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Early high dose corticosteroid therapy in hematopoietic stem cell transplantation patients with acute respiratory distress syndrome: a propensity score matched study

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Abstract

Background: Acute respiratory distress syndrome (ARDS) is one of the pulmonary complications after hematopoietic cell transplantation (HSCT) with a poor prognosis. The effects of corticosteroid therapy in HSCT patients with ARDS have never been described. In this study, we aim to evaluate the effect of corticosteroid on hospital mortality and other outcomes in patients with HSCT and ARDS.

Methods: In this bicenter retrospective study, data were collected from patients diagnosed with ARDS and HSCT. Patients were divided into an early high dose steroids group (receiving a cumulative dose ⩾480 mg of methylprednisolone or its equivalent within the first 3 days after ARDS onset) and a no early high dose steroids group. Univariate and multivariate analyses were used to determine the risk factors of hospital mortality. Cox regression was performed to assess the effect of early high dose steroids on patient survival. A propensity score matched cohort was built to validate the results from the original study cohort.

Results: Two hundred and sixty-four patients were included in the original study cohort; 89 (33.71%) patients received early high dose steroids; these patients had higher ventilator free days at day 28 (7.68 ± 4.32 *versus* 6.48 ± 4.76, $p = 0.046$); there was no difference in hospital mortality (64.04% *versus* 53.14%, $p = 0.091$). Patients with early high dose steroids had a higher incidence of new onset bacteremia (17.98% *versus* 4%, $p < 0.001$) and viremia (13.48% *versus* 3.43%, $p = 0.002$). The results were further confirmed in the propensity score matched cohort, except for the improvement of ventilator free days (6.02 ± 5.51 *versus* 5.57 ± 5.54, $p = 0.643$).

Conclusion: In this cohort of HSCT patients with ARDS, early high dose coticosteroids had no effect on hospital mortality. In addition, the incidences of new onset bacteremia and viremia were increased after early high dose steroids.

The reviews of this paper are available via the supplemental material section.

Keywords: acute respiratory distress syndrome, corticosteroids, hematopoietic stem cell transplantation

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Introduction

Hematopoietic stem cell transplantation (HSCT) is now widely performed and was proved to be curative for patients with various hematological or non-hematological diseases. However, it is still a high-risk procedure that is associated with many complications.[1,2] Acute respiratory distress syndrome (ARDS) is one of the pulmonary complications, which has an incidence of 15.6% after allogeneic HSCT.[3] Recent studies[3–5] indicate that despite advances in mechanical ventilation and other life-supporting methods, the prognosis of HSCT patients with ARDS is rather poor, with intensive care unit (ICU) mortality up to 76.0%.

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Corticosteroids have long been applied in the treatment of ARDS patients. Their theoretical mechanisms are based on suppression of systemic inflammation and pulmonary fibrosis,[6] which both were drivers in the pathogenesis of ARDS.[7,8] Some randomized controlled trials[9,10] showed a decrease in hospital mortality or increase of ventilator free days with corticosteroids, while others[11,12] failed to validate these effects. Even though many HSCT patients with acute respiratory failure were frequently treated with corticosteroids,[13–15] there were no relative studies focused on corticosteroid therapy in ARDS for this population. Hence, in this bicenter retrospective study, we aim to evaluate the effect of corticosteroids on hospital mortality and other outcomes of patients with HSCT and ARDS.

Methods

This bicenter retrospective study was approved by the ethics and research board of Peking University International Hospital and Peking University People's Hospital.

Patients

Data of patients (in Peking University International Hospital: from August 2015 to August 2019; in Peking University People's Hospital: from August 2009 to August 2019) who were admitted into ICUs were retrieved from the medical record system. We included adult patients with an admission diagnosis of HSCT and ARDS. The diagnosis of ARDS was based on the Berlin definition.[16]

The exclusion criteria were as follows. (1) Application of corticosteroid or other immunosuppressive agents within 30 days prior to ARDS onset. (2) Initiation of corticosteroid therapy later than 7 days of ARDS onset. (3) Patients with comorbidities that may be influenced by corticosteroids: asthma, pulmonary fibrosis, diffuse alveolar hemorrhage, organizing pneumonia, *et cetera*.

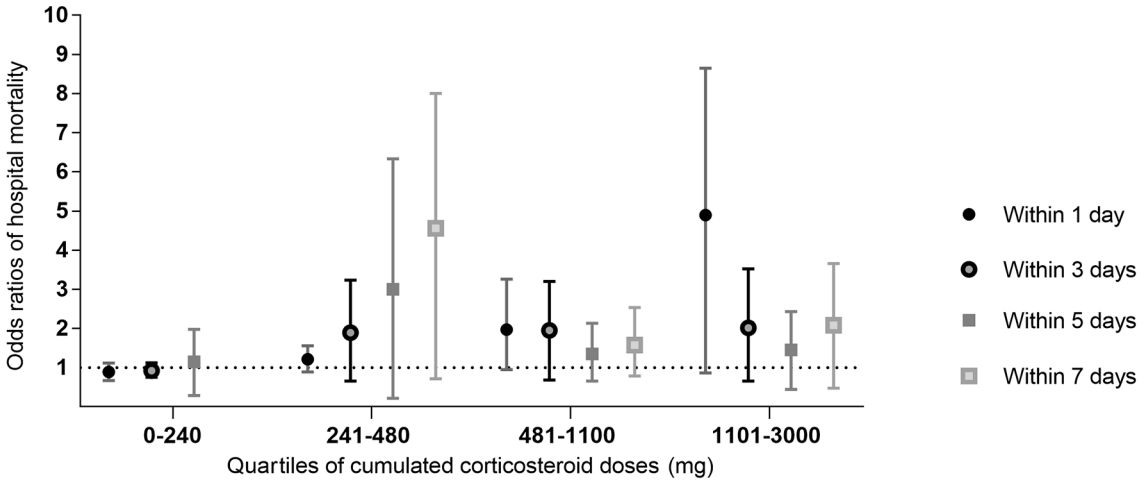
Data collection and patient grouping

The baseline characteristics of included patients were recorded on the day of ARDS onset, including age, sex, body mass index (BMI), Sequential Organ Failure Assessment (SOFA) score, partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FiO_2) in arterial blood gas analysis, the origin of ARDS, white blood cell count, lymphocyte count, granulocyte count, hemoglobin level and C-reactive protein level. All blood samples mentioned above were collected from arterial catheter. Variables that related to HSCT were also recorded at the same time point, including type of hematopoietic stem cell transplantation (allogeneic or autologous), post transplantation days, human leukocyte antigen (HLA) matching, graft *versus* host disease (GvHD) within 3 months, disease relapse after HSCT and the diagnosis of the malignancy.

Patients would be screened for suspicious infections with pathogen analysis by polymerase chain reaction (PCR) tests or pathogen culture, with samples from bronchoalveolar lavage fluids or blood; PCR tests for viremia were performed weekly during hospital stay for HSCT patients.

The following variables were recorded or analyzed at the time of discharge (from hospital) or death, including adjunctive therapies for ARDS, details of corticosteroid therapy (time of corticosteroid initiation relative to mechanical ventilation, type of drug administered, dosage and duration of the therapy) and outcomes of patients (hospital mortality, hospital days in survivors, ICU days in survivors, ventilator free days, duration of mechanical ventilation, new onset of bacteremia or viremia). Among the outcomes, hospital mortality is the primary outcome; others are secondary outcomes.

We performed a multivariate regression to test the effect of different accumulated doses (on various days after ARDS onset) of corticosteroids on hospital mortality (Figure 1), and not one combination indicated a significantly higher risk of in-hospital mortality. However, through multivariate logistic regression, if a patient received $\geqslant$480 mg of methylprednisolone or its equivalent within the first 3 days after ARDS onset, they had a significantly higher risk of new onset bacteremia or viremia, and a higher number of ventilator free days (see Supplemental Material Tables S2, S3, S4 of the Additional File 1 online). Thus, we made the definition of "early high dose steroids" as receiving an accumulated dose $\geqslant$480 mg of methylprednisolone or its equivalent within the first 3 days after ARDS onset. Patients were divided into early high dose steroids group and no early high dose steroids group. Patients in this cohort have a bodyweight ranging from 30 kg to 83 kg, thus the daily doses in the early high dose steroids



	At day 1	At day 3	At day 5 [1]	At day 7 [2]
0-240 mg	93	85	61	0
241-480 mg	57	34	22	12
481-1100 mg	48	53	76	85
1101-3000 mg	10	36	39	42

Number of patients with different cumulated steroid doses

Figure 1. Adjusted odds ratios of hospital mortality for various cumulated corticosteroid doses on different days after acute respiratory distress syndrome onset.
[1]At day 5, 10 patients had cumulative doses above the upper limit.
[2]At day 7, 69 patients had cumulative doses above the upper limit.
Odds ratios adjusted for risk factors of hospital mortality including granulocyte count, lymphocyte count, graft *versus* host disease within 3 months, Sequential Organ Failure Assessment score; see Table S1 in Supplemental File 1.

group are higher than 1–2 mg/kg of methylprednisolone in previous randomized controlled trails.[9,11]

Statistical analysis

The normality of data was tested using the Kolmogorov–Smirnov test. Normal distributed continuous variables were presented as mean ± standard deviation (normal distributed). Non-normal distributed variables were presented as median (interquartile range), categorical variables were presented as number (percentage). Comparison of two groups of continuous variables was performed with Student's *t*-test or Mann–Whitney *U* test as appropriate. Comparison of categorical variables was achieved using χ^2 test or Fisher's exact test as appropriate. Univariate and multivariate logistic models were used to investigate potential risk factors of hospital mortality, variables with a $p < 0.1$ in univariate analysis were entered into multivariate analysis, variables were selected with the backward stepwise elimination method. Cox proportional hazards regression was performed to evaluate the effects of variables on mortality. All tests were two-sided and $p < 0.05$ was considered statistically significant.

To account for the confounding effect from the indication of corticosteroid therapy and baseline imbalances between study groups, propensity score matching was performed on the complete cohort. Propensity scores were produced by a logistic regression model which included variables that may be associated with the indication of corticosteroid therapy (SOFA score, PaO_2/FiO_2 in arterial blood gas analysis, white blood cell count, C-reactive protein level, GvHD within 3 months) and baseline variables (age, sex, BMI). Matching was performed on a nearest neighbor basis, with 1:1 ratio without a replacement algorithm. The caliper was set at 0.02, post matching balance was evaluated with the standardized mean difference, the optimal balance was considered as <0.1. All previously mentioned analyses were re-performed in the matched cohort to validate the original conclusions.

All statistical analyses were performed on SPSS (Version 25, IBM Corp, Armonk, NY, USA), Some figures were illustrated with GraphPad Prism (Version 8.0, GraphPad Software, San Diego, CA, USA).

Results

Patients

Three hundred and ninety-eight patients with the diagnosis of HSCT and ARDS were admitted into the two study center in the study period; 134 patients were excluded (123 patients with previous application of corticosteroid or other immunosuppressive agents within 30 days prior to ARDS onset, five patients with corticosteroid therapy later than 7 days of ARDS onset, six patients with comorbidities that may be influenced by corticosteroid therapy). A total of 264 patients were included in the original study cohort; 89 (33.71%) patients received early high dose steroids, while 175 (66.29%) patients were without early high dose steroids. The baseline characteristics did not differ significantly between these two groups except for the sex ratio (Table 1).

Corticosteroid therapy

The details of corticosteroid therapy are presented in Table 2. In the original study cohort, 208 (78.79%) patients were treated with corticosteroid, among them 89 (33.71%) patients received $\geqslant$480 mg of methylprednisolone or its equivalent within the first 3 days after ARDS onset. The most frequently prescribed corticosteroid was methylprednisolone (85.23%), followed by dexamethasone (11.74%), prednisone (2.27%) and hydrocortisone (0.76%). Patients received a median dose of 88 (38–332) mg or 1.5 mg/kg methylprednisolone (or its equivalent) per day, the length of corticosteroid therapy was 15 (12–21) days. The median time from ARDS onset to corticosteroid therapy was 0 (0–2) days. PaO_2/FiO_2 on ARDS diagnosis before corticosteroid therapy was significantly lower than those without corticosteroid therapy (144.79 ± 25.38 *versus* 225.36 ± 15.21, $p < 0.001$).

Outcomes of patients with or without early high dose steroids

Table 3 records the outcomes of patients. There were no significant differences in hospital mortality between patients with early high dose steroids and patients without early high dose steroids (64.04% *versus* 53.14%, $p = 0.091$). Patients with early high dose steroids had a higher number of ventilator free days (7.65 ± 4.32 *versus* 6.48 ± 4.76, $p = 0.046$) and higher incidence of new onset bacteremia (17.98% *versus* 4%, $p < 0.001$) and new onset viremia (13.48% *versus* 3.43%, $p = 0.002$) than patients in the other group. Results of the blood culture and PCR tests are reported in Table S7 of the Supplemental File 1. No significant differences existed in hospital days, ICU days or duration of mechanical ventilation.

Adjusted odds ratios of different corticosteroid doses to hospital mortality

The effect of different cumulative corticosteroid doses (at different days after ARDS onset) on hospital mortality was further assessed by multivariate regression, with previously discovered risk factors (granulocyte count, lymphocyte count, GvHD within 3 months, SOFA score; see Table S1 in Supplemental File 1) and sex ratio also entered analysis. Doses of corticosteroid were divided into four quartiles (0–240 mg, 241–480 mg, 481–1000 mg, 1001–3000 mg). Figure 1 depicts the adjusted odds ratios of hospital mortality for various cumulated corticosteroid doses on different days after ARDS onset. Not a single combination of dose and days was an indicating factor of hospital mortality, even though odds ratios were higher for quartiles of 241–480 mg, 481–1000 mg, 1001–3000 mg.

Survival analysis

Figure 2 depicts the survival curve of patients with or without early high dose steroids through Cox regression, which was adjusted by risk factors of hospital mortality (granulocyte count, lymphocyte count, GvHD within 3 months, SOFA score) and baseline difference between the two study groups (sex). There was no difference of survival time between the two groups (log-rank $p = 0.172$).

Propensity score matching and validation of results in the matched cohort

A propensity score matched cohort was built to further validate the study results in the original study cohort. The baseline characteristics of the

Table 1. Baseline characteristics of patients with or without early high dose steroids before and after propensity score matching.

	Original study cohort				Matched cohort			
	No early high dose steroids *n* = 175–66.29%	**Early high dose steroids *n* = 89–33.71%**	***p***	**SMD**	**No early high dose steroids *n* = 65–50%**	**Early high dose steroids *n* = 65–50%**	***p***	**SMD**
Age, years[a]	39 ± 12.98	41 ± 15.62	0.27	0.144	39.83 ± 9.34	39.11 ± 7.06	0.62	0.087
Sex[a]			0.049	1.05			0.86	0.031
Female (%)	74 (42.28)	49 (55.06)			32 (49.23)	33 (50.77)		
Male (%)	101 (57.71)	40 (44.94)			33 (50.77)	32 (49.23)		
BMI[a], kg/m^2	21.74 ± 3.33	20.66 ± 6.27	0.069	0.238	21.17 ± 3.38	21.08 ± 2.94	0.872	0.028
SOFA score[a]	6.7 ± 2.47	7.5 ± 4.66	0.069	0.215	6.83 ± 2.76	6.70 ± 2.35	0.773	0.051
PaO_2/FiO_2[a], mmHg	147.25 ± 37.21	154.3 ± 67.76	0.276	0.129	154.66 ± 71.53	153.22 ± 52.33	0.896	0.023
Origin of ARDS			0.805	0.067			0.842	0.075
Pneumonia	156 (89.14)	77 (86.52)			57 (87.70)	58 (89.23)		
Sepsis	12 (6.86)	8 (8.99)			6 (9.23)	6 (9.23)		
Others	7 (4.00)	4 (4.49)			2 (3.07)	1 (1.54)		
Laboratory data								
WBC count[a], ×10^9/L	3.88 ± 3.21	3.35 ± 2.54	0.176	0.1770.142	3.52 ± 3.16	3.35 ± 2.01	0.715	0.064
Lymphocyte count, ×10^9/L	0.57 ± 0.65	0.49 ± 0.33	0.2760.403	0.11	0.58 ± 0.53	0.48 ± 0.42	0.235	0.209
Granulocyte count, ×10^9/L	3.47 ± 2.52	3.73 ± 2.09	0.339	0.125	3.49 ± 2.82	3.73 ± 2.17	0.856	0.095
Hemoglobin, g/dL	84.82 ± 19.35	82.55 ± 15.66	0.121	0.203	84.33 ± 19.05	81.54 ± 18.66	0.401	0.148
C-reactive protein[a], mg/L	19.58 ± 7.33	21.24 ± 9.67			20.52 ± 8.13	21.24 ± 10.16	0.656	0.078
Type of HSCT								
Allogenic	175 (100)	89 (100)	1	N/A	65	65	1	N/A
Autologous	0	0			0	0		
Post-transplantation days	170 (64–346)	165 (76–259)	0.312	0.026	167 (69–225)	165 (68–220)	0.624	0.086
HLA matching			0.641	0.068			0.716	0.073
Identical (%)	95 (54.29)	51 (57.31)			40 (61.54)	42 (64.62)		
Haploidentical (%)	80 (45.71)	38 (42.69)			25 (38.46)	23 (35.38)		
GvHD within 3 months[a]			0.105	0.259			0.704	0.079
Affected (%)	136 (77.71)	61 (68.54)			44 (67.69)	46 (70.77)		
Not affected (%)	39 (22.29)	28 (31.46)			21 (32.31)	19 (29.23)		
Disease relapse after HSCT			0.206	0.457			0.403	0.399
Affected (%)	10 (7.4)	3 (3.4)			4 (6.56)	2 (3.08)		
Not affected (%)	125 (92.6)	86 (96.6)			61 (93.85)	63 (96.92)		

(Continued)

Table 1. (Continued)

	Original study cohort				Matched cohort			
	No early high dose steroids *n* = 175–66.29%	**Early high dose steroids *n* = 89–33.71%**	***p***	**SMD**	**No early high dose steroids *n* = 65–50%**	**Early high dose steroids *n* = 65–50%**	***p***	**SMD**
Type of malignancy			0.268	0.067			0.674	0.234
Acute myelogenous leukemia	59	35			28	30		
Acute lymphocytic leukemia	47	38			16	26		
Chronic myelocytic leukemia	12	3			9	2		
Myelodysplastic syndrome	10	5			9	4		
Lymphoma	3	3			2	1		
Multiple myeloma	2	4			0	2		
Other malignancy	2	1			1	0		
Adjunctive therapies								
Prone positioning	11 (6.29)	5 (5.62)	0.83	0.028	3 (4.62)	2 (3.08)	0.648	0.081
Neuromuscular blockade	7 (4.00)	9 (10.1)	0.089	0.258	3 (4.62)	5 (7.70)	0.465	0.115
ECMO	2 (1.14)	3 (3.37)	0.209	0.164	0 (0)	1 (1.54)	0.323	0.177

Values are given as mean ± standardized deviation, median (interquartile range) or number (%).
[a]This variable was matched by propensity score matching.
ARDS, acute respiratory distress syndrome; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; GvHD, graft *versus* host disease; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; N/A, not applicable; PaO_2, partial pressure of oxygen in arterial blood; SMD, standardized mean difference; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell.

matched cohort were presented in Table 1. As evaluated by standardized mean difference, most variables were well balanced between the two groups. In the matched cohort, 65 patients received early high dose steroids while the other 65 patients did not.

Outcomes of patients in the matched cohort are recorded in Table S5 in Supplemental File 1. There was no difference of hospital mortality, hospital days (in survivors), ICU days (in survivors), and duration of mechanical ventilation between the two groups. The higher number of ventilator free days in the early high dose steroids group that was observed in the original study cohort did not exist in the matched cohort (6.02 ± 5.51 *versus* 5.57 ± 5.54, $p = 0.643$). Higher incidences of new onset bacteremia (18.46% *versus* 3.08%, $p = 0.005$) and viremia (15.38% *versus* 4.62%, $p = 0.041$) were validated in the matched cohort.

As presented in Supplemental Table S6, through univariate and multivariate regression, early high dose steroids was not an indicating factor for hospital mortality (odds ratio 1.27, 95% confidence interval 0.763–1.964, $p = 0.117$). In Cox regression (Supplemental Figure S1), after adjusting for risk factors of hospital mortality in the matched cohort (granulocyte count, lymphocyte count, SOFA score) there was no difference of survival time between the two study groups (log-rank $p = 0.253$).

Discussion

The use of corticosteroids in patients with ARDS is still controversial. In patients after HSCT, no study had previously focused on this issue. In the present cohort of HSCT patients with ARDS, early high dose steroids was not related to hospital mortality in either the original study cohort or the propensity score matched cohort. In addition, the incidence of

Table 2. Details of corticosteroid therapy in included hematopoietic stem cell transplantation patients with ARDS.

	Number (%), median (interquartile range) or mean ± standardized deviation
Corticosteroid therapy	208 (78.79)
Early high dose steroids[a]	89 (33.71)
Types of corticosteroid	
Methylprednisolone	225 (85.23)
Dexamethasone	31 (11.74)
Prednisone	6 (2.27)
Hydrocortisone	2 (0.76)
Length of corticosteroid therapy, days	15 (12–21)
Methylprednisolone equivalent doses per day, mg	88 (38–332)
Methylprednisolone equivalent doses per day, mg/kg	1.50 (0.62–5.85)
Duration between ARDS onset and corticosteroid therapy, days	0 (0–2)
PaO_2/FiO_2 on ARDS diagnosis before corticosteroid therapy, cmH_2O[b]	144.79 ± 25.38

[a]Received ⩾480 mg of methylprednisolone or its equivalent within the first 3 days after ARDS onset.
[b]Significant when compared with PaO_2/FiO_2 on ARDS diagnosis for patients without corticosteroid therapy, which was 211.36 ± 15.21 cmH_2O ($p < 0.001$).
ARDS, acute respiratory distress syndrome; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen in arterial blood.

Table 3. Comparison of outcomes between patients with or without early high dose steroids in original cohort.

	No early high dose steroids	Early high dose steroids	*p*
Hospital days in survivors	15 (8–33)	32 (8–41)	0.279
ICU days in survivors	9 (5–15)	6 (3–15)	0.233
Hospital mortality (%)	93 (53.14)	57 (64.04)	0.091
Ventilator free days at day 28	6.48 ± 4.76	7.68 ± 4.32	0.046
Duration of mechanical ventilation, days	9 (5–14)	6 (4–13)	0.428
New onset bacteremia (%)	7 (4.00)	16 (17.98)	<0.001
New onset viremia (%)	6 (3.43)	12 (13.48)	0.002

Values are given as median (interquartile range), mean ± standardized deviation or number (%).
ICU, intensive care unit.

new onset bacteremia and viremia increased significantly after early high dose steroids.

In our cohort, a substantial proportion (78.79%) of patients were treated with corticosteroids, higher than previous studies[17,18] on different populations (57.6–71.5%). The propensity for corticosteroid use in these patients might be due to the experience of physicians in using corticosteroids for acute respiratory failure of various causes in

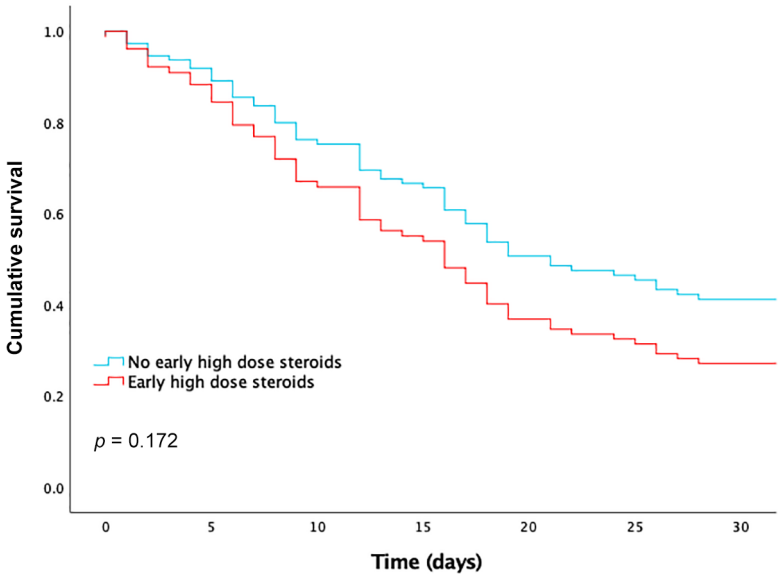


Figure 2. Survival curve of patients with or without early high dose steroids after acute respiratory distress syndrome onset. Adjusted by risk factors of hospital mortality (granulocyte count, lymphocyte count, graft *versus* host disease within 3 months, Sequential Organ Failure Assessment score) and baseline difference between the two study groups (sex). No difference in survival time between the two groups (log rank $p = 0.172$).

HSCT patients, as reported in previous studies.[13–15] On the other hand, there were only 56 patients without corticosteroid therapy, whose severity of ARDS was much lower than those treated with corticosteroids (Table 2), and the small sample size had limited the process of propensity score matching, which made the direct comparison of treatments with or without corticosteroids ineffective. Therefore, we focused mainly on evaluating unconventional high dose treatments, as previously defined as "early high dose steroids".

Studies[9,10,19] with varying levels of evidence have reported improvement in survival or prolongation of ventilator free days[10,11] with corticosteroid in ARDS patients, while some studies[11,12] failed to validate this benefit. In the 2017 European Society of Intensive Care Medicine guideline,[20,21] corticosteroids were recommended for patients with community acquired pneumonia, septic shock and ARDS. In a recent randomized controlled trial, Villar *et al.*[10] found a survival benefit from early use of dexamethasone in a group of patients in whom approximately 75% of ARDS was caused by sepsis or pneumonia, suggesting that patients with certain comorbidities may benefit more from corticosteroids and their anti-inflammatory effects.[22] In contrast, patients in our cohort rarely had a diagnosis of sepsis, and rarely had high markers of inflammation – high leukocyte counts or C-reactive protein levels (Table 1). Moreover, etiologic analysis of patients who received bronchoalveolar lavage and pathogen PCR testing showed that (in patients with positive PCR) more than half of the cases of ARDS were from viral pneumonia (Supplemental File 1, Table S8), a similar finding was reported in a previous study.[23] No studies were focusing on corticosteroids in non-influenza viral pneumonia, but no corticosteroid associated improvement of survival was observed in influenza pneumonia,[24,25] all of which may explain why the patients in our study did not benefit from early use of corticosteroids.

Even though the general role of corticosteroid therapy is still not clear in patients with ARDS, many studies[18,26,27] have reported a possible worsening of prognosis with high doses of corticosteroids. In their 1987 randomized controlled trail, Bernard *et al.*[26] set criteria of high dose as 30 mg/kg of methylprednisolone every 6 h for 24 h; no survival benefit was found in the high dose group as compared with the control group. Tataki *et al.*[27] found that an initial dose of 1000 mg methylprednisolone per day (for 3 days then tapered) was significantly associated with increased 60-day mortality and low ventilator free days. A recent study[18] using the Japanese nationwide database suggested a higher mortality rate within 3 months in patients who received more than 500 mg of methylprednisolone for at least 1 day. In our study, patients with unconventional cumulative methylprednisolone doses on different days after ARDS onset had high adjusted odds ratios for hospital mortality (Figure 1), although none was significant – which may result from the limited sample size on each dosing level.

Another phenomenon we observed in the study cohort was an increased incidence of new-onset bacteremia or viremia in patients on early high dose steroids; even after propensity score matching, the difference was still significant. Corticosteroid, as a commonly used agent immune suppression after HSCT, has been identified as a risk factor for various viremias and bacteremias.[28–30] As reported by a recent study,[31]

a higher cumulative corticosteroid dose within 30 days after HSCT (>7 mg/kg of prednisolone or its equivalents) was a predictive factor for future bacteremia or cytomegalovirus (CMV) viremia. In the present study, corticosteroids were used in patients with a long post-HSCT day length (Table 1, median 150 days), but high cumulative doses were also associated with a higher incidence of bacteremia and viremia, indicating that the influence of corticosteroids may not be relevant to post transplantation days. CMV viremia after HSCT was associated with an increased 1-year mortality of up to 25.5%,[32] and the 1-year mortality of patients with bacteremia was approximately 50% in one study.[33]

The result of this study must be comprehended in the context of several limitations. (1) Due to the observational nature of our study, not all potential confounding factors can be adjusted for in the analysis. Although propensity score matching may yield a well-matched study cohort, some undetected confounding factors may still exist. However, this is the first study focusing on the effect of corticosteroid in HSCT patients with ARDS. Our findings may provide clinicians with a better reference in the treatment of this specified patient group, and support the design of studies with a more reasonable methodology. (2) We have used multiple analyses to generate a cutoff value (480 mg) of steroid dose; this will cause a minor bias that exaggerates the test performance.[34] However, there are no previous study that focused on steroids for ARDS in patients after HSCT; the cutoff value derived from the general population may not fit well in HSCT patients. It is necessary to test this cutoff value in further studies. (3) Limited by our data resources, not all related parameters can be retrieved in this study. For example, we do not have complete data on blood glucose level to evaluate the incidence of hyperglycemia, which is another adverse effect of corticosteroid. In addition, we have not performed a complete follow-up in all patients, so the long-term survival cannot be evaluated either. (4) Adjunctive treatments for severe ARDS, especially extracorporeal membrane oxygenation, were rarely used in our cohort, which may be related to the poor coagulation function and high risk of catheter-related infections in most HSCT patients, so the impact of these therapies cannot be fully assessed in our study.

Conclusion

In this cohort of HSCT patients with ARDS, early high dose corticosteroids had no effect on hospital mortality. In addition, the incidences of new onset bacteremia and viremia were increased after early high dose steroids.

Author contributions

YH and SL were responsible for study concept and design. YH and JS were responsible for the acquisition, statistical analysis, and interpretation of the data. YH drafted the manuscript. YA and SL were responsible for the critical revision of the manuscript. All authors read and approved the final manuscript.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethics approval and consent to participate

The Science and Ethics Committee of Peking University International Hospital and Peking University Peoples' Hospital approved this retrospective study and waived the need for informed consent.

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Supplemental material

The reviews of this paper are available via the supplemental material section.

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