performed by using a Cox regression analysis. Data processing and statistical analysis were performed by using SPSS 25.0.

Results

Patients enrolled

During the study period, 2,038 patients were admitted to the ICU in all of the participating units due to acute respiratory failure; among these patients, 672 patients were diagnosed with ARDS, according to the Berlin definition. A total of 145 patients were excluded, according to the exclusion criteria. Ultimately, 527 patients were enrolled in the study for further analyses (shown in *Figure 1*). The distribution of patients in different hospitals is shown in Figure S1A.

Corticosteroid administration

A total of 303 patients (57.4%) were treated with corticosteroids, among whom 65 patients (12.3%) received low-dose corticosteroids and 41 (7.8%) received high-dose corticosteroids. In the low-dose group, 55/65 patients (84.6%) were given corticosteroids beginning on the day of diagnosis; the median duration of administration was 10 [7–14] days, and the median daily dose was 0.67 (0.57–0.81) mg/kg methylprednisolone equivalent. In the high-dose group, the median daily dose was 1.50 (1.28–2.42) mg/kg methylprednisolone equivalent. A total of 33/41 patients (80.5%) began receiving corticosteroids on the day of diagnosis, and the median duration of administration was 11 [7–14] days. Eight patients (1.5%) received corticosteroid pulse therapy. All eight patients had moderate or severe ARDS; among them, six patients received 500 $mg \cdot d^{-1}$ methylprednisolone equivalent, and two patients received 1,000 $mg \cdot d^{-1}$. Other corticosteroid administrations were not discussed further from a statistical perspective (n=189, 35.8%), due to the pronounced heterogeneity of the dosage and timing. Patients who did not receive corticosteroids (n=224, 42.5%) were treated as the control group. The distribution of the low-dose corticosteroid group and control group in different hospitals is shown in Figure S1B,S1C.

Clinical characteristics

In low-dose corticosteroid and control groups (n=289), most of the patients were male (n=201, 69.6%), and the median age was 57.0 (45.0–69.0) years. The proportions of patients with mild, moderate, and severe ARDS were 30

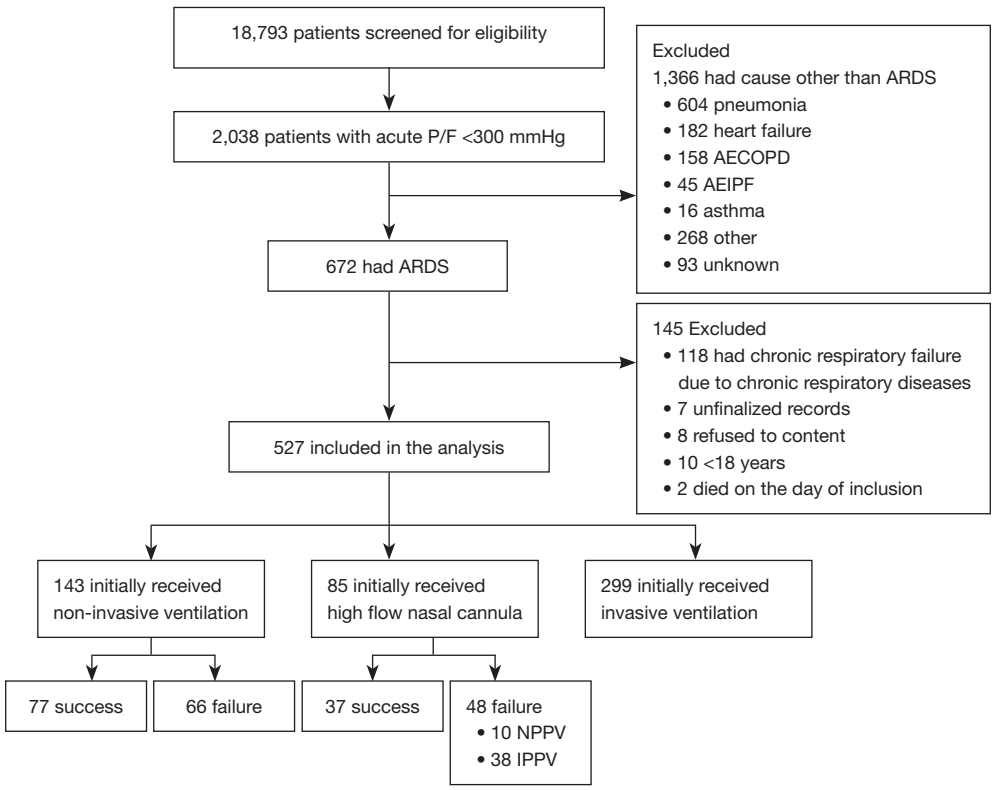

Figure 1 Flowchart of patient screening and enrolment. P/F, PaO_2/FiO_2; ARDS, acute respiratory distress syndrome; AECOPD, acute exacerbations of chronic obstructive pulmonary disease; AEIPF, acute exacerbation of idiopathic pulmonary fibrosis; NPPV, non-invasive positive pressure ventilation; IPPV, invasive positive pressure ventilation.

(10.4%), 142 (49.1%), and 117 (40.5%), respectively. The median P/F ratio was 111.0 (83.5–162.0) mmHg. A total of 83.7% (n=242) of ARDS was induced by intrapulmonary factors. Furthermore, the main risk factors for ARDS were pneumonia (n=219, 75.8%), extrapulmonary sepsis (n=21, 7.3%), aspiration (n=11, 4.2%), and pancreatitis (n=11, 3.8%). Aetiological diagnoses were obtained in 111 patients with pneumonia. The most common pathogens were the influenza virus (n=48, 21.9%) and gram-negative bacilli (n=18, 8.2%) (detailed data are provided in Tables S1,S2).

The clinical characteristics of the patients who were treated or not treated with low-dose corticosteroids are shown in *Table 1*. The baseline characteristics of the high-dose group and other corticosteroid groups are shown in Tables S3,S4. There was a significant difference in the incidence of immunosuppressed patients (49.2% *vs.* 17.4%, P=0.000). In addition, the incidence of intrapulmonary ARDS in the low-dose group was higher than that in the control group (92.3% *vs.* 81.3%, P=0.033). No differences were found among the other variables.

To minimize the influence of the different baseline characteristics, 1:2 propensity score matching was performed. A total of 120 patients were included in the matching analysis. The baseline characteristics of the matched sample are shown in *Table 1*. To ensure an adequate sample size, mechanical ventilation-related variables were not included in the matching protocol, and these variables had no significant effect on the risk of death in the matched sample (data not shown).

Mortality analysis

The outcomes of the matched sample between the two groups are displayed in *Table 2* (the original sample is displayed in Table S5). The hospital patient mortality in the two groups was 27.5% and 42.5% (P=0.110). This difference in mortality was not significantly different. The median ICU and hospital lengths of stay were increased by 7.0 days (18.0 *vs.* 11.0, P=0.001) and 7.0 days (24.0 *vs.* 17.0 , P=0.002), respectively. In the survivors, the length of hospital stay between the two groups was 25.0 (19.0–37.0)

Table 1 Comparison of baseline characteristics between low-dose and control groups in the original sample and propensity score-matched sample

Variable	Original sample			Matched sample		
	Low-dose corticosteroid (n=65)	Non-corticosteroid (n=224)	P value	Low-dose corticosteroid (n=40)	Non-corticosteroid (n=80)	P value
Male sex, n (%)	45 (69.2)	156 (69.6)	0.949	29 (72.5)	60 (75.0)	0.768
Age, median (IQR), years	58.0 (44.0–70.0)	57.0 (45.0–69.0)	0.874	62.0 (44.0–72.3)	56.0 (46.3–66.8)	0.488
BMI, median (IQR)	24.2 (22.0–26.2)	24.2 (21.5–26.7)	0.776	23.9 (22.4–26.9)	24.4 (22.1–26.3)	0.878
PaO_2/FiO_2 at admission (mmHg)	107.0 (80.0–162.8)	113.0 (84.1–160.1)	0.695	98.3 (68.3–136.3)	100.0 (71.9–149.8)	0.686
APACHE II score, median (IQR)	17 [10–23]	15 [10–21]	0.240	17.5 (10.8–22.3)	15.5 (11.0–20.0)	0.457
SOFA score, median (IQR)	7 [4–9]	6 [4–10]	0.972	6.5 (3.8–9.0)	6.0 (4.0–10.0)	0.568
Intrapulmonary ARDS, n (%)	60 (92.3)	182 (81.3)	0.033	36 (90.0)	70 (87.5)	0.688
Underlying disease condition, n (%)						
Hypertension	24 (36.9)	65 (29.3)	0.241	16 (40.0)	27 (34.2)	0.532
Diabetes mellitus	14 (21.5)	43 (19.4)	0.700	9 (22.5)	12 (15.2)	0.323
Chronic cardiac insufficiency	3 (4.6)	8 (3.6)	0.716	2 (5.0)	1 (1.3)	0.220
Chronic kidney disease	6 (9.2)	20 (9.0)	0.956	1 (2.5)	4 (5.1)	0.510
Immunosuppression[a]	32 (49.2)	39 (17.4)	0.000	7 (17.5)	15 (18.8)	0.868
Laboratory test results at ICU admission						
D0 WBC, median (IQR) ($\times 10^9$/L)	11.3 (8.9–16.4)	10.0 (6.3–15.3)	0.150	11.1 (7.4–15.5)	10.0 (5.3–15.0)	0.334
D0 PCT, median (IQR) (ng/mL)	1.1 (0.3–5.0)	2.0 (0.4–10.5)	0.077	1.8 (0.3–7.0)	2.1 (0.6–9.6)	0.221
D0 CRP, median (IQR) (mg/L)	130.1 (60.7–211.7)	124.7 (42.4–200.0)	0.648	160.9 (82.7–222.4)	133.8 (72.7–189.8)	0.227
D0 lactic acid, median (IQR) (mmol/L)	1.9 (1.2–2.7)	1.8 (1.1–2.8)	0.905	1.9 (1.2–2.6)	1.6 (1.1–2.6)	0.946
Mechanical ventilation management[b]						
Intubation rate, n (%)	51 (78.5)	158 (70.5)	0.209	33 (82.5)	57 (71.3)	0.180
PEEP median (IQR), cmH_2O	10 [8–12]	8 [5–10]	0.002	10 [8–12]	8 [6–10]	0.008
V_T, median (IQR) (mL/kg PBW)	6.0 (5.7–6.9)	6.8 (6.0–7.7)	0.049	6.0 (5.5–6.7)	6.8 (6.1–7.5)	0.050
Plateau pressure, median (IQR), cmH_2O	23 [18–28]	20 [15–24]	0.010	20 [15–28]	21 [15–24]	0.858
Driving pressure, median (IQR), cmH_2O	13 [8–18]	12 [7–16]	0.183	11 [7–17]	13 [7–15]	0.451

[a], immunosuppression was defined as a haematologic malignancy or a solid tumour; or administration of steroids or any immunosuppressive drug within a month; or administration of radiation therapy or chemotherapy within a year. [b], only patients with intubation were included. IQR, interquartile range; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; WBC, white blood cell; PCT, procalcitonin; CRP, C reactive protein; PEEP, positive end expiratory pressure; V_T, tidal volume; PBW, predicted body weight.

vs. 23.0 days (14.0–29.5), P=0.106, and the length of ICU stay was 18.0 (10.5–26.8) *vs.* 11.0 days (7.0–22.0), P=0.026. In the nonsurvivors, the length of hospital stay between the two groups was 21.0 (15.0–25.0) *vs.* 12.0 days (4.8–20.3), P=0.009, and the length of ICU stay was 19.0 (13.0–24.0) *vs.* 9.0 days (4.0–17.3), P=0.011. The incidence rates of nosocomial infection and other organ failure events were not significantly different. The outcomes of the high-dose group and other corticosteroid groups are shown in Tables S6,S7.

Kaplan-Meier survival curves were constructed to

Table 2 Comparison of outcomes between the low-dose and control groups in the propensity score-matched sample

Outcome	Low-dose corticosteroid (n=40)	Non-corticosteroid (n=80)	P value
Duration of mechanical ventilation* (days)	11.0 (6.0–14.0)	6.5 (0.0–11.0)	0.007
Nosocomial infection, n (%)	12 (30.0)	27 (33.8)	0.679
New organ failure, n (%)	11 (27.5)	34 (42.5)	0.110
Ventilator free days at day 28, d	16.0 (2.0–22.0)	14.0 (0.0–28.0)	0.980
ICU length of stay (days)	18.0 (12.0–24.0)	11.0 (5.0–19.0)	0.001
Hospital length of stay (days)	24.0 (19.0–33.0)	17.0 (10.0–28.0)	0.002
ICU mortality, n (%)	11 (27.5)	33 (41.3)	0.141
Hospital mortality, n (%)	11 (27.5)	34 (42.5)	0.110

*, only patients with intubation were included. ICU, intensive care unit.

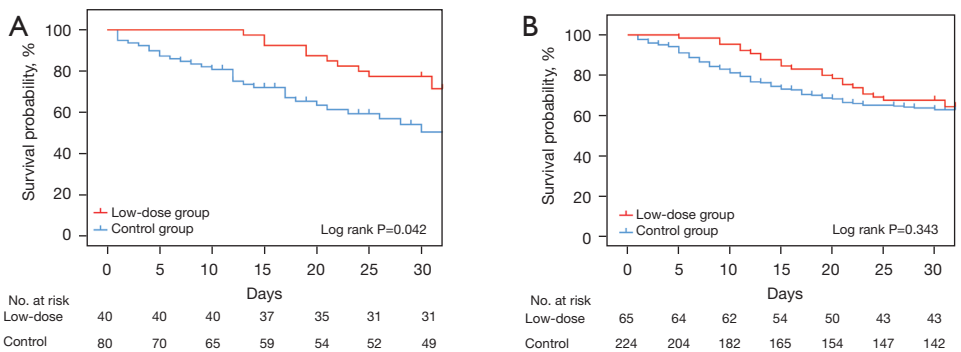

Figure 2 The Kaplan-Meier analysis shows 30-day mortality between the two groups in the matched sample (A) and original sample (B).

illustrate the 30-day survival rates in the two groups (shown in *Figure 2A,2B*). The mortality decreased significantly in the low-dose corticosteroid group in the matched sample (P=0.042). In addition, the curve showed that corticosteroids had no effect on the intubation rate (shown in Figure S2A,S2B).

To eliminate potential confounding factors, univariate and multivariate Cox regression analyses were performed in matched samples (*Figures 3,4*) and original samples (Tables S8,S9), respectively. The multivariate Cox regression analysis of hospital mortality identified low-dose corticosteroids as being a protective factor in matched samples (HR: 0.48; 95% CI: 0.24–0.97; P=0.040). Administration of low-dose corticosteroids showed a lower risk of death in patients with intrapulmonary ARDS in the matched sample (shown in *Table 3*, data of original sample shown in Table S10).

Adverse effects of low-dose corticosteroids

The adverse effects of corticosteroids may cause the conditions of patients to deteriorate and even influence outcomes, and secondary infection was observed to be the most severe threat. To investigate the acute adverse events associated with corticosteroids, the incidence of nosocomial infection was analysed via a Kaplan-Meier analysis in matched samples and original samples (shown in *Figure 5A,5B*). No significant difference was found in the nosocomial infection rate between the two groups (P=0.146). Hyperglycaemia and ICU-acquired weakness were not recorded.

Discussion

To date, the present study is the largest observational study focusing on corticosteroid administration in ARDS patients in China. In this study, we determined two main conclusions about the administration of low-dose corticosteroids in patients with ARDS. First, our results show that low-dose corticosteroid therapy may play a protective role in ARDS patients, although the lengths of ICU and hospital stays are

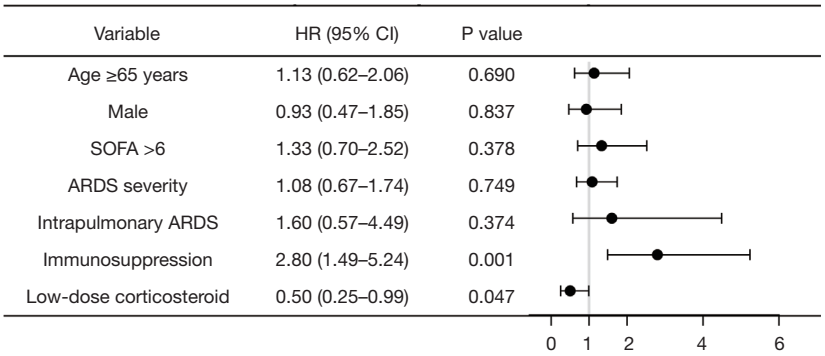

Figure 3 Univariate Cox regression analysis for factors associated with hospital mortality in matched sample. SOFA, Sequential Organ Failure Assessment; ARDS, acute respiratory distress syndrome.

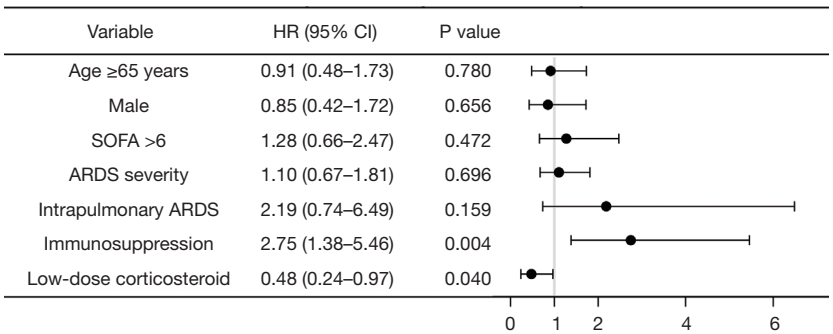

Figure 4 Multivariate Cox regression analysis for factors associated with hospital mortality in matched sample. SOFA, Sequential Organ Failure Assessment; ARDS, acute respiratory distress syndrome.

Table 3 Effects of low-dose corticosteroids on mortality using multivariate Cox regression analysis in matched sample

Subgroup	Hospital mortality	
	HR (95% CI)	P
All patients (n=120)	0.48 (0.24–0.97)	0.040
Patients with intrapulmonary ARDS (n=106)	0.36 (0.17–0.77)	0.009
Patients with mechanical ventilation (n=90)	0.50 (0.25–1.03)	0.062
Patients with shock (n=39)	0.92 (0.23–1.47)	0.250
Patients without immunosuppression (n=98)	0.53 (0.23–1.23)	0.142

ARDS, acute respiratory distress syndrome.

prolonged. Second, no significant relationship was found between low-dose corticosteroids and the nosocomial infection rate.

The efficacy and safety of low-dose corticosteroids ($\leq$1 mg·kg^{-1}·d^{-1}) in ARDS patients is still controversial. A randomized controlled trial (RCT) reported by Meduri *et al.* suggested that the administration of low-dose (1 mg·kg^{-1}·d^{-1}) methylprednisolone in the early stage could significantly reduce mortality, compared to that in the placebo group (20.6% *vs.* 42.9%, P=0.03) (11). These researchers subsequently published numerous meta-analyses that all supported the notion that the administration of a low dose of corticosteroids could reduce the mortality rate and shorten the length of hospital stay for ARDS patients (15,16). Furthermore, a double-blind, single-centre RCT conducted by Tongyoo *et al.* suggested that, although corticosteroids do not reduce mortality (22.5% *vs.* 27.3%, P=0.51), secondary endpoints, such as the P/F ratio and lung injury score, were improved (P=0.01) (12). In contrast, a meta-analysis by Ruan *et al.* showed that corticosteroids did not significantly affect ICU mortality or the 60-day mortality rate (13). Additionally, the results of a meta-analysis by Horita *et al.* showed that the benefit of corticosteroids for ARDS patients was uncertain (14);

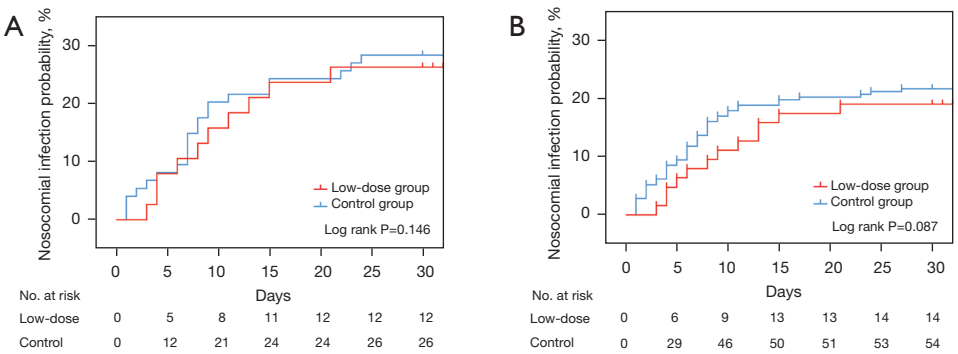

Figure 5 The Kaplan-Meier analysis showed that there was no significant difference in 30-day nosocomial infection between the two groups in the matched sample (A) and original sample (B).

therefore, corticosteroids should not be used as a routine treatment.

The studies referred above have shown inconsistent conclusions, largely due to the heterogeneity of the ARDS patients. Therefore, more subgroup studies are needed to reduce heterogeneity. In recent years, many large, controlled studies and retrospective studies have confirmed that the administration of corticosteroids in influenza-related ARDS patients significantly increases mortality or the risk of nosocomial infections (9,17,18).

Our findings are partially consistent with previous results. Although there was no significant difference in mortality, according to the univariate analysis (27.5% *vs.* 42.5%, P=0.110), the Cox regression analysis revealed that a low-dose corticosteroid administration may reduce ICU and hospital mortality. This potential benefit can be explained by the anti-inflammatory function of corticosteroids, by which the systemic inflammation experienced in ARDS was relieved. Although we did not collect serum for cytokine determinations, previous *in vivo* experiments have also demonstrated this point (19,20). Furthermore, the reason for the prolonged ICU and hospital stays may be that the administration of corticosteroids increases the risk of ICU-acquired weakness and may delay the clearance of pathogens (21,22). Thus, it is necessary to realize that the potential benefits and risks are equally important.

In the present study, the purpose of corticosteroid administration was not recorded on the case report form. Due to the use of oral corticosteroids in patients with other autoimmune diseases or in ARDS patients, immunosuppression may overlap with low-dose corticosteroid administration. Meanwhile, immunosuppression has been shown to increase mortality due to superinfections and ICU-acquired infection (23,24). Our study also supports this notion. Therefore, we performed propensity score matching to eliminate confounding factors. The results from the matched samples further support this conclusion.

The second key finding is that low-dose corticosteroid administration had no relationship with nosocomial infections within 30 days after diagnosis (30.0% *vs.* 33.8%, P=0.679). This conclusion is in accordance with a report by Cao *et al.* (17), which suggested that rates of HAP were higher in the high-dose corticosteroid group than in the control group, but not in the low-dose group. Notably, our data encompassed only 14 days after the diagnosis; thus, we cannot conclusively state the effects of long-course corticosteroid treatment (>14 days) on nosocomial infections.

In clinical practice, the variation in corticosteroid dosages is large. Therefore, it is difficult to describe the strategy of corticosteroid administration in an observational study. To achieve the number of patients and a balance of consistency, we finally defined a representative dose (daily doses of 0.5–1.0 mg·kg^{-1} for at least 5 days) as the low-dose group, based on clinical practice in China. This standard guaranteed the consistency of the corticosteroid dose to a certain extent; however, many patients were not analysed. Although the standardization of the corticosteroid dose was not fully achieved, we considered that it still has positive implications.

There were limitations to this study. First, this study was an observational study; therefore, ensuring the internal consistency of patients in the different groups is problematic. Although propensity score matching was performed, there may also be some potentially hard-to-eliminate differences between the two groups. In addition, incomplete data on adjunctive measures in the two groups may be a major deficiency. Second, a lack of purpose regarding corticosteroid use made our grouping scheme less

accurate (to a certain extent), which may be why a portion of the data was not truly utilized. Third, the sample size was small, especially in the propensity score matching sample. It also restricted further analysis about the role of high-dose corticosteroid group. Last, the missing data for aetiologic diagnoses in some patients may lead to potential diagnosis biases in ARDS. Therefore, further random clinical trials are needed.

Conclusions

Based on our limited observational data, the administration of low-dose corticosteroids may reduce mortality in patients with ARDS, and the lengths of ICU and hospital stays are prolonged. Moreover, no significant relationship was found between low-dose corticosteroids and the nosocomial infection rate.

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committees of all of the participating study centers (No. 2015-77) and informed consent was taken from all the patients.

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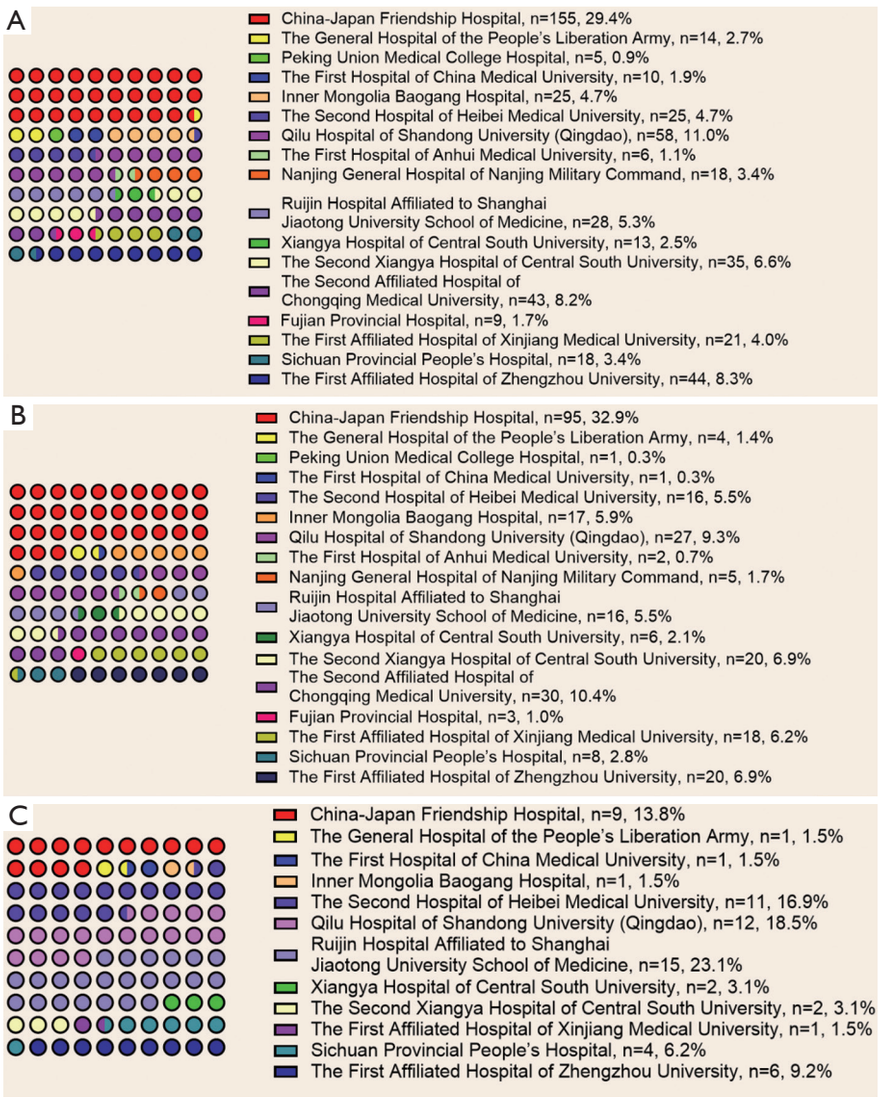

Figure S1 (A) The distribution of patients in 17 participating hospitals (n=527). (B) The distribution of low-dose corticosteroid and control groups in different hospitals (n=289). (C) The distribution of the low-dose corticosteroid group in different hospitals (n=65).

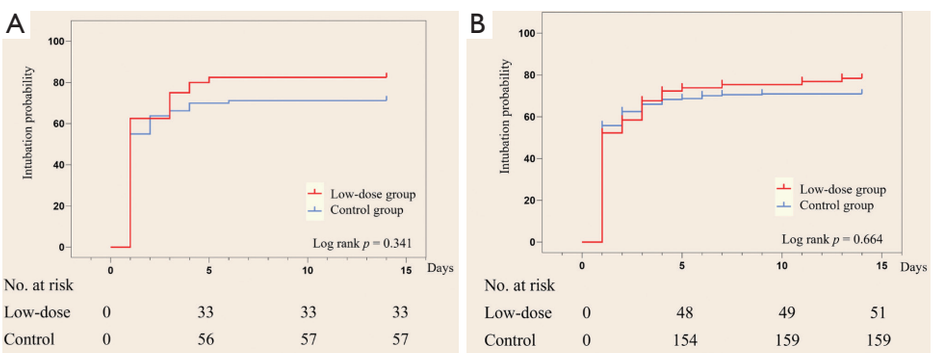

Figure S2 Intubation rate curves for the low-dose and control groups within a 14-day period in the matched sample (A) and original sample (B).

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Table S1 Distribution of acute respiratory distress syndrome risk factors in the low-dose and control groups. There was no significant difference between two groups (P=0.433)

Risk factor	Low-dose corticosteroid (n=65), n (%)	Non-corticosteroid (n=224), n (%)
Pneumonia	52 (81.3)	167 (74.6)
Aspiration	5 (7.8)	7 (3.1)
Drowning	0	1 (0.4)
Pulmonary contusion	1 (1.6)	6 (2.7)
Trauma	0	5 (2.2)
Extrapulmonary sepsis	3 (4.7)	18 (8.0)
Pancreatitis	1 (1.6)	10 (4.5)
Others	2 (3.1)	10 (4.5)
Missing data	1 (1.5)	0

Table S2 Aetiological diagnoses in patients with pneumonia-related acute respiratory distress syndrome in the low-dose and control groups. There was no significant difference between two groups (P=0.574)

Pathogen	Low-dose corticosteroid (n=52), n (%)	Non-corticosteroid (n=167), n (%)
Gram– bacillus	3 (5.7)	15 (8.9)
Gram+ coccus	0	1 (0.6)
Fungus	1 (1.9)	6 (3.6)
Influenza virus	10 (19.2)	38 (22.8)
Other viruses	2 (3.9)	2 (1.2)
Pneumocystis	2 (3.9)	1 (0.6)
Tuberculosis bacillus	0	1 (0.6)
Atypical pathogens	0	4 (2.4)
Mixed infection	5 (9.6)	20 (12.0)
Unknown	29 (55.8)	79 (47.3)

Table S3 Comparison of baseline characteristics between high-dose and control groups

Variable	High-dose corticosteroid (n=65)	Non-corticosteroid (n=224)	P value
Male sex, n (%)	45 (69.2)	156 (69.6)	0.949
Age, median (IQR), years	58.0 (44.0–70.0)	57.0 (45.0–69.0)	0.874
BMI, median (IQR)	24.2 (22.0–26.2)	24.2 (21.5–26.7)	0.776
PFR at admission (mmHg)	107.0 (80.0–162.8)	115.2 (84.3–162.0)	0.695
APACHE II score, median (IQR)	17 (10–23)	15 (10–21)	0.240
SOFA score, median (IQR)	7 (4–9)	6 (4–10)	0.972
Intrapulmonary ARDS, n (%)	60 (92.3)	182 (81.3)	0.033
Underlying disease condition, n (%)			
Hypertension	24 (36.9)	65 (29.3)	0.241
Diabetes mellitus	14 (21.5)	43 (19.4)	0.700
Chronic cardiac insufficiency	3 (4.6)	8 (3.6)	0.716
Chronic kidney disease	6 (9.2)	20 (9.0)	0.956
Immunosuppression*	32 (49.2)	39 (17.4)	0.000
Laboratory test results at ICU admission			
D0 WBC, median (IQR) ($\times 10^9$/L)	11.3 (8.9–16.4)	10.0 (6.3–15.3)	0.150
D0 PCT, median (IQR) (ng/mL)	1.1(0.3–5.0)	2.0 (0.4–10.5)	0.077
D0 CRP, median (IQR) (mg/L)	130.1 (60.7–211.7)	124.7 (42.4–200.0)	0.648
D0 lactic acid, median (IQR) (mmol/L)	1.9 (1.2–2.7)	1.8 (1.1–2.8)	0.905

*, immunosuppression was defined as a haematologic malignancy or a solid tumour; or administration of steroids or any immunosuppressive drug within a month; or administration of radiation therapy or chemotherapy within a year (Same as *Table 1*).

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Table S4 Comparison of baseline characteristics between other dose corticosteroid group and control groups

Variable	Other-dose corticosteroid (n=189)	Non-corticosteroid (n=224)	P value
Male sex, n (%)	137 (72.5)	156 (69.6)	0.526
Age, median (IQR), years	55.0 (43.0–68.0)	57.0 (45.0–69.0)	0.666
BMI, median (IQR)	24.0 (21.7–26.1)	24.2 (21.5–26.7)	0.458
PFR at admission (mmHg)	110.5 (74.0–160.0)	113.0 (84.1–160.1)	0.310
APACHE II score, median (IQR)	18.0 (13.0–23.5)	15.0 (10.0-21.0)	0.002
SOFA score, median (IQR)	8.0 (5.0–11.0)	6.0 (4.0–10.0)	0.002
Intrapulmonary ARDS, n (%)	158 (83.6)	182 (81.3)	0.533
Underlying disease condition, n (%)			
Hypertension	70 (37.0)	65 (29.3)	0.095
Diabetes mellitus	39 (20.7)	43 (19.4)	0.729
Chronic cardiac insufficiency	12 (6.3)	8 (3.6)	0.197
Chronic kidney disease	22 (11.7)	20 (9.0)	0.370
Immunosuppression*	67 (35.4)	39 (17.4)	0.000
Laboratory test results at ICU admission			
D0 WBC, median (IQR) ($\times 10^9$/L)	10.6 (5.7–13.9)	10.4 (6.3–15.3)	0.910
D0 PCT, median (IQR) (ng/mL)	0.9 (0.3–5.0)	2.0 (0.4–10.5)	0.052
D0 CRP, median (IQR) (mg/L)	107.8 (39.3–180.4)	124.7 (46.8–200.0)	0.114
D0 lactic acid, median (IQR) (mmol/L)	1.9 (1.3–2.8)	1.8 (1.1–2.8)	0.468

*, immunosuppression was defined as a haematologic malignancy or a solid tumour; or administration of steroids or any immunosuppressive drug within a month; or administration of radiation therapy or chemotherapy within a year (Same as *Table 1*).

Table S5 Comparison of outcomes between the low-dose and control groups in the original sample

Outcome	Low-dose corticosteroid (n=65)	Non-corticosteroid (n=224)	P value
Duration of mechanical ventilation* (days)	11.0 (7.0–14.0)	8.0 (5.0–12.0)	0.001
Nosocomial infection, n (%)	14 (21.5)	59 (26.3)	0.433
New organ failure, n (%)	27 (41.5)	94 (42.0)	0.951
Ventilator free days at day 28, d	14.0 (1.5–19.5)	17.0 (1.0–27.8)	0.188
ICU length of stay (days)	15.5 (10.0–24.0)	10.0 (6.0–17.0)	0.000
Hospital length of stay (days)	23.0 (16.0–36.3)	17.0 (10.0–26.0)	0.000
ICU mortality, n (%)	28 (43.1)	87 (38.8)	0.539
Hospital mortality, n (%)	29 (44.6)	91 (40.6)	0.565

*, Only patients with intubation were included.

Table S6 Comparison of outcomes between the high-dose and control groups

Outcome	High-dose corticosteroid (n=41)	Non-corticosteroid (n=224)	P value
Duration of mechanical ventilation* (days)	10.0 (4.0–14.0)	10.0 (5.0–13.6)	0.378
Nosocomial infection, n (%)	9 (22.0)	59 (26.3)	0.554
New organ failure, n (%)	15 (36.6)	94 (42.0)	0.520
Ventilator free days at day 28 (days)	16.0 (0.5–28.0)	17.0 (1.0–27.3)	0.581
ICU length of stay (days)	14.0 (7.5–35.0)	10.0 (6.0–17.0)	0.001
Hospital length of stay (days)	23.0 (12.5–26.0)	17.0 (10.0–26.0)	0.002
ICU mortality, n (%)	16 (39.0)	87 (38.8)	0.982
Hospital mortality, n (%)	17 (41.5)	91 (40.6)	0.920

*, Only patients with intubation were included.

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Table S7 Comparison of outcomes between the other dose corticosteroid group and control groups

Outcome	Other dose corticosteroid (n=189)	Non-corticosteroid (n=224)	P value
Duration of mechanical ventilation* (days)	7.0 (3.0–11.0)	5.0 (0.0–10.0)	0.024
Nosocomial infection, n (%)	49 (25.9)	59 (26.3)	0.924
New organ failure, n (%)	101 (53.4)	94 (42.0)	0.020
Ventilator free days at day 28 (days)	4.0 (0.0–21.0)	17.0 (1.0–27.8)	0.000
ICU length of stay (days)	11.0 (6.0–21.0)	10.0 (6.0–17.0)	0.063
Hospital length of stay (days)	17.0 (8.8–30.3)	17.0 (10.0–26.0)	0.444
ICU mortality, n (%)	96 (50.8)	87 (38.8)	0.015
Hospital mortality, n (%)	101 (53.4)	91 (40.6)	0.009

*, Only patients with intubation were included.

Table S8. Univariate Cox regression analysis for factors associated with hospital mortality in original sample

Variable	HR (95% CI)	p value
Age⩾65 years	1.71(1.19-2.46)	.004
Male	1.06(0.71-1.59)	.763
SOFA≥6	1.66(1.11-2.49)	.013
ARDS Severity	1.27(0.95-1.71)	.108
Intrapulmonary ARDS	1.30(0.77-2.21)	.326
Immunosuppression	1.68(1.15-2.44)	.007
Low-dose corticosteroid	0.82(0.54-1.25)	.348

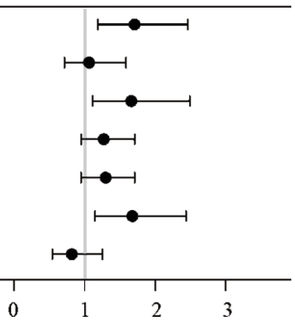

Table S9. Multivariate Cox regression analysis for factors associated with hospital mortality in original sample

Variable	HR (95% CI)	p value
Age⩾65 years	1.58(1.09-2.28)	.016
Male	1.02(0.67-1.55)	.930
SOFA≥6	1.64(1.09-2.47)	.018
ARDS Severity	1.29(0.96-1.72)	.095
Intrapulmonary ARDS	1.45(0.84-2.50)	.181
Immunosuppression	1.58(1.05-2.39)	.029
Low-dose corticosteroid	0.62(0.39-0.98)	.041

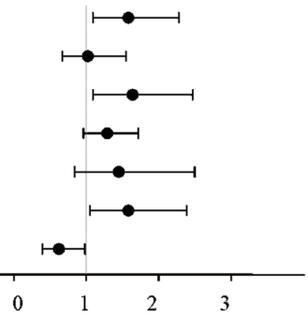

Table S10 Effects of corticosteroids on mortality using multivariate Cox regression analysis in the original sample

Subgroup	Hospital mortality	
	HR (95% CI)	P
All patients (n=289)	0.63 (0.39–0.98)	0.041
Patients with intrapulmonary ARDS (n=242)	0.55 (0.34–0.90)	0.017
Patients with mechanical ventilation (n=209)	0.55 (0.34–0.91)	0.019
Patients with shock (n=97)	0.64 (0.35–1.18)	0.635
Patients with influenza (n=48)	0.27 (0.07–1.03)	0.056
Patients without immunosuppression (n=218)	0.41 (0.20–0.87)	0.020

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