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Effect of methylprednisolone vs hydrocortisone on 30-day mortality in critically ill adults with septic shock: an analysis of the MIMIC-IV database

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Abstract

Background Methylprednisolone is still used to treat adults with septic shock in real-world clinical settings, despite current international guidelines recommending hydrocortisone. The aim of this study was to assess the effect of methylprednisolone vs hydrocortisone on 30-day mortality among critically ill patients with septic shock.

Methods We conducted a retrospective cohort study on adults with septic shock using the MIMIC-IV v3.0 database. Patients who received methylprednisolone after diagnosis were matched using propensity score matching (PSM) with those received hydrocortisone, to balance confounding factors between groups. The primary outcome was the 30-day mortality rate. Subgroup and sensitivity analyses were performed to assess the robustness of the conclusions.

Results A total of 1,607 septic shock patents were enrolled in this study, with an overall 30-day mortality rate of 42.1%. After 1:1 PSM, 376 pairs were successfully matched. The primary outcome occurred in 141 patients (37.5%) and in 131 patients (34.8%) in the methylprednisolone and hydrocortisone groups, respectively (HR = 1.105, 95% CI: 0.871–1.402, $P = 0.410$). In subgroup analyses based on age, sex, blood culture positivity, pneumonia, and invasive mechanical ventilation (IMV), along with sensitivity analyses for deletion of missing values, findings remained consistent. However, the methylprednisolone group exhibited a longer ICU stay, elevated blood glucose levels, and a shorter maintenance duration for vasopressin compared to the hydrocortisone group.

Conclusions Among adults with septic shock, there was no significant difference in 30-day mortality between those administered methylprednisolone and hydrocortisone. It needs to be further verified in prospective, randomized controlled trials.

Keywords Methylprednisolone, Hydrocortisone, Septic shock, MIMIC-IV database, Propensity score matching

Introduction

Sepsis is defined as life-threatening organ dysfunction due to infection and is recognized as a global health priority [1]. It is estimated to cause 48.9 million cases worldwide annually, resulting in 11 million deaths and accounting for 19.7% of all global mortality [2]. In China, sepsis affects one-fifth of ICU patients, with an ICU incidence rate of 20.6%. The ICU mortality rate and 90-day

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mortality rate in China are 29.6% and 35.5%, respectively. If sepsis progresses to septic shock, the mortality rate can significantly increase to 51.94% [3]. Consequently, the international guidelines for managing sepsis and septic shock undergo updates every few years, with evidence-based recommendations proposed to guide clinicians.

Corticosteroids have been used as adjunctive therapy for severe infections in the ICU for several decades [4]. Intravenous (IV) corticosteroids are administered to restore vascular responsiveness to catecholamine in these patients. The Surviving Sepsis Campaign (SSC) 2021 guidelines recommend IV hydrocortisone for adults with septic shock who have an ongoing requirement for vasopressor therapy [5].

However, it is a weak recommendation with moderate-quality evidence. The 2024 focused update still suggests administering corticosteroids to adults with septic shock but recommends against the use of high-dose, short-duration corticosteroids (>400 mg/day hydrocortisone equivalent for <3 days) [6]. A meta-analysis has indicated that IV corticosteroids may reduce the duration of vasopressor therapy, invasive mechanical ventilation (IMV), and ICU length of stay (LOS), though without significant impact on either short- or long-term mortality [7]. Nevertheless, several randomized controlled trials (RCTs) have evaluated the efficacy of low-dose corticosteroids in reducing mortality in septic shock, with a primary focus on glucocorticoids such as hydrocortisone (with or without fludrocortisone) [8–11]; in contrast, few studies have assessed methylprednisolone, except in the context of severe community-acquired pneumonia [12, 13]. Although the guidelines recommend hydrocortisone, methylprednisolone remains used in real-world clinical practice.

Therefore, we plan to conduct an observational cohort study using the Medical Information Mart for Intensive Care (MIMIC-IV) v3.0 database to provide further guidance on the clinical use of corticosteroids. Specifically, our aim is to compare the therapeutic effects of methylprednisolone and hydrocortisone in critically ill adults with septic shock.

Methods

Database

The study data was extracted from the MIMIC-IV v3.0 database [14, 15], which include over 94,458 critically ill patients admitted to the Beth Israel Deaconess Medical Center (BIDMC) ICU from 2008 to 2022. As the study utilized a pre-existing, de-identified public database, which had already received Institutional Review Board (IRB) approval, the patient's informed consent was waived. All methods were performed in accordance with the relevant guidelines and regulations. We obtained the data use agreement for the MIMIC-IV (v3.0) after we completed the Collaborative Institutional Training Initiative (CITI) Program course and passed the online exams (record ID: 48615099).

Patients

Our study's inclusion criteria were as follows: 1) adults (age ≥ 18 years old) were admitted to ICU with a diagnosis of sepsis based on Sepsis-3 criteria [1], which occurred less than one day before or after ICU admission; 2) only data from the patient's first admission to the ICU was included; 3) patients with septic shock were identified with hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) of at least 65 mm Hg and a serum lactate level greater than 2 mmol/L; 4) methylprednisolone or hydrocortisone was administered individually within 48 h of septic shock onset. Patients who satisfied all of these requirements were included in our analysis. Furthermore, multiple imputation by chained equations (MICE) was used to address missing values under 10%.

Outcomes

The primary outcome was 30-day mortality from the first day of ICU admission. Secondary outcomes included 90-day mortality, peak blood glucose levels within 48 h of IV corticosteroid administration, duration of various vasopressors, duration of IMV and continuous renal replacement therapy (CRRT), and length of ICU and hospital stays.

Variables

Data in the original dataset included: identification number, age, sex, weight, comorbidities (diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease (COPD), chronic renal disease, liver cirrhosis, carcinoma, and metastatic cancer), laboratory tests (white blood cell (WBC) count, hemoglobin, platelet count, sodium, chloride, bicarbonate, creatinine, lactate, prothrombin time (PT), and blood glucose), severity at ICU admission measured by sequential organ failure assessment (SOFA) score and simplified acute physiology score II (SAPS II) score, diagnosed with COVID-19, pneumonia, or acute respiratory distress syndrome (ARDS), time from hypotension to vasopressor administration, blood culture positivity, urine output, as well as outcomes at ICU discharge and hospital discharge (such as being alive, transferred, or deceased). Additionally, information about the use of fluid administration, antibiotics, thiamine, various vasopressors (such as norepinephrine, epinephrine, dopamine, and vasopressin), corticosteroids, IMV, and CRRT at septic shock onset

also need to be obtained, as well as their start and end times.

The Sepsis-3 criteria for sepsis were extracted as suspected infection with associated organ dysfunction (SOFA ≥ 2) [1]. The septic shock onset was defined as the time of catecholamine vasopressor initiation to maintain MAP ≥ 65 mm Hg.

Statistical methods

Continuous variables are expressed as the mean (± standard deviation) or median (IQR 25%–75%), and categorical variables were reported with a number (%). For a two-group comparison, statistical significance was tested with a Student's t-test or Mann–Whitney U test for the continuous variables and a Chi-square test or Fisher's exact test for the categorical variables, as appropriate. All statistical analyses and drawing were performed using R language v4.4.1 or python v3.9.12. A two-sided analysis with a $p < 0.05$ was considered statistically significant.

Propensity score matching (PSM) analysis was conducted with the 1:1 optimal matching method and a caliper width of 0.05 by the "MatchIt" package in R software to establish a balance in baseline characteristics between the methylprednisolone and hydrocortisone groups. We subsequently compared the effects of methylprednisolone and hydrocortisone on primary and secondary outcomes among septic shock patients. A Cox proportional-hazard model was applied for 30-day mortality after testing the proportional hazards assumption, and Kaplan–Meier survival curves were generated to show survival probabilities between the two groups. The hazard ratio (HR) and 95% confidence interval (CI) were calculated. Subgroup analyses for the primary outcome by age, sex, carcinoma, blood culture positivity, and IMV status were performed, and an interaction *p*-value across subgroups was also calculated. A sensitivity analysis was conducted with missing data excluded.

Results

Cohort characteristic

The flowchart of the study cohort selection was shown in Fig. 1. The final cohort consisted of 1,607 adults with septic shock, with 555 patients in the methylprednisolone group and 1,052 patients in the hydrocortisone group. Table 1 presented the principal baseline characteristics of the two groups in this study. Before PSM, patients receiving hydrocortisone were older and more likely to have comorbidities (e.g., chronic heart failure, chronic renal disease, and metastatic cancer). They exhibited higher levels of WBC, PT, creatinine, and lactate, significantly higher SOFA and SAPS II scores, and more frequent use of norepinephrine, epinephrine, vasopressin, antibiotics, thiamine, and CRRT at the onset of shock. Additionally, these patients were more likely to have positive blood cultures and COVID-19. Conversely, the methylprednisolone group exhibited a higher incidence of COPD and liver cirrhosis, elevated levels of hemoglobin, sodium, and bicarbonate, a lower volume of IV fluids on day one, duration of corticosteroid, and greater use of IMV at shock onset.

After 1:1 PSM, 752 septic shock patients were matched: 376 in the methylprednisolone group and 376 in the hydrocortisone group. The baseline characteristics of all variables were well-balanced, with a *P*-value greater than 0.05. The absolute standardized mean differences between the original and matched cohorts were compared, as shown in Figure S1.

Primary outcome and secondary outcomes

After PSM, the primary outcome of 30-day mortality was similar in the two groups was similar (37.5% vs 34.8%, $P = 0.495$) (Table 2). No statistical difference was also observed between the two groups based on the Kaplan–Meier survival curve analysis (HR = 1.105, 95% CI: 0.871–1.402, $P = 0.410$), which was shown in Fig. 2.

Additionally, regarding secondary outcomes, the 90-day mortality rate was similar between the two groups (42.8% vs 43.1%). However, the methylprednisolone group exhibited a longer ICU stay, elevated blood glucose levels, and a shorter maintenance duration for vasopressin compared to the hydrocortisone group. The durations of norepinephrine, epinephrine, dopamine, and CRRT, as well as the hospital LOS, showed no significant differences between the two groups.

Subgroups analysis

In a subgroup analysis according to age, sex, blood culture positivity, pneumonia, and IMV, no statistical difference in 30-day mortality rate was observed between the two patient groups (Fig. 3). Additionally, all *p*-values of proportional hazard assumptions exceeded 0.05.

Sensitivity analyses

A sensitivity analysis was also conducted on the dataset without missing values, resulting in the matching of 313 pairs (Table S1 and S2). The baseline characteristics of the two groups after PSM are also balanced, as shown in Figure S2. Finally, the 30-day mortality rate after the deletion of missing values in sensitivity analyses also showed no statistically significant difference between the two groups (HR = 1.051, 95% CI: 0.808–1.366, $P = 0.720$) (Fig. 4).

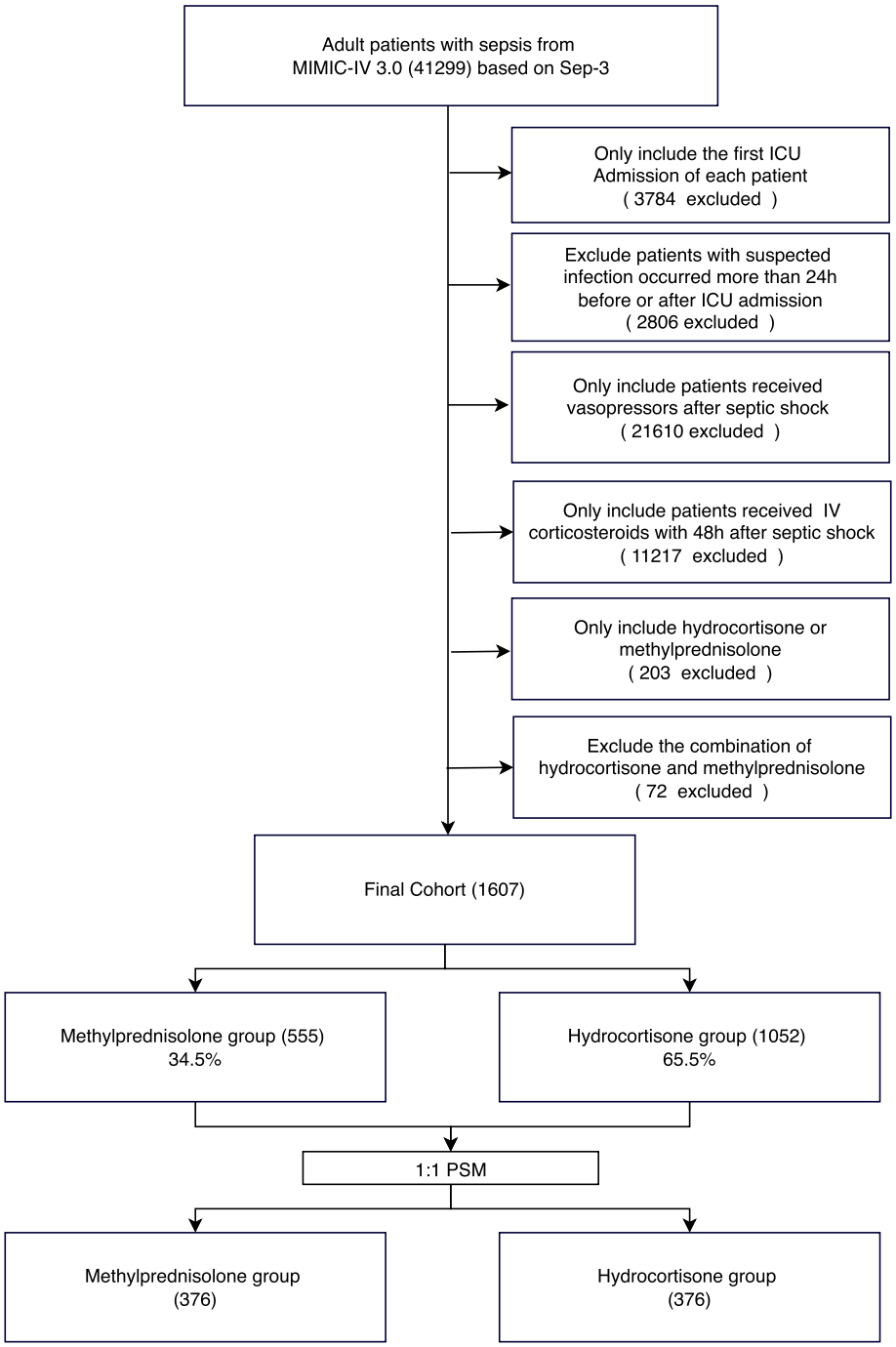

Fig. 1 Flow diagram of the patient inclusion and exclusion process. MIMIC, Medical Information Mart in Intensive Care; ICU, intensive care unit; IV, intravenous; PSM, propensity score matching

Discussion

In this retrospective cohort study, we found no significant difference in 30-day mortality between the methylprednisolone and hydrocortisone groups in the matched analysis of critically ill adults with septic shock. The same conclusion was reached in the sensitivity analysis after the deletion of missing values. In subgroups grouped according to age, sex, blood culture positivity, pneumonia, and IMV, the results still did not change. However, the methylprednisolone group exhibited higher blood glucose levels, and a shorter maintenance duration of vasopressin compared to the

Table 1 Distribution of covariates of interest in the before and after propensity score matching cohort

Variables	Original cohort			Matched cohort			Missing data (%)
	Methylprednisolone group	Hydrocortisone group	P	Methylprednisolone group	Hydrocortisone group	P	
N	555	1052		376	376		NA
Age, yr, [Median (IQR)]	64.0 [55.0, 74.0]	69.0 [58.8, 78.0]	< 0.001	65.0 [56.0, 76.0]	67.0 [57.0, 77.0]	0.323	0.0
Male, n (%)	235 (42.3)	463 (44.0)	0.556	174 (46.3)	170 (45.2)	0.826	0.0
Weight, kg, [Median (IQR)]	80.0 [66.9, 97.0]	78.6 [64.8, 94.4]	0.342	78.8 [66.8, 93.0]	76.0 [64.0, 93.1]	0.284	0.0
Comorbidities, n (%)							
Diabetes mellitus	159 (28.6)	330 (31.4)	0.285	113 (30.1)	106 (28.2)	0.630	0.0
Chronic heart failure	158 (28.5)	400 (38.0)	< 0.001	127 (33.8)	131 (34.8)	0.818	0.0
COPD	236 (42.5)	327 (31.1)	< 0.001	145 (38.6)	147 (39.1)	0.940	0.0
Chronic renal disease	119 (21.4)	314 (29.8)	< 0.001	94 (25.0)	91 (24.2)	0.866	0.0
Liver cirrhosis	167 (30.1)	234 (22.2)	0.001	96 (25.5)	86 (22.9)	0.444	0.0
Carcinoma	121 (21.8)	210 (20.0)	0.422	79 (21.0)	79 (21.0)	1.000	0.0
Metastatic cancer	23 (4.1)	89 (8.5)	0.002	20 (5.3)	19 (5.1)	1.000	0.0
Laboratory variables, [Median (IQR)]							
WBC	14.9 [10.1, 19.0]	17.1 [10.8, 24.7]	< 0.001	15.3 [10.4, 20.0]	15.5 [11.0, 22.1]	0.246	1.2
Hemoglobin	9.3 [8.0, 10.8]	9.1 [7.7, 10.6]	0.009	9.3 [7.8, 10.5]	9.3 [8.0, 10.8]	0.395	1.1
Platelet	149.0 [79.0, 222.5]	146.0 [79.7, 220.0]	0.923	152.5 [82.0, 228.3]	147.0 [85.0, 212.3]	0.764	1.1
PT	16.5 [13.6, 23.8]	18.9 [15.1, 26.1]	< 0.001	16.5 [13.8, 23.8]	17.4 [14.4, 23.8]	0.126	6.5
Creatinine	1.4 [1.0, 2.2]	1.9 [1.2, 3.1]	< 0.001	1.5 [1.1, 2.3]	1.4 [0.9, 2.4]	0.195	1.1
Lactate	3.3 [1.8, 5.2]	4.4 [2.1, 7.7]	< 0.001	3.3 [1.9, 5.3]	3.3 [1.9, 5.2]	0.935	5.9
Bicarbonate	20.0 [17.0, 24.0]	17.0 [12.0, 21.0]	< 0.001	19.0 [16.0, 22.0]	20.0 [16.0, 23.0]	0.597	1.1
Sodium	141.0 [138.0, 144.0]	140.0 [136.0, 143.0]	< 0.001	140.0 [137.0, 143.0]	140.0 [137.0, 143.0]	0.924	1.1
Chloride	106.0 [102.0, 110.0]	106.0 [101.0, 110.0]	0.603	106.0 [102.0, 110.0]	106.0 [102.00, 110.3]	0.399	1.1
Blood culture positive, n (%)	52 (9.4)	192 (18.3)	< 0.001	44 (11.7)	37 (9.8)	0.480	0.0
Scoring system, [Median (IQR)]							
SAPS II	42.0 [35.0, 53.0]	50.0 [39.0, 63.0]	< 0.001	44.5 [36.0, 55.0]	44.5 [35.0, 56.3]	0.999	0.0
SOFA	4.0 [3.0, 6.0]	4.0 [3.0, 6.0]	0.001	4.0 [3.0, 6.0]	4.0 [3.0, 5.0]	0.714	0.0
COVID-19, n (%)	1 (0.2)	20 (1.9)	0.008	1 (0.3)	1 (0.3)	1.000	0.0
ARDS, n (%)	310 (55.9)	575 (54.7)	0.684	201 (53.5)	204 (54.3)	0.884	0.0
Characteristics at shock onset							
IV fluid day 1, mL, [Median (IQR)]	3635.1 [2178.8, 5766.6]	4570.9 [2600.3, 7664.5]	< 0.001	3947.9 [2268.1, 6053.8]	3604.5 [2116.8, 5663.2]	0.264	0.0
Norepinephrine, n (%)	401 (72.3)	958 (91.1)	< 0.001	304 (80.9)	305 (81.1)	1.000	0.0
Epinephrine, n (%)	34 (6.1)	234 (22.2)	< 0.001	32 (8.5)	37 (9.8)	0.613	0.0
Dopamine, n (%)	34 (6.1)	91 (8.7)	0.089	27 (7.2)	23 (6.1)	0.661	0.0
Vasopressin, n (%)	125 (22.5)	543 (51.6)	< 0.001	111 (29.5)	114 (30.3)	0.873	0.0
Antibiotics, n (%)	451 (81.3)	907 (86.2)	0.011	310 (82.4)	314 (83.5)	0.771	0.0
IV thiamine, n (%)	31 (5.6)	164 (15.6)	< 0.001	27 (7.2)	29 (7.7)	0.890	0.0
IMV, n (%)	457 (82.3)	730 (69.4)	< 0.001	282 (75.0)	288 (76.6)	0.670	0.0

Table 1 (continued)

Variables	Original cohort			Matched cohort			Missing data (%)
	Methylprednisolone group	Hydrocortisone group	P	Methylprednisolone group	Hydrocortisone group	P	
CRRT, n (%)	64 (11.5)	178 (16.9)	0.005	42 (11.2)	42 (11.2)	1.000	0.0
I/O balance within 7 days, mL, [Median (IQR)]	−455.8 [−3961.9, 3776.6]	3129.8 [−468.4, 9232.5]	< 0.001	488.6 [−2902.8, 4533.2]	924.1 [−2956.7, 4656.4]	0.851	0.0
Dose of corticosteroids, mg/day, [Median (IQR)]	73.6 [27.8, 175.0]	50.0 [25.0, 83.3]	< 0.001	65.8 [26.7, 150.0]	50.0 [25.0, 75.0]	< 0.001	0.0
Duration of corticosteroids, d, [Median (IQR)]	3.0 [2.0, 5.0]	2.0 [1.0, 4.0]	< 0.001	3.0 [1.0, 5.0]	3.0 [1.0, 4.3]	0.097	0.0

Abbreviations: *IQR* interquartile range, *COPD* chronic obstructive pulmonary disease, *WBC* white blood cell, *PT* prothrombin time, *SOFA* sequential organ failure assessment, *SAPS II* simplified acute physiology score II, *ARDS* acute respiratory distress syndrome, *IV* Intravenous, *IMV* invasive mechanical ventilation, *CRRT* continuous renal replacement therapy, *I/O* input/output

Table 2 Primary and secondary outcomes analysis between the original cohort and the matched cohort

Outcomes	Original cohort			Matched cohort		
	Methylprednisolone group	Hydrocortisone group	p	Methylprednisolone group	Hydrocortisone group	p
n	555	1052		376	376	
Primary outcome						
30-day mortality, n (%)	185 (33.3)	492 (46.8)	< 0.001	141 (37.5)	131 (34.8)	0.495
Secondary outcomes						
90-day mortality, n (%)	215 (38.7)	569 (54.1)	< 0.001	161 (42.8)	162 (43.1)	1.000
Norepinephrine duration, h, [Median (IQR)]	25.0 [8.6, 48.3]	33.2 [14.0, 67.6]	< 0.001	25.9 [10.9, 51.3]	28.4 [11.9, 57.1]	0.306
Epinephrine duration, h, [Median (IQR)]	4.4 [1.4, 15.9]	9.0 [3.6, 19.1]	0.014	5.2 [1.5, 15.2]	8.5 [3.9, 16.9]	0.124
Dopamine duration, h, [Median (IQR)]	10.1 [2.4, 18.3]	6.8 [2.6, 20.6]	0.533	11.5 [3.4, 20.6]	6.6 [2.9, 16.8]	0.492
Vasopressin duration, h, [Median (IQR)]	20.4 [7.6, 36.6]	32.6 [15.7, 65.5]	< 0.001	20.8 [7.3, 36.5]	31.4 [17.4, 58.3]	< 0.001
Length of IMV, d, [Median (IQR)]	3.0 [1.0, 6.0]	2.0 [1.0, 6.0]	0.187	3.0 [1.0, 6.5]	2.0 [1.0, 6.0]	0.068
Length of CRRT, d, [Median (IQR)]	3.0 [1.0, 7.0]	3.0 [1.0, 7.0]	0.376	3.0 [1.0, 7.0]	2.0 [1.0, 5.5]	0.248
ICU LOS, d, [Median (IQR)]	5.0 [3.0, 10.0]	4.0 [2.0, 8.0]	< 0.001	5.0 [3.0, 9.0]	4.0 [2.0, 8.0]	0.013
Hospital LOS, d, [Median (IQR)]	11.0 [6.0, 21.0]	9.0 [4.0, 18.0]	< 0.001	11.0 [5.0, 21.0]	9.0 [5.00, 18.0]	0.181
Glucose, mg/dl, [Median (IQR)]	204.0 [152.0, 274.0]	179.0 [136.0, 248.0]	< 0.001	204.0 [152.0, 274.3]	169.0 [129.0, 225.0]	< 0.001

Abbreviations: *ICU* intensive care unit, *IQR* interquartile range, *IMV* invasive mechanical ventilation, *CRRT* continuous renal replacement therapy, *IV* intravenous, *LOS* length of stay

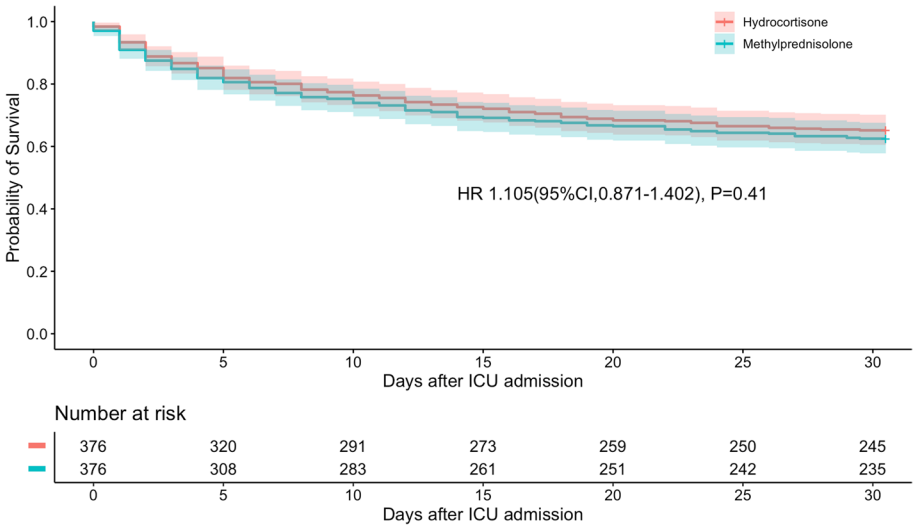

Fig. 2 Kaplan–Meier Analysis of Survival at 30 days. Shown is the percentage of patients who were alive at the 30-days after ICU admission (235 patients [62.5%] in the methylprednisolone group and 245 [65.2%] in the hydrocortisone group), which was a primary outcome in our study

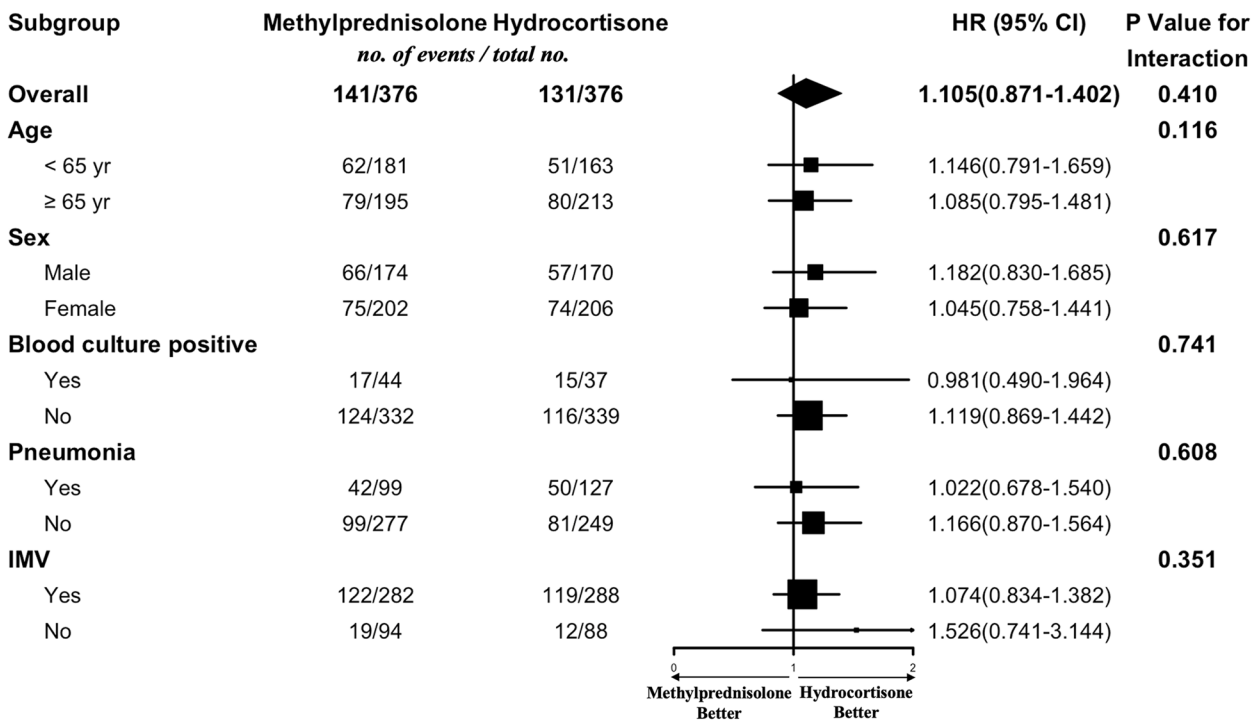

Fig. 3 Subgroup Analyses. Shown is the hazard ratio with 95% confidence intervals for the primary outcome in five prespecified subgroups. The size of each black box is proportional to the size of the corresponding subset. *P* values are for the interaction of the effect of the trial regimen on the primary outcome in each subgroup

hydrocortisone group, as revealed through our analysis of secondary outcomes.

Corticosteroids, a class of hormones produced by the adrenal cortex, exert a wide range of effects on the body, including anti-inflammatory, immunosuppressive, mineralocorticoid, and vasoactive effects [16]. Activation of the hypothalamic–pituitary–adrenal (HPA) axis during septic shock triggers the production of adrenocortical glucocorticoids, which are crucial for maintaining homeostasis. Nonetheless, the natural activation of

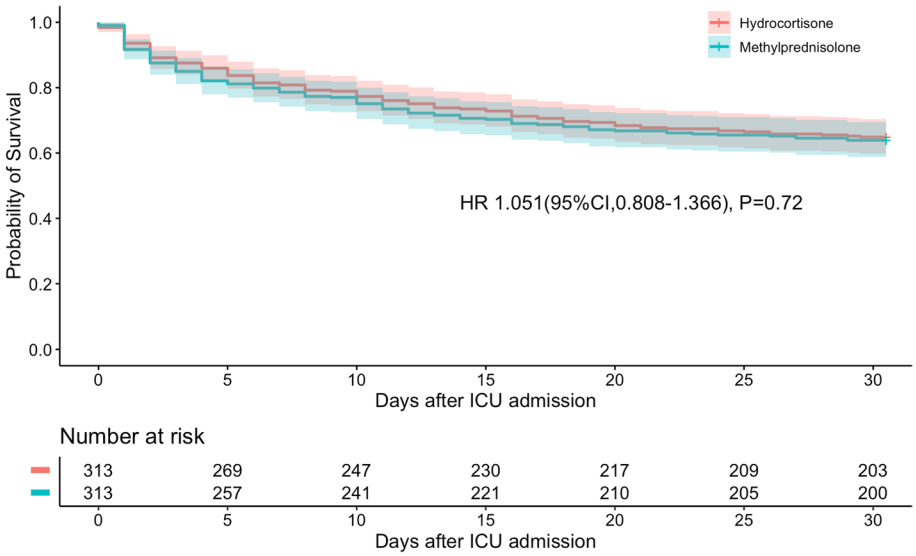

Fig. 4 Kaplan–Meier Analysis of Survival at 30 days after deleting missing values. Shown is the percentage of patients who were alive at the 30-days after ICU admission (200 patients [63.9%] in the methylprednisolone group and 203 [64.9%] in the hydrocortisone group)

adrenocortical hormones that regulate homeostasis is compromised in many critically ill patients. Research indicates that impairment of the HPA axis occurs in 10–20% of critically ill patients and increases to 60% in patients with septic shock [17]. Thus, corticosteroid supplementation appears reasonable for patients in septic shock with critical illness-related corticosteroid insufficiency (CIRCI) or glucocorticoid resistance. However, some studies suggest that a stress dose of hydrocortisone (200 mg/day) should not be used to treat patients with septic shock based on the assumption of insufficient cortisol supply or widespread glucocorticoid resistance [18].

It is widely known that the standard management of sepsis or septic shock includes controlling the source of infection, fluid resuscitation, administering oxygen with or without respiratory support, and using vasopressors as necessary. Despite over four decades of research, the use of corticosteroids as an adjunctive treatment for sepsis remains one of the most controversial aspects of sepsis management. In 2018, two important clinical trials, namely the ADRENAL trial (Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock) and the APROCCHSS trial (Activated Protein C and Corticosteroids for Human Septic Shock), were published in *The New England Journal of Medicine*. They reported no survival benefits or, at best, a slight reduction in mortality with low-dose corticosteroid treatment for septic shock, but patients treated with corticosteroids in both studies experienced significantly shorter times to resolution of shock, cessation of MV and discharge from the ICU [10, 11]. Thus, the SCC 2021 guidelines suggest using IV hydrocortisone rather than methylprednisolone for patients with septic shock who require ongoing vasopressor therapy [19]. Despite this fact, methylprednisolone use is still found in some literatures [12, 20] and in a real-world setting. Therefore, we designed this study to compare the therapeutic impacts of methylprednisolone and hydrocortisone for patients with septic shock.

The typical corticosteroid used in adults with septic shock is IV hydrocortisone at a dose of 200 mg/day given as 50 mg intravenously every 6 h or as a continuous infusion [19]. It is important to note that not all corticosteroids are the same. Different types of corticosteroids can have different glucocorticoid and mineralocorticoid effects to a varying degree of potency, even at equivalent doses [16]. The major difference between methylprednisolone and hydrocortisone is that methylprednisolone boasts greater relative glucocorticoid potency, whereas hydrocortisone has the advantage of possessing higher relative mineralocorticoid potency. The glucocorticoid potency leads to greater anti-inflammatory capacity, and the mineralocorticoid potency results in fluid and sodium retention in the blood vessels. However, our study revealed no significant difference in 30-day mortality between methylprednisolone and hydrocortisone for critical ill adults with septic shock. Our results are consistent with the findings of the Yu et al. study [21], although the patient numbers in their work were very small. The mineralocorticoid potency of hydrocortisone does not appear to improve outcomes in patients with septic shock, and subgroup analyses, including those with pneumonia, have not shown any advantage.

Consequently, an increasing number of studies are proposing a combination treatment option that involves adding fludrocortisone to hydrocortisone [22]. A systematic review and Bayesian network meta-analysis by Lai et al. showed that the combination of hydrocortisone and fludrocortisone improved short-term survival with minimal adverse events in adults with septic shock compared to hydrocortisone alone or placebo [23]. Another meta-analysis corroborated these findings [24]. Nonetheless, the mechanisms underlying this mortality benefit remain unclear. This may primarily involve the distinct biological effects of glucocorticoids and mineralocorticoids, as well as tissue-specific and receptor-independent effects [25]. Another favored combination treatment option in clinical practice includes corticosteroids, ascorbic acid, and thiamine, as all three have demonstrated protective but limited effects. The findings of the meta-analysis indicate that this approach may reduce the duration of vasopressor utilization and lower SOFA scores within the first 72 h [26, 27]. Thus, we also included thiamine as a confounding factor in PSM. However, the enhancement observed is relatively modest, and its clinical relevance remains questionable.

Furthermore, the timing of corticosteroid use is critically important. Some studies have demonstrated that administering corticosteroids within 12 h after shock onset led to shock reversal and a reduction in both ICU and hospital LOS [28, 29]. However, corticosteroid administration has been associated with potential adverse effects, such as hyperglycemia, hypernatremia, fluid retention, immunosuppression, neuromuscular weakness, and an increased risk of infection. Our findings indicated that methylprednisolone may raise blood glucose levels more significantly than hydrocortisone.

Interestingly, our study results indicated that the methylprednisolone group outperformed the hydrocortisone group in some secondary outcomes, such as duration of vasopressin maintenance and urinary output on day two. A systematic review and network meta-analysis reached a different conclusion, suggesting that hydrocortisone boluses and infusions may be more effective than methylprednisolone boluses for shock reversal [30]. Among oncology patients with septic shock, hydrocortisone versus methylprednisolone did not significantly impact time to shock reversal or reduce 28-day mortality [31], consistent with our subgroup analysis. An additional MIMIC database study found no association between corticosteroid therapy for blood pressure maintenance and improved mortality in immunocompromised patients with septic shock [32]. The corticosteroids used in the article included dexamethasone, hydrocortisone, and methylprednisolone. In fact, septic shock is a heterogenous syndrome encompassing several subphenotypes [33] that may respond differently to corticosteroids [34]. Cohen et al. discovered that differences in gene expression may contribute to the diversity of treatment responses to corticosteroids in patients with septic shock [35]. Thus, distinct corticosteroid types may yield varied prognostic effects. Management of septic shock is not limited to hydrocortisone, but may also consider using other corticosteroids, such as methylprednisolone or combination with fludrocortisone. Therapeutic choice should consider the patient's unique condition alongside the clinician's professional judgment.

Our study has several limitations. First, this is a retrospective design, which is vulnerable to unmeasured confounders, although the baseline characteristics of the two groups were balanced by using PSM. Second, this study did not assess the outcome of different doses of methylprednisolone and hydrocortisone. Third, the site of septic shock infection was unknown and not stratified in our research. Fourth, some laboratory test data was lacking in the databases.

Conclusions

Corticosteroids play an important role in the management of septic shock patients, especially in those with higher doses of vasopressor. However, the therapeutic benefits of corticosteroids are not limited to hydrocortisone alone. Our results show that no significant difference in 30-day mortality between those administered methylprednisolone and hydrocortisone. The different effect of methylprednisolone or hydrocortisone in septic shock need to be further verified in prospective, randomized controlled trials.

Abbreviations

MIMIC	Medical Information Mart in Intensive Care
IV	Intravenous
ICU	Intensive care unit
PSM	Propensity score matching
OR	Odds ratio
IQR	Interquartile range
CI	Confidence interval
SMD	Standardized mean difference
CRRT	Continuous renal replacement therapy
LOS	Length of stay
COPD	Chronic obstructive pulmonary disease
SSC	Surviving sepsis campaign
IMV	Invasive mechanical ventilation
RCTs	Randomized controlled trials
BIDMC	Beth Israel Deaconess Medical Center
IRB	Institutional Review Board
CITI	Collaborative Institutional Training Initiative
MAP	Mean arterial pressure
WBC	White blood cell
PT	Prothrombin time
SOFA	Sequential organ failure assessment
SAPS II	Simplified acute physiology score II
HR	Hazard ratio
HPA	Hypothalamic–pituitary–adrenal
CIRCI	Critical-illness-related corticosteroid insufficiency
ADRENAL	Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock
APROCCHSS	Activated Protein C and Corticosteroids for Human Septic Shock
PSM	Propensity score matching

Supplementary Information

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Supplementary Material 1: Figure S1. Summaries of variables before and after propensity score matching. COPD, chronic obstructive pulmonary disease; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment; MV, mechanical ventilation; LODS, logistic organ dysfunction system; PT, prothrombin time; Cr; WBC, white blood cell; CRRT, continuous renal replacement therapy; PLT, platelet; SMD, standardized mean difference; ARDS, acute respiratory distress syndrome.

Supplementary Material 2: Figure S2. Summaries of variables before and after propensity score matching after deleting missing values. COPD, chronic obstructive pulmonary disease; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment; MV, mechanical ventilation; LODS, logistic organ dysfunction system; PT, prothrombin time; Cr; WBC, white blood cell; CRRT, continuous renal replacement therapy; PLT, platelet; SMD, standardized mean difference; ARDS, acute respiratory distress syndrome.

Supplementary Material 3: Table S1. Distribution of covariates of interest after deletion of missing values.

Supplementary Material 4: Table S2. Primary and secondary outcomes analysis after deletion of missing values.

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Authors' contributions
Jun Xu contributed to data curation, data analysis, and manuscript writing. Xia Zheng and Hongliu Cai contributed to the study design and revised the manuscript. All authors approved the final manuscript and are responsible for the content.

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Data availability
The dataset in this study was obtained from MIMIC-IV v3.0. We had completed the CITI Program course known as Human Research and Data or Specimens Only Research to apply for permission to access the database (Record ID: 48615099).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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