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Impact of Methylprednisolone on Short- and Long-Term Outcomes in Critically Ill Patients with Sepsis: A Cohort Study Using the MIMIC-IV Database

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Abstract

Background: Low-dose hydrocortisone reduces mortality in sepsis, but the dose–response profile of methylprednisolone (MP) remains unclear. We assessed the independent associations of the initial dose, cumulative dose, and frequency of methylprednisolone administration with 30-day and 1-year mortality in critically ill adults with sepsis. **Methods:** This retrospective cohort study included 9,876 adults meeting Sepsis-3 criteria from the MIMIC-IV database (2008–2022). Exposures were categorized as: initial dose (<100 mg vs ≥100 mg), cumulative dose (<100 mg vs ≥100 mg), and number of MP administrations (1, 2–4, 5–9, ≥10). Cox proportional-hazards models, Boruta feature selection, and extensive sensitivity analyses were used to estimate adjusted hazard ratios (HRs) with 95 % confidence intervals (CIs). **Results:** MP exposure increased 30-day mortality by 23 % (HR 1.23, 95 % CI 1.10–1.38) and 365-day mortality by 26 % (HR 1.26, 95 % CI 1.15–1.38). Risk plateaued when the initial or cumulative dose reached ≥100 mg. A single administration carried the highest risk (30-day HR 1.48, 365-day HR 1.39). Two-to-four administrations also sustained elevated risk (30-day HR 1.20, P = 0.045; 365-day HR 1.25, P = 0.001). Five-to-nine administrations yielded point estimates <1, but 95 % CIs included unity (30-day HR 0.84, P = 0.27; 365-day HR 0.99, P = 0.94), indicating no significant benefit. ≥10 administrations significantly reduced only 30-day mortality (HR 0.30, 95 % CI 0.10–0.93) without improving 365-day survival (HR 1.08, 95 % CI 0.70–1.66). Boruta ranked MP as the important predictor of death. All sensitivity analyses were consistent. **Conclusion:** Intravenous MP is independently associated with increased 30-day and 1-year mortality in sepsis; risk plateaus at initial or cumulative doses ≥100 mg. Frequency analyses show single-bolus administration is most harmful, 5–9 low-dose administrations confer no significant benefit, and ≥10 administrations only short-term reduce 30-day mortality without improving long-term survival. When MP is clinically necessary, we recommend the “three-low” rule: low initial dose, low daily dose, low total cumulative dose, with reassessment for prompt discontinuation within 5–9 days. Multicenter prospective cohort studies are warranted to refine daily dosing and indications to minimize sepsis mortality.

Keywords: Methylprednisolone; sepsis; dose–response relationship; mortality;

machine learning

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Even in high-income countries, hospital mortality for patients admitted to intensive care units (ICUs) with sepsis exceeds 25 % [2]. Despite prompt antimicrobial therapy, source control and Surviving Sepsis Campaign bundles, approximately one-third of survivors develop persistent cognitive, immune and cardiovascular impairment, tripling their long-term risk of death [3, 4]. The 2020 Global Burden of Disease Study estimated 489 million incident sepsis cases and 11 million sepsis-related deaths worldwide—accounting for 19.7 % of all-cause mortality [5]. Interventions that both save lives in the acute phase and attenuate the long-term "post-sepsis syndrome" are therefore urgently needed [6].

Glucocorticoids were among the first adjunctive agents tested in sepsis, attenuating cytokine storms, stabilising haemodynamics and reducing endothelial–leukocyte adhesion [7]. Early small trials suggested survival benefit, but subsequent meta-analyses yielded conflicting conclusions because of heterogeneity in dose, timing, patient phenotype and concomitant therapies [8]. Interest was rekindled by the 2018 ADRENAL trial and the 2022 APROCCHSS trial: continuous low-dose hydrocortisone shortened shock-reversal time, and APROCCHSS demonstrated reduced 90-day mortality in septic-shock patients with a hyper-inflammatory phenotype [9, 10]. Evidence for methylprednisolone (MP)—a more potent, intermediate-acting glucocorticoid with negligible mineralocorticoid activity—remains scarce. A post-hoc analysis of the HYPRESS trial found that a single 200 mg hydrocortisone bolus followed by 200 mg day^{-1} for 5 days decreased progression to septic shock in patients with severe sepsis [11]. A 2020 systematic review and meta-analysis of 37 RCTs (n = 9 527) found a J-shaped relationship between glucocorticoid dose and mortality in sepsis: short courses (<3 days) or very high cumulative doses (>1 000 mg hydrocortisone-equivalent) were associated with increased 28-day mortality, whereas moderate-dose MP was associated with reduced mortality [12]. These conflicting signals underscore

the need for dose- and duration-stratified data to define the optimal timing and cumulative exposure of MP in sepsis.

Beyond acute survival, accumulating evidence links early glucocorticoid exposure to long-term outcomes. A U.S. nationwide cohort study of 38 818 sepsis survivors found that exposure to systemic glucocorticoids during index hospitalisation was associated with significantly higher 1-year mortality, primarily due to cardiovascular events and secondary infections [13]. Mechanistically, glucocorticoids induce persistent monocyte deactivation, down-regulate HLA-DR expression and inhibit T-cell proliferation, potentially increasing the risk of secondary infections and malignancy [14, 15]. Conversely, they accelerate resolution of ARDS-associated inflammation and fibroproliferation, possibly reducing late respiratory death [16]. Whether net harm or benefit ensues may depend on cumulative steroid dose and host immune endotype, as suggested by a recent systematic review linking early glucocorticoid exposure to increased risk of rehospitalisation and late mortality in sepsis survivors [17]. Unfortunately, most randomised trials have used 28- or 90-day mortality as the primary end-point, leaving a paucity of granular dose–response data within the first post-sepsis year.

Using the high-resolution, publicly available MIMIC-IV database (2008–2022), we dissected the impact of MP—quantified by first dose, number of administrations and cumulative dose—on short-term (30-day) and long-term (365-day) mortality in a large cohort of critically ill adults with sepsis. Our findings aim to inform precision glucocorticoid stewardship and to generate mechanistic hypotheses for future trials targeting the acute-to-chronic transition of sepsis.

Methods

Study design, data source and ethics

This retrospective cohort study used the Medical Information Mart for Intensive Care IV (MIMIC-IV, v3.1) relational database, which contains de-identified electronic health

records for 94,458 ICU admissions at Beth Israel Deaconess Medical Center (Boston, MA, USA) between 2008 and 2022 [18]. The database includes demographics, vital signs, laboratory results, medications, procedures and survival data linked to the Social Security Death Master File. The Massachusetts Institute of Technology Institutional Review Board approved the study (ID 49995491) and waived informed consent because all data were de-identified.

Study population

Inclusion criteria

1. Age ≥ 18 years

2. First ICU admission

3. Sepsis-3 criteria: suspected or documented infection AND acute increase in SOFA score ≥ 2 points [19,20]

Exclusion criteria

- ICU length of stay < 24 h

- Missing survival data

- > 16 MP administrations (to exclude prolonged immunosuppressive protocols). The patient-flow diagram is shown in Figure 1.

Exposure definition

The primary exposure was intravenous MP administered during the ICU stay, identified from the inputevents and pharmacy tables using generic drug names and NDC code ATC H02AB04. MP exposure was characterised in four dimensions:

1. Any use (yes/no)

2. First dose (< 100 mg vs ≥ 100 mg)

3. Cumulative dose (< 100 mg vs ≥ 100 mg)

4. Number of administrations (1, 2–4, 5–9, ≥ 10)

Outcomes

- Primary short-term outcome: 30-day all-cause mortality

- Primary long-term outcome: 365-day all-cause mortality

Both intervals were calculated from ICU admission; death dates were obtained from the MIMIC-IV-linked Social Security Death Master File [18].

Covariate selection

To control confounding while avoiding over-adjustment we used a two-step "clinical prior + data-driven" strategy: 1. Clinical candidate pool: 39 variables previously associated with sepsis mortality (demographics, comorbidities, illness severity, vital signs, concomitant drugs). 2. Collinearity screen: variance inflation factor ≥ 5 was considered redundant [21]; all VIFs were < 5 (Table S1). 3. Machine-learning importance: among patients never exposed to MP, Boruta ensemble feature selection (1 000 random-forest permutations) was applied separately to 30-day and 365-day mortality. Variables with Z-scores higher than the mean of shadow attributes were retained; the union of both rankings constituted the final adjustment set. 4. Final covariates: gender, age, race, renal disease, CHF, PVD, CVD, chronic pulmonary disease, asthma, prior MI, AST, ALT, serum creatinine, BUN, serum calcium, platelet count, RBC count, WBC count, SOFA, SAPS II, APS III, and concomitant use of aspirin, furosemide, metoprolol, statin and heparin.

Statistical analysis

Continuous variables are presented as mean ± SD or median (IQR); categorical variables as n (%). Group comparisons used χ^2, Student's t or Mann–Whitney U tests. Time-to-event analyses were performed with Cox proportional-hazards models; the proportional-hazards assumption was verified by Schoenfeld residuals (all $P > 0.05$). Three hierarchical models were constructed: Model I: unadjusted; Model II: adjusted for age, sex and race; Model III: adjusted for the final covariate set.

Results are reported as hazard ratios (HRs) with 95 % confidence intervals (CIs). Trend tests across dose or frequency categories were performed by entering the ordinal variable as a continuous term in the Cox model. Kaplan–Meier curves stratified by MP exposure were plotted for 30-day (Fig. 3A) and 365-day (Fig. 3B) survival, with log-

rank tests for comparison.

Laboratory values were missing for < 20 % of patients; missing data were handled by multiple imputation (5 imputations) [22-24]. Baseline characteristics were similar before and after imputation (Table S2); the primary analysis used one randomly selected imputed dataset. Two pre-specified sensitivity analyses were conducted: (1) exclusion of AST and ALT to reduce hepatic-marker influence, and (2) additional exclusion of SAPS II to minimise over-adjustment for acute illness severity.

All analyses followed the STROBE guideline [25] and were performed with R software, EmpowerStats and Free Stats. A two-sided $P < 0.05$ was considered statistically significant.

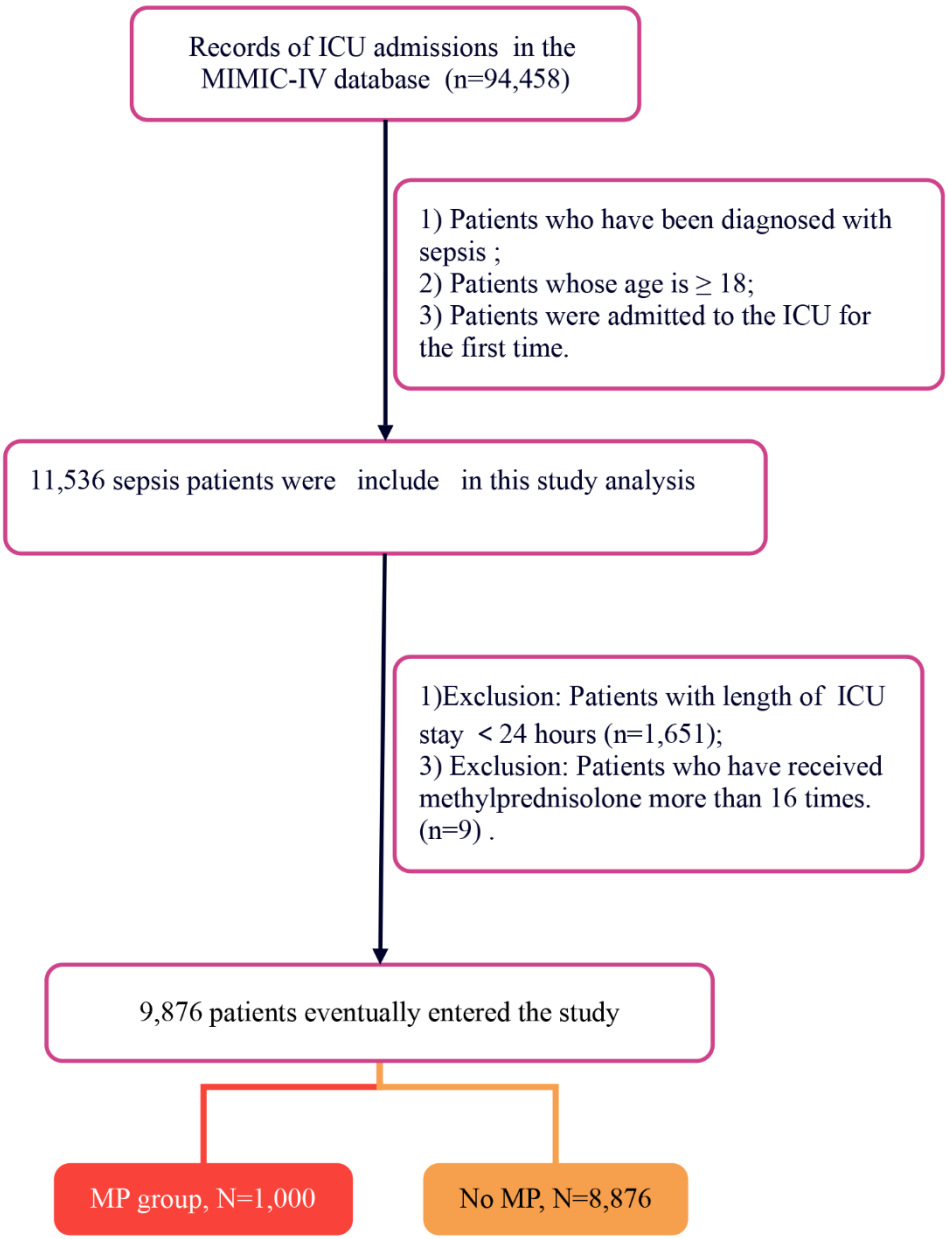


Fig.1 Flowchart of the selection of patients

3 Results

3.1 Characteristics of participants

A total of 9,876 adults with severe sepsis were enrolled, of whom 1,000 (10.1%) received intravenous MP. Table 1 summarises baseline characteristics after multiple imputation; imputed and complete-case data were virtually identical (all standardised

differences <0.1, Table S2). Patients given MP were younger (64.5±15.2 vs 67.8±16.1 years, P<0.001), had longer ICU stays (median 6.2 vs 3.5 days, P<0.001) and higher APS III scores (58 vs 55, P=0.002), whereas SOFA scores were comparable. Chronic pulmonary disease (41.3% vs 25.2%, P<0.001) and concomitant use of furosemide, insulin and heparin were more frequent in the MP group (all P<0.001). Sex, race and other major comorbidities did not differ significantly (Table 1).

Table 1 Characteristics of study participants.

Characteristics	All	No MP group	MP group	P-value
N	9876	8876	1000	
Age (years)	67.47 ± 16.01	67.81 ± 16.06	64.47 ± 15.21	<0.001
LOS-ICU, (IQR), (day)	3.67 (1.97-8.08)	3.49 (1.93-7.65)	6.16 (2.90-13.75)	<0.001
HR, (bpm)	91.47 ± 17.40	91.33 ± 17.44	92.67 ± 17.05	0.022
SBP, (mmHg)	111.08 ± 13.92	110.89 ± 13.87	112.78 ± 14.24	<0.001
DBP, (mmHg)	60.70 ± 9.83	60.50 ± 9.77	62.41 ± 10.24	<0.001
RR, (bpm)	21.22 ± 4.43	21.17 ± 4.41	21.73 ± 4.57	<0.001
SPO2, (%)	96.51 ± 2.39	96.54 ± 2.37	96.19 ± 2.59	<0.001
T, (℃)	36.95 ± 0.62	36.95 ± 0.62	36.93 ± 0.65	0.240
PLT, (IQR), (10^9/L)	184.00 (119.33-268.50)	185.00 (121.19-269.00)	174.17 (103.10-262.54)	0.001
RBC, (10^{12}/L)	3.36 ± 0.69	3.37 ± 0.69	3.31 ± 0.70	0.017
WBC, (IQR), (10^9/L)	13.33 (8.97-18.83)	13.43 (9.09-18.95)	12.31 (8.04-18.16)	0.028
BUN, (IQR), (mmol/L)	25.00 (14.00-43.00)	24.50 (14.00-43.00)	25.50 (15.00-42.00)	0.607
Scr, (IQR), (mg/dL)	1.40 (0.85-2.25)	1.40 (0.85-2.25)	1.30 (0.85-2.15)	0.050
AST, (IQR), (U/L)	38.00 (17.00-99.50)	26.00 (12.00-72.50)	27.00 (12.88-74.50)	0.022
ALT, (IQR), (U/L)	26.00 (12.00-72.50)	38.00 (17.00-99.50)	38.00 (17.00-96.88)	0.416
Serum calcium, (mmol/L）	8.02 ± 1.14	8.00 ± 1.14	8.17 ± 1.12	<0.001
Illness severity scores				
SOFA score, (IQR)	7.00 (4.00-10.00)	7.00 (4.00-10.00)	7.00 (4.00-10.00)	<0.001
SAPSII score, (IQR)	43.00 (34.00-54.00)	43.00 (34.00-54.00)	44.00 (35.00-55.00)	0.023
APSIII score, (IQR)	55.00 (43.00-72.00)	55.00 (43.00-72.00)	58.00 (44.00-75.00)	0.002
Gender, n (%)				0.081
Man	5481 (55.50)	4952 (55.79)	529 (52.90)	
Female	4395 (44.50)	3924 (44.21)	471 (47.10)	
Race, n (%)				0.412
Whight	6825 (69.11)	6151 (69.30)	674 (67.40)	
Black	1041 (10.54)	930 (10.48)	111 (11.10)	
Yellow	395 (4.00)	359 (4.04)	36 (3.60)	
Unknown	1615 (16.35)	1436 (16.18)	179 (17.90)	

Comorbidities, n (%)				
Renal disease, n (%)	2686 (27.20)	2433 (27.41)	253 (25.30)	0.155
CHF, n (%)	3384 (34.26)	3035 (34.19)	349 (34.90)	0.655
PVD, n (%)	1084 (10.98)	990 (11.15)	94 (9.40)	0.093
CVD, n (%)	1242 (12.58)	1130 (12.73)	112 (11.20)	0.166
CPD, n (%)	2651 (26.84)	2238 (25.21)	413 (41.30)	<0.001
History diseases, n (%)				
Cardiac surgery, n (%)	2018 (20.43)	1822 (20.53)	196 (19.60)	0.491
Diabetes, n (%)	3736 (37.83)	3371 (37.98)	365 (36.50)	0.361
Hypertension, n (%)	5613 (56.83)	5014 (56.49)	599 (59.90)	0.039
MI, n (%)	1830 (18.53)	1673 (18.85)	157 (15.70)	0.015
stroke, n (%)	47 (0.48)	40 (0.45)	7 (0.70)	0.277
Asthma, n (%)	1113 (11.27)	925 (10.42)	188 (18.80)	<0.001
Used medicine				
Aspirin, n (%)	3870 (39.19)	3483 (39.24)	387 (38.70)	0.740
Furosemide, n (%)	6080 (61.56)	5301 (59.72)	779 (77.90)	<0.001
Metoprolol, n (%)	4501 (45.58)	4020 (45.29)	481 (48.10)	0.091
Insulin, n (%)	6198 (62.76)	5418 (61.04)	780 (78.00)	<0.001
Statin, n (%)	4650 (47.08)	4159 (46.86)	491 (49.10)	0.178
Heparin, n (%)	9400 (95.18)	8442 (95.11)	958 (95.80)	0.334
30-day Mortality, n (%)	3050 (30.88)	2697 (30.39)	353 (35.30)	0.001
365-day Mortality, n (%)	4955 (50.17)	4381 (49.36)	574 (57.40)	<0.001

Continuous variables are summarized as mean (SD) or median (trisection interval); categorical variables are presented as percentages (%).LOS, length of stay; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RR, respiratory Rate; SPO2, peripheral oxygen saturation; T, temperature; SOFA, sequential organ failure assessment; SAPS II score, simplified acute physiology score II; APS III, acute physiology score III; PTL, platelet count; RBC, red blood cell count; WBC, white blood cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; Scr, serum creatinine, CHF, chronic heart failure; PVD, peripheral vascular disease; CVD, cardiovascular disease; CPD, chronic pulmonary disease; MI, myocardial infarction; ICU, intensive care unit; MP, methylprednisolone.

3.2. Mortality Outcomes

Overall, 30-day mortality was 30.9 % (3,050/9,876) and 1-year mortality was 50.2 % (4,955/9,876). The MP group carried a significantly higher death burden than the non-MP group (30-day: 35.3 % vs 30.4 %; 365-day: 57.4 % vs 49.4 %, both P<0.001) (Table 1). As illustrated in Figure 2, mortality rose stepwise with age: 30-day rates were ≈12 % in patients <40 years and reached 45 % in those ≥70 years, with males experiencing slightly higher rates across all strata. Kaplan–Meier curves (Figure 3) showed early separation within the first ICU week that persisted to the end of follow-up; log-rank tests were highly significant at both 30 days (P=0.0004) and 365 days (P<0.0001), reinforcing the temporal association between MP exposure and reduced survival.

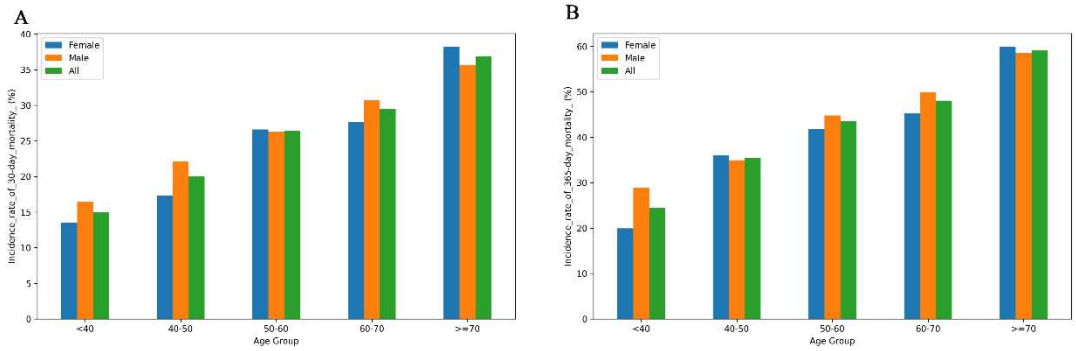


Fig.2 Age- and sex-specific mortality incidence in the study cohort.

Rates are shown for males (red) and females (blue) across five age strata (< 40, 40–50, 50–60, 60–70 and > 70 years); panel A depicts 30-day mortality and panel B 365-day mortality.

3.2 Kaplan–Meier Analysis of MP on Short- and Long-Term Prognosis in Patients with sepsis

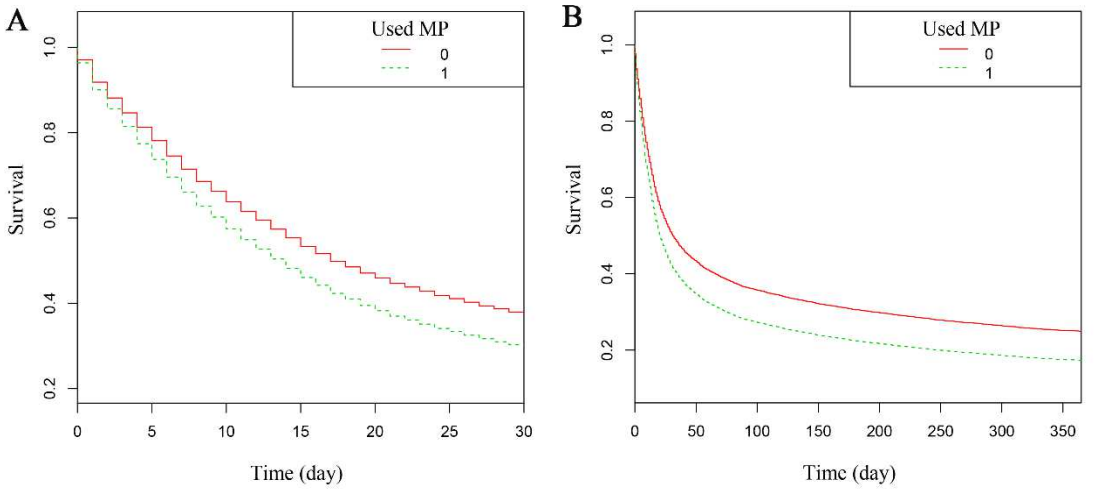


Fig. 3 Adjusted Kaplan–Meier survival curves for 30-day (panel A) and 365-day (panel B) mortality according to methylprednisolone exposure status. Curves were stratified by MP use (red: no-MP group; green: MP group) and adjusted for gender, age, race, renal disease, CHF, PVD, CVD, CPD, asthma, prior MI, AST, ALT, Scr, BUN, serum calcium; PLT, RBC, WBC, SOFA, SAPS II, APS III, and concomitant use of aspirin, furosemide, metoprolol, statin and heparin.

Univariate associations with mortality

Prior to multivariable modelling, we screened all 39 candidate predictors using univariate Cox proportional-hazards regression (Table S3). Every 1-year increase in age was associated with a 2 % higher hazard of both 30-day and 365-day mortality (HR

= 1.02, 95 % CI: 1.02–1.02, P < 0.0001). Among vital-sign parameters, elevated heart rate, respiratory rate and temperature, as well as lower SBP, DBP and SpO_2, were significantly linked to earlier death (all P < 0.0001). Laboratory indices indicative of organ dysfunction—higher SOFA, SAPS II, APS III, creatinine, BUN, AST, ALT and lower serum calcium, RBC and platelet count—also showed strong univariate associations (P ≤ 0.0066). Notably, exposure to MP emerged as a significant predictor, with univariate HRs of 1.16 (30-day) and 1.23 (365-day) (both P < 0.0074), providing the rationale for its retention in all subsequent multivariable models.

Feature selection and predictor importance

As shown in Figure4, the Boruta ensemble analysis identified age, SOFA score, serum creatinine, red-blood-cell count, and MP exposure as the most influential predictors of both short- and long-term mortality. MP use consistently ranked among the top variables, with a mean Z-score exceeding the shadow-variable threshold, indicating an independent contribution to death risk and justifying its retention in all subsequent multivariable models.

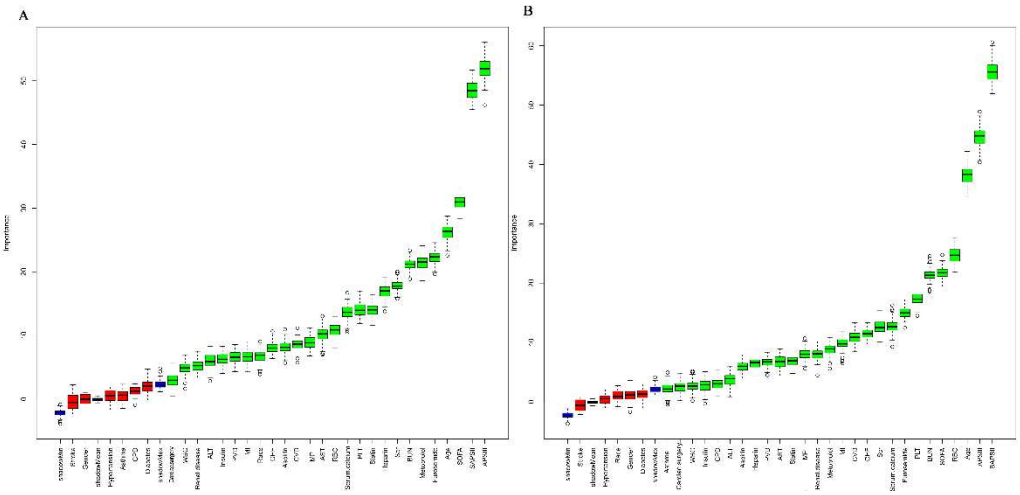


Fig. 4 Variable-importance ranking (Boruta algorithm) for the mortality-risk prediction model in critically ill patients with sepsis. Panel A: 30-day mortality; Panel B: 365-day mortality.

3.3 Results from multivariate analyses using Cox proportional hazards regression methods.

3.3.1 MP independently increases 30-day and 1-year mortality in sepsis.

After confirming that the proportional-hazards assumption was satisfied (all Schoenfeld $P > 0.05$), we constructed a series of Cox models (Table 2). In the fully adjusted model (Model III), intravenous MP exposure remained independently associated with increased mortality: 30-day all-cause death HR = 1.23, 95 % CI 1.10–1.38, P = 0.0004; 365-day all-cause death HR = 1.26, 95 % CI 1.15–1.38, P < 0.0001. The effect estimate remained stable across sequentially adjusted models, indicating minimal residual confounding by demographic characteristics or baseline organ dysfunction. A significant exposure–response trend (P-trend < 0.0001 at both end-points) further reinforces the finding that MP use is closely linked to excess short- and long-term mortality in critically ill patients with sepsis.

Table 2. Association between MP use and mortality in patients with sepsis.

Group	Exposure	Number	Event (%)	Model I (HR,95%CI) P	Model II (HR,95%CI) P	Model III (HR,95%CI) P
	Used MP					
30-day mortality	No	8876	2697 (30.39)	1(Ref)	1(Ref)	1(Ref)
	Yes	1000	353 (35.30)	1.16 (1.04, 1.30) 0.0074	1.24 (1.11, 1.39) 0.0001	1.23 (1.10, 1.38) 0.0004
	P for trend			<0.0001	<0.0001	<0.0001
	Used MP					
365-day mortality	No	8876	4381 (49.36)	1(Ref)	1(Ref)	1(Ref)
	Yes	1000	574 (57.40)	1.23 (1.13, 1.34) <0.0001	1.33 (1.22, 1.45) <0.0001	1.26 (1.15, 1.38) <0.0001
	P for trend			<0.0001	<0.0001	<0.0001

Model I: we did not account for additional variables.

Model II: we adjusted gender, age and race.

Model III: we adjusted gender, age, race, renal disease; CHF; PVD; CVD; CPD; Asthma; MI; AST; ALT; serum calcium; Scr; BUN; PLT; RBC; WBC; SOFA; SAPS II; APS III; used aspirin; used furosemide; used metoprolol; used statin; used heparin. HR, Hazard Ratios; CI, confidence; Ref, reference.

3.3.2. Dose–response by initial MP dose

First-dose analysis (Table 3) showed that patients receiving an initial MP dose ≥100 mg had a significantly higher 30-day mortality risk than those given <100 mg (HR 1.44 vs 1.13; P-trend <0.0001); the same pattern was observed at 365 days.

Table 3. Impact of MP initiation dose on mortality in patients with sepsis.

Group	Exposure	Model I (HR,95%CI) P	Model II (HR,95%CI) P	Model III (HR,95%CI) P
	Used MP (mg)			
	0	1(Ref)	1(Ref)	1(Ref)
30-day mortality	＜100	1.07 (0.93, 1.22) 0.3672	1.12 (0.98, 1.29) 0.1053	1.13 (0.98, 1.29) 0.0999
	≥100	1.37 (1.15, 1.63) 0.0004	1.51 (1.27, 1.80) <0.0001	1.44 (1.21, 1.72) <0.0001
	P for trend	<0.0001	<0.0001	<0.0001
	Used MP (mg)			
	0	1(Ref)	1(Ref)	1(Ref)
365-day mortality	＜100	1.19 (1.07, 1.32) 0.0013	1.26 (1.14, 1.40) <0.0001	1.22 (1.10, 1.36) 0.0002
	≥100	1.31 (1.14, 1.51) 0.0002	1.48 (1.29, 1.71) <0.0001	1.33 (1.15, 1.54) <0.0001
	P for trend	<0.0001	<0.0001	<0.0001

Model I: we did not account for additional variables.

Model II: we adjusted gender, age and race.

Model III: we adjusted gender, age, race, renal disease; CHF; PVD; CVD; CPD; Asthma; MI; AST; ALT; serum calcium; Scr; BUN; PLT; RBC; WBC; SOFA; SAPS II; APS III; used aspirin; used furosemide; used metoprolol; used statin; used heparin. HR, Hazard Ratios; CI, confidence; Ref, reference.

3.3.3. Cumulative-Dose–Response Relationship

Cumulative exposure (Table 4) confirmed these findings: total MP ≥100 mg was associated with a 30-day HR of 1.27, versus 1.17 for cumulative doses <100 mg, with a significant dose–response trend (P-trend <0.0001).

Table 4. **Impact of cumulative MP dose on mortality in patients with sepsis**

Group	Exposure	Model I (HR,95%CI) P	Model II (HR,95%CI) P	Model III (HR,95%CI) P
	Used MP (mg)			
	0	1(Ref)	1(Ref)	1(Ref)
30-day mortality	＜100	1.11 (0.94, 1.31) 0.2145	1.17 (0.99, 1.38) 0.0658	1.17 (0.99, 1.38) 0.0686
	≥100	1.20 (1.05, 1.39) 0.0100	1.30 (1.13, 1.50) 0.0003	1.27 (1.10, 1.47) 0.0010
	P for trend	<0.0001	<0.0001	<0.0001
	Used MP (mg)			
	0	1(Ref)	1(Ref)	1(Ref)
365-day mortality	＜100	1.12 (0.99, 1.28) 0.0810	1.20 (1.05, 1.36) 0.0081	1.17 (1.03, 1.34) 0.0183
	≥100	1.31 (1.18, 1.47) <0.0001	1.44 (1.29, 1.61) <0.0001	1.33 (1.18, 1.48) <0.0001
	P for trend	<0.0001	<0.0001	<0.0001

Model I: we did not account for additional variables.

Model II: we adjusted gender, age and race.

Model III: we adjusted gender, age, race, renal disease; CHF; PVD; CVD; CPD; Asthma; MI; AST; ALT; serum calcium; Scr; BUN; PLT; RBC; WBC; SOFA; SAPS II; APS III; used aspirin; used furosemide; used metoprolol; used statin; used heparin. HR, Hazard Ratios; CI, confidence; Ref, reference.

3.3.4. Frequency–Response Relationship

Frequency analysis (Table 5) shows that, compared with no exposure, a single course of MP was significantly associated with higher 30-day and 365-day mortality (Model III: 30-day HR 1.48, 95 % CI 1.27–1.72, P < 0.001; 365-day HR 1.39, 95 % CI 1.22–1.58, P < 0.001). Two to four courses likewise conferred a sustained increase in risk (30-day HR 1.20, P = 0.045; 365-day HR 1.25, P = 0.001).

For five to nine courses, the point estimates lay below 1.0, but the 95 % CIs crossed unity (30-day HR 0.84, 95 % CI 0.61–1.15, P = 0.27; 365-day HR 0.99, 95 % CI 0.79–1.25, P = 0.94); thus no significant benefit could be claimed. Continuous use for ≥10 courses significantly reduced 30-day mortality (HR 0.30, 95 % CI 0.10–0.93, P = 0.038), yet this protective effect was no longer evident at 365 days (HR 1.08, 95 % CI 0.70–1.66, P = 0.74).

Table 5. Impact of MP on mortality in patients with sepsis by timing of use.

Group	Exposure	Model I (HR,95%CI) P	Model II (HR,95%CI) P	Model III (HR,95%CI) P
	Used MP (times)			
	0	1(Ref)	1(Ref)	1(Ref)
30-day mortality	1	1.43 (1.23, 1.67) <0.0001	1.47 (1.27, 1.71) <0.0001	1.48 (1.27, 1.72) <0.0001
	2-4	1.13 (0.94, 1.34) 0.1846	1.18 (0.99, 1.41) 0.0633	1.20 (1.00, 1.43) 0.0447
	5-9	0.85 (0.62, 1.16) 0.3034	0.99 (0.73, 1.36) 0.9599	0.84 (0.61, 1.15) 0.2704
	≥10	0.20 (0.06, 0.62) 0.0052	0.27 (0.09, 0.82) 0.0218	0.30 (0.10, 0.93) 0.0378
P for trend		<0.0001	<0.0001	<0.0001
	Used MP (times)			
	0	1(Ref)	1(Ref)	1(Ref)
365-day mortality	1	1.33 (1.17, 1.51) <0.0001	1.38 (1.22, 1.57) <0.0001	1.39 (1.22, 1.58) <0.0001
	2-4	1.24 (1.08, 1.42) 0.0018	1.31 (1.15, 1.50) <0.0001	1.25 (1.09, 1.44) 0.0012
	5-9	1.05 (0.84, 1.32) 0.6561	1.26 (1.01, 1.58) 0.0451	0.99 (0.79, 1.25) 0.9394
	≥10	0.88 (0.58, 1.36) 0.5758	1.18 (0.77, 1.81) 0.4573	1.08 (0.70, 1.66) 0.7385
P for trend		<0.0001	<0.0001	<0.0001

Model I: we did not account for additional variables.
Model II: we adjusted gender, age and race.
Model III: we adjusted gender, age, race, renal disease; CHF; PVD; CVD; CPD; Asthma; MI; AST; ALT; serum calcium; Scr; BUN; PLT; RBC; WBC; SOFA; SAPS II; APS III; used aspirin; used furosemide; used metoprolol; used statin; used heparin. HR, Hazard Ratios; CI, confidence; Ref, reference.

Sensitivity analyses

To verify the robustness of our primary findings, we first repeated the three-stage Cox modelling on the complete-case dataset before multiple imputation (Table S4). In this unimputed cohort, MP exposure remained significantly associated with mortality: 30-day Model III HR = 1.16 (95 % CI 1.02–1.31, P = 0.021); 365-day Model III HR = 1.19 (95 % CI 1.08–1.31, P = 0.0006). Trend tests were consistently significant (P-trend < 0.0001), indicating that imputation did not introduce detectable bias.

Further, Table S5 shows that excluding hepatic markers (AST, ALT) left the estimates virtually unchanged: 30-day HR = 1.23 (95 % CI 1.10–1.38, P = 0.0004); 365-day HR = 1.26 (95 % CI 1.15–1.38, P < 0.0001). When SAPS II was additionally removed, effect sizes remained stable: 30-day HR = 1.24 (95 % CI 1.11–1.39, P = 0.0002); 365-day HR = 1.28 (95 % CI 1.17–1.40, P < 0.0001). The consistency of direction and magnitude across these analyses demonstrates that the association between MP exposure and increased short- and long-term mortality in sepsis is robust to the inclusion or exclusion of multiple imputation, hepatic markers or SAPS II.

Discussion

In this large longitudinal cohort of 9,876 adults who met Sepsis-3 criteria in MIMIC-IV (2008–2022), intravenous MP displayed a consistent and steep dose–response hazard curve. After full adjustment, MP exposure increased 30-day mortality by 23 % and 1-year mortality by 26 % (Model III). Importantly, the harm was not linearly cumulative: risk plateaued once the first or cumulative dose reached ≥ 100 mg, whereas frequency showed a “single-bolus peak” phenomenon—patients given only one bolus carried the highest death risk, those receiving 5–9 low-dose administrations exhibited a possible trend toward benefit, and ≥ 10 low-dose days reduced the 30-day hazard to

0.30 without improving 1-year survival (HR 1.08). Thus, short-term immunosuppressive gain was not translated into sustained survival. The Boruta machine-learning algorithm ranked MP as a key predictor of mortality, and all sensitivity analyses (removing SAPS II, AST/ALT, or imputation status) preserved both the direction and magnitude of the effect, further reinforcing the robustness of the signal. Taken together, MP-associated harm in sepsis follows a stepwise pattern: high-dose single-bolus > high-dose repeated > low-dose prolonged, providing precise dose–effect boundaries for mechanistic studies and bedside decisions.

Despite global implementation of Surviving Sepsis Campaign bundles, hospital mortality for ICU-treated sepsis in high-income countries remains 25–30 %, with 1-year fatality approaching 50 % [2]. We observed 30-day and 365-day rates of 30.9 % and 50.2 %, respectively—congruent with the 2023 Global Burden of Disease estimate of 11 million annual sepsis deaths [5], and Danish nationwide cohort 49 % 1-year mortality [13]. These figures indicate that current supportive care has reached a plateau, highlighting the need for adjunctive immunomodulatory strategies that do not increase late deaths.

The rationale for glucocorticoids in sepsis rests on their ability to blunt cytokine storms, stabilise haemodynamics and shorten shock duration [7,26]. Yet “which hormone, what dose, when to stop” has remained contentious for two decades. The landmark ADRENAL and APROCCHSS trials confirmed that low-dose hydrocortisone accelerates shock reversal and, in APROCCHSS, reduced 90-day mortality in hyper-inflammatory septic shock [9,10], but explicitly discouraged extrapolation to “high-dose, non-hydrocortisone preparations” [9]. MP—possessing five-fold greater glucocorticoid receptor affinity, negligible mineralocorticoid activity and a longer half-life than hydrocortisone [26]—is nevertheless widely used in clinical practice for rapid control of excessive inflammation, despite the lack of high-quality evidence specific to this agent [27]. High-quality MP-specific evidence is scarce: existing RCTs are small, short-followed, and often pool steroids as “hydrocortisone-equivalents”, precluding

identification of MP-specific effects [8]. Consequently, clinicians frequently default to empirical “125–250 mg MP stat” boluses, creating an evidence vacuum around MP dose–exposure–risk relationships that the present study addresses.

Building on the 2024 dose-response meta-analysis by Pitre et al. [28], we performed four “fine-mapping” extensions and provide immediately actionable clinical thresholds. we performed four “fine-mapping” extensions and provide immediately actionable clinical thresholds. 1. First-dose threshold: Using 100 mg as the cut-off, we found 30-day mortality HR 1.44 (95 % CI 1.21–1.72) for ≥100 mg versus 1.13 (0.98–1.29) for <100 mg; thus, the very first bolus determines the risk plateau, drawing a clear red line for initial prescribing in emergency departments and ICUs. 2. Frequency–survival dynamics: Five to nine low-dose administrations conferred stable short- and long-term outcomes, whereas ≥10 days reduced 30-day HR to 0.30 (0.10–0.93) but yielded 365-day HR 1.08 (0.70–1.66). This “early-benefit–late-fade” pattern indicates an immunosuppressive window of ≈1 month, with additional courses failing to translate into sustained survival, thereby anchoring the decision of when to stop. 3. Cumulative-dose/time modelling: Cumulative MP ≥100 mg remained associated with significantly higher 1-year mortality (HR 1.33). Simply prolonging treatment without reducing daily dose did not dilute harm; combining our findings mandates “daily dose ≤20 mg + total dose <100 mg” to avoid late injury, refining the BLISS-ICU “4–6-day safety window” into a two-dimensional “low-daily-dose + total cap” boundary. 4. Machine-learning/epidemiology cross-validation: Boruta ranked MP among the top predictors of 30- and 365-day death across >39 variables, and effect sizes remained stable (HR change <5 %) after removal of SAPS II, hepatic enzymes, or imputation status, avoiding p-value-driven selection bias and enhancing generalisability.

Pharmacologically, 1 mg MP equals 5 mg hydrocortisone; a 125 mg bolus rapidly achieves supra-physiological glucocorticoid receptor saturation, provoking sustained monocyte deactivation, decreased HLA-DR expression and increased secondary infection risk [14]. Early high-dose steroids also delay microbial clearance, promote

hyperglycaemia and ICU-acquired myopathy, and amplify post-sepsis immune exhaustion—all pathways linked to late mortality [28]. In contrast, divided low-dose administrations may permit immunomodulation without profound immunosuppression, explaining the plateau observed with 5–9 doses, whereas ≥10 days reduced short-term risk.

In summary, we validate the BLISS-ICU J-shaped concept and refine it into a three-dimensional safety boundary: first dose ≤100 mg, total dose <100 mg, and 5–9 administrations, while providing the first 1-year follow-up evidence. Clinicians can adopt a "low first-dose, low daily-dose, total cap, reassess at day 5–9" MP protocol or prefer the proven low-dose hydrocortisone regimen, thereby achieving truly precision glucocorticoid management aligned with the 2017 CIRCI guidelines [29].

There are some strengths and limitation. Strengths include 14-year high-resolution MIMIC-IV data, exclusion of prior systemic steroids to reduce selection bias, machine-learning covariate selection to prevent over-adjustment, and consistent results across multiple imputation and sensitivity analyses, enhancing internal validity. Limitations are inherent to the retrospective design: residual confounding cannot be excluded, and indication, tapering protocols and biochemical adrenal function data were unavailable, impeding full causal inference. MIMIC-IV reflects well-resourced health systems, limiting generalisability to low- and middle-income countries where sepsis mortality is highest. Future multicentre prospective or adaptive platform trials should (i) protocolise daily MP dosing and indication, (ii) stratify patients by adrenal function and inflammatory endotype, and (iii) integrate immune-phenotyping (HLA-DR, IL-6, transcriptomics) to distinguish responders from non-responders.

Conclusion

Among 9,876 Sepsis-3 patients in MIMIC-IV, intravenous MP independently increased 30-day and 1-year mortality, with risk plateauing once the initial or cumulative dose

reached ⩾100 mg. A single bolus carried the highest hazard, 5–9 low-dose administrations conferred no significantly survival benefit, and ⩾10 courses only transiently reduced 30-day mortality without improving long-term outcomes. We therefore define a safety boundary of "small first dose, small daily dose, small total dose," mandating reassessment and consideration of discontinuation on days 5–9. Multicentre prospective cohorts are needed to standardise daily MP dosing and indications, stratify patients by adrenal function and inflammatory endotypes (IL-6, HLA-DR, transcriptomics), and directly compare equipotent hydrocortisone regimens with divided MP to identify sepsis subgroups that may benefit without late harm.

Data availability statement

The datasets discussed in this research are available in online repositories. Below are the names of the repository or repositories along with the accession number(s): https://physionet.org/content/mimiciv/3.1/.

Declarations

Ethics approval

This study used fully de-identified data from the MIMIC-IV database, which was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. The requirement for individual informed consent was waived for this secondary analysis. All authors completed the NIH "Protecting Human Research Participants" training and obtained data-use certification (Record ID: 49995491).

Clinical trial number

Not applicable.

Human Ethics and Consent to Participate declarations

Not applicable.

Author contributions

Zhenhua Huang, Jiagui Zhao and Qinghua Yuan: Data curation, Methodology, Software, Supervision, Writing – original draft. Xiaoan Yang and Xin Li: Data curation, Writing – review & editing.

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Conflict of interest

The authors affirm that the research was carried out without any commercial or financial relationships that might be interpreted as a possible conflict of interest.

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