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Steroid administration, timing, and dose in patients with septic shock in the emergency department: retrospective analysis of a multicenter prospective cohort study

Running head: Steroid in septic shock

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Abstract

Background: The benefit and optimal timing of corticosteroids in septic shock remain debated. Most evidence comes from intensive care unit-based studies, although key treatment decisions are often made early in the emergency department (ED).

Aim: This study evaluated the association between steroid administration, including hydrocortisone timing and dose, and mortality in patients with septic shock in the ED.

Methods: This retrospective observational study used an ED-based prospective multicenter septic shock registry from the Korean Shock Society (KoSS). The association between steroid administration and 28-day mortality was evaluated in adult patients with septic shock using multivariable regression models. Among hydrocortisone-treated patients, the associations of time from first vasopressor initiation to first hydrocortisone administration, norepinephrine-equivalent dose, and hydrocortisone dose with mortality were analyzed.

Results: From 2015 to 2023, a total of 5,127 patients were included. After adjustment, steroid use was associated with lower 28-day mortality (steroid: adjusted odds ratio [aOR] 0.752, 95% confidence interval [CI] 0.637–0.887;

hydrocortisone: aOR 0.745, 95% CI 0.627–0.884; both $p=0.001$).

Multivariable analyses after PSM, IPTW, multivariable Cox proportional hazards models, and multivariable time-dependent Cox proportional hazards models showed similar findings. This association remained in the vasopressin subgroup (aOR 0.631, 95% CI 0.494–0.805, $p<0.001$) but not in patients who did not receive vasopressin (aOR 0.967, 95% CI 0.773–1.209, $p=0.769$; interaction $p=0.025$). Among 1,529 patients with septic shock who received hydrocortisone, a higher norepinephrine-equivalent dose at first steroid administration (aOR 2.014, 95% CI 1.302–3.114, $p=0.002$) and a longer interval from first vasopressor initiation to first steroid administration (aOR 1.018, 95% CI 1.003–1.033, $p=0.017$) were associated with increased mortality, as was hydrocortisone dosing >300 mg/day (aOR 1.577, 95% CI 1.179–2.110, $p=0.002$).

Conclusions: In this multicenter ED-based registry, steroid administration in the ED was associated with lower 28-day mortality among patients with septic shock, particularly those receiving vasopressin. Among hydrocortisone-treated patients, higher norepinephrine-equivalent dose at hydrocortisone initiation, a longer interval from vasopressor initiation to hydrocortisone administration, and hydrocortisone dose >300 mg/day were associated with increased mortality; however, these findings should be interpreted cautiously as observational and hypothesis-generating.

Keywords: sepsis, septic shock, steroid, hydrocortisone, steroid timing, steroid dose, vasopressin interaction, emergency department

Abbreviations

aOR = Adjusted Odds Ratio

APACHE = Acute Physiology and Chronic Health Evaluation

CI = Confidence Interval

ED = Emergency Department

ICU = Intensive Care Unit

IPTW = Inverse Probability of Treatment Weighting

KoSS = Korean Shock Society

PSM = Propensity Score Matching

RCS = Restricted Cubic Spline

SOFA = Sequential Organ Failure Assessment

SMD = Standardized Mean Differences

Introduction

Sepsis is a life-threatening condition resulting from a dysregulated host response to infection [1-3]. Septic shock represents its most severe form, with profound circulatory and metabolic derangements and the highest mortality risk [1-3]. Despite advances in sepsis management, its global incidence and mortality remain high [1-5].

Corticosteroids have long been used to restore vascular responsiveness and attenuate excessive inflammation [6,7]; however, their optimal use remains uncertain. Numerous randomized controlled trials and meta-analyses have reported mixed results, with observed benefits varying according to disease severity, vasopressor requirements, and timing of administration [8-16]. Although corticosteroids may shorten the duration of shock, their effects on survival have been inconsistent [8-18]. Emerging evidence suggests that heterogeneity in sepsis pathophysiology and variability in thresholds for steroid initiation may obscure treatment effects.

Current international guidelines weakly recommend hydrocortisone for patients with septic shock who require ongoing vasopressor support [2,3]. Beyond this broad recommendation, key elements of an optimal steroid strategy—including vasopressor dose at initiation, timing relative to circulatory failure, and appropriate steroid dosing—remain incompletely defined. In addition, vasopressin, a well-established second-line vasopressor in septic shock [2,3,18,19], may interact with corticosteroids, as suggested by experimental and clinical studies; however, existing findings are inconsistent and warrant further clarification [17-24]. A comprehensive evaluation of vasopressin-steroid interactions, along with steroid timing and dose, may help identify patients most likely to benefit and support more precise steroid use.

The emergency department (ED) differs fundamentally from the intensive care unit (ICU). Patients in the ED typically present during the earliest and

most dynamic phase of septic shock, often before adequate resuscitation, hemodynamic stabilization, or initiation of advanced organ support.

Because the clinical environment and therapeutic timing in the ED differ markedly from those in the ICU, findings from ICU-based studies may not fully reflect the effects of steroid therapy during this early phase.

ED-based data are therefore essential for clarifying whether steroid initiation during this early phase is associated with clinical outcomes.

Accordingly, this study aimed to (1) assess whether corticosteroid use in the ED is independently associated with lower 28-day mortality in patients with septic shock and whether this association differs according to vasopressin use, and (2) determine how hydrocortisone initiation timing (time from first vasopressor initiation to first hydrocortisone administration), vasopressor requirement at hydrocortisone initiation (norepinephrine-equivalent dose at first hydrocortisone administration), and hydrocortisone dose are associated with outcomes among patients receiving hydrocortisone. We hypothesized that steroid administration in the ED after the onset of septic shock would be associated with lower short-term mortality, particularly among patients receiving vasopressin, and that earlier administration and certain dosing would be associated with short-term mortality.

Methods

Study Design and Setting

This observational study used data from the Korean Shock Society (KoSS)

registry, an ED-based prospective multicenter septic shock registry established in university teaching hospitals in the Republic of Korea since 2015 [25,26]. Because data collection for the KoSS registry began before publication of the Sepsis-3 definitions, the registry included adult patients with confirmed or suspected infection who exhibited refractory hypotension or hyperlactatemia. Refractory hypotension was defined as hypotension despite fluid resuscitation or the requirement for vasopressor support. Patients were excluded if they met the inclusion criteria more than 6 h after ED arrival, were transferred from other hospitals without meeting the inclusion criteria, were transferred from a participating ED to another hospital, or had a do-not-resuscitate order. Data collection for the KoSS registry was approved by the Institutional Review Board of each participating hospital.

This study was approved by the Institutional Review Board of the Korea University Ansan Hospital (2025AS0150), which waived the requirement for informed consent because of the observational nature of the study. All research was performed in accordance with relevant guidelines/regulations.

Study Population

To evaluate the effect of steroids on outcomes, adult patients with septic shock according to the Sepsis-3 definitions who were enrolled in the KoSS registry were included. The study period was from October 1, 2015, through December 31, 2023. Patients with unknown outcomes, unknown timing of

steroid administration, steroid administration before the onset of septic shock for other indications, or long-term steroid use due to underlying conditions were excluded.

To evaluate the effects of hydrocortisone timing and dose on outcomes, patients who received steroids were selected from the above-mentioned cohort. Patients who received steroids other than hydrocortisone, patients with unknown hydrocortisone dose, and patients with unknown vasopressor dose at the time of initial hydrocortisone administration were further excluded.

Definitions and Data Collection

Sepsis was defined as an acute increase in the Sequential Organ Failure Assessment (SOFA) score of ≥ 2 points from baseline due to infection [1–3,27,28]. Septic shock was defined as the requirement for vasopressors to maintain a mean arterial pressure of ≥ 65 mmHg and a serum lactate level > 2 mmol/L despite adequate fluid resuscitation. Vasopressin and steroid administration were made at the discretion of physicians.

To evaluate the association of steroids with outcomes, the primary exposure variable was steroid administration in the ED after the diagnosis of septic shock. To evaluate the associations of hydrocortisone initiation patterns and dose with outcomes, we assessed two complementary initiation variables: (1) time from first vasopressor initiation to first hydrocortisone administration and (2) norepinephrine-equivalent dose [29] at first

hydrocortisone administration, which reflects the hemodynamic context at which hydrocortisone was initiated in routine practice. Hydrocortisone dose was evaluated as the administered daily hydrocortisone dose.

Norepinephrine-equivalent dose was categorized using two approaches: binary (<0.250 or ≥ 0.250 $\mu\text{g/kg/min}$ [2,3]) and ternary (<0.250 , 0.250 – 0.500 , or >0.500 $\mu\text{g/kg/min}$ [2,3,30]). The time from first vasopressor initiation to first hydrocortisone administration was categorized as <6 , 6 – 12 , or >12 h [31,32]. Hydrocortisone dose was categorized as <200 , 200 – 300 , or >300 mg/day [12]. The selected cutoffs were determined based on previous literature [2,3,12,30–32] and selected to allow for practical application in the ED.

The KoSS registry prospectively enrolled patients with septic shock presenting to the ED and followed them for up to 90 days. Data extraction and analysis were conducted between January and June 2025. The following data were extracted: age, sex, SOFA score, Acute Physiology and Chronic Health Evaluation (APACHE) II score, infection focus, comorbidities, lactate levels (initial and nearest to steroid administration), vasopressor use, vasopressor dose at first steroid administration, and steroid administration time and dose.

Outcomes

The primary outcome was 28-day mortality. Categorized timing, restricted cubic spline (RCS), and sensitivity analyses were considered exploratory.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation or median [interquartile range] and were compared using the Student's t-test or the Mann-Whitney U test, depending on normality. Categorical variables were expressed as counts (percentages) and were compared using the chi-square test or Fisher's exact test, as appropriate.

Multivariable logistic regression was used to evaluate independent associations between variables of interest and outcomes after adjustment for potential confounders. To assess the associations between steroid administration and outcome, two models were constructed: model 1 adjusted for sex, admission year, APACHE II score, infection focus, initial lactate level, and use of ≥ 2 vasopressor types (primary model) because the data collection for the KoSS registry began before publication of the Sepsis-3 definitions and recent guidelines that recommend vasopressin as a second-line vasopressor in septic shock [1-3]; and model 2 adjusted for sex, admission year, APACHE II score, infection focus, initial lactate level, and vasopressin use (alternative model) to evaluate further potential interaction between vasopressin and corticosteroids [17-24] in subgroup analysis.

To further address potential confounding, multivariable logistic regression analyses adjusting for abovementioned covariables after propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were performed. Propensity score for steroid administration was calculated

using a multivariable logistic regression model with abovementioned covariables. PSM was performed using nearest-neighbor matching method without replacement at a 1:1 ratio, with a caliper width of 0.1. Balance before and after matching was assessed using standardized mean differences (SMD), with an SMD <0.1 indicating adequate balance. IPTW was conducted using stabilized weights derived from the propensity scores.

To address time-dependent confounding, multivariable Cox proportional hazards models were performed after adjusting for abovementioned covariables. To address potential immortal time bias, multivariable time-dependent Cox proportional hazards models were additionally performed. Steroid administration was treated as a time-varying covariable.

Exploratory analyses were conducted after categorizing patients into groups based on the time from first vasopressor to first steroid administration (4 category: no steroid administration, <6 , $6-12$, >12 h; 3 category: no steroid administration, <12 , ≥ 12 h).

To assess the associations of hydrocortisone timing and dose with outcome, multivariable logistic regression analyses were performed and variables were analyzed using two approaches: (1) norepinephrine-equivalent dose at first hydrocortisone administration, time from first vasopressor initiation to first hydrocortisone administration, and hydrocortisone dose were each entered separately into multivariable models adjusted for sex, admission year, APACHE II score, infection focus, lactate level nearest to

hydrocortisone administration, and use of ≥ 2 vasopressor types (primary model); and (2) the same three variables were entered simultaneously into a single multivariable model adjusted for the same covariables (exploratory model). Each variable was evaluated as both a continuous and a categorical variable.

Model fit was assessed using the Hosmer-Lemeshow test. Concordance statistic (C-statistic) was assessed to evaluate the model's discrimination.

As an exploratory analysis, restricted cubic spline regression analysis was conducted to evaluate potential non-linear associations between variables of interest and outcomes. The RCS models were adjusted for the same covariables as the main multivariable analyses and used four knots. To assess robustness and sampling variability of predicted probabilities and derived cutoffs, nonparametric bootstrap resampling with 1,000 iterations was performed. The reference point was defined as the value at which the adjusted predicted probability of mortality was lowest. Cutoffs were conservatively defined as the points at which the lower bound of the 95% confidence interval (CI) for the adjusted odds ratio consistently exceeded 1.

Subgroup analyses were performed according to vasopressin use.

Interaction analysis was performed after including interaction term (vasopressin use $\times$ steroid administration) in model 2 that evaluated the associations between steroid administration and outcome. A sensitivity analysis was conducted using hydrocortisone-equivalent doses after

including patients who received steroids other than hydrocortisone. An additional sensitivity analysis was performed after multiple imputation using Multivariate Imputation by Chained Equations (the “mice” package) [33] for cases with missing steroid dose or vasopressor dose at initial hydrocortisone administration. Additional analyses were performed after adjustment or matching for the previously mentioned covariables, chronic lung disease, chronic renal disease, chronic liver disease, malignancy, AIDS, immunosuppressive disorders, and length of stay in the ED.

A p-value <0.05 was considered statistically significant. All analyses were performed using R version 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Steroids in septic shock

From 2015 to 2023, a total of 5,883 adult patients with septic shock were screened from the KoSS registry. Of these, 197 were excluded because of unknown outcomes, 110 due to unknown steroid administration time, 159 because steroids were administered before the onset of septic shock, and 290 due to long-term steroid use. Ultimately, 5,127 patients were included in the analysis (Figure 1).

The median age of the study population was 69 years, 60.2% were men, and respiratory infection was the most common infection focus (31.0%). The mean SOFA score was 9.9, the mean APACHE II score was 23.4. The

median length of stay in ED was 9.4 [5.8–18.0] h, and the overall 28-day mortality rate was 30.8%. Steroids were administered to 34.0% of patients, among whom hydrocortisone was the predominant steroid type (93.6%). The distribution of ED length of stay according to steroid administration and the patient flow diagram for ED length of stay were shown in Supplementary Figure 1 and 2.

In univariable analyses, non-survivors had significantly higher age, SOFA scores, APACHE II scores, and lactate levels than survivors (Table 1). Respiratory infection, use of ≥ 2 types of vasopressors, and vasopressin use were more frequent among non-survivors. Steroid administration was also significantly more frequent in the non-surviving group than in the surviving group (42.3% vs. 30.3%, $p < 0.001$).

In multivariable analyses, steroid administration was independently associated with lower 28-day mortality after adjustment in both models (adjusted odds ratio [aOR] 0.752, 95% CI 0.637–0.887, $p = 0.001$ in model 1; aOR 0.796, 95% CI 0.675–0.940, $p = 0.007$ in model 2; Table 2). C-statistics were 0.737 in model 1 and 0.734 in model 2. Additional adjustments for chronic lung disease, chronic renal disease, chronic liver disease, malignancy, AIDS, immunosuppressive disorders, and length of stay in ED showed similar findings (aOR 0.745, 95% CI 0.630–0.882, $p = 0.001$ in model 1 and aOR 0.797, 95% CI 0.675–0.943, $p = 0.008$ in model 2; Supplementary Table 1). When the analysis was restricted to hydrocortisone use, hydrocortisone administration remained independently associated with

lower 28-day mortality after adjustment in both models (aOR 0.745, 95% CI 0.627-0.884, $p=0.001$ in model 1; aOR 0.800, 95% CI 0.673-0.950, $p=0.013$ in model 2; Table 2). C-statistics were 0.734 in model 1 and 0.734 in model 2. Additional adjustments for chronic lung disease, chronic renal disease, chronic liver disease, malignancy, AIDS, immunosuppressive disorders, and length of stay in ED showed similar findings (aOR 0.736, 95% CI 0.619-0.876, $p=0.001$ in model 1 and aOR 0.798, 95% CI 0.671-0.949, $p=0.011$ in model 2; Supplementary Table 1). The Hosmer-Lemeshow test indicated good model fit for all models ($p>0.05$).

Multivariable analyses after PSM, IPTW, multivariable Cox proportional hazards models, and multivariable time-dependent Cox proportional hazards models showed similar findings (Table 2 and Supplementary Table 2).

In subgroup analyses, steroid administration was independently associated with decreased 28-day mortality in patients who received vasopressin (aOR 0.629, 95% CI 0.492-0.803, $p<0.001$; Supplementary Table 2). In contrast, steroid administration was not associated with 28-day mortality in patients who did not receive vasopressin (aOR 0.904, 95% CI 0.721-1.135, $p=0.386$). A significant interaction was observed between vasopressin use and steroid administration (p for interaction= 0.025). Consistently, steroid administration was independently associated with lower 28-day mortality among patients receiving vasopressin (aOR 0.631, 95% CI 0.494-0.805, $p<0.001$), but not among those who did not receive vasopressin (aOR 0.967,

95% CI 0.773–1.209, $p=0.769$). Additional analyses showed similar results (Supplementary Table 3).

In exploratory analyses, groups with shorter time from first vasopressor to first steroid administration were independently associated with lower 28-day mortality (Supplementary Table 2 and 3)

Hydrocortisone timing and dose in septic shock

Among the 5,127 patients analyzed for steroid use in septic shock, 3,384 were excluded because steroids were not administered, 112 because steroids other than hydrocortisone were administered, 91 due to an unknown hydrocortisone dose, and 11 due to an unknown vasopressor dose at the time of initial steroid administration. Consequently, 1,529 patients who received hydrocortisone were included in the analysis of hydrocortisone timing and dose (Figure 1).

The mean age of this cohort was 68.2 years, and 61.5% were men. Respiratory infection was the most common infection focus (33.9%), the mean SOFA score was 11.8, the mean APACHE II score was 28.5, and the 28-day mortality rate was 38.8%.

In univariable analyses, non-survivors had significantly higher age, SOFA scores, APACHE II scores, and lactate levels measured nearest to initial hydrocortisone administration than survivors (Table 3). Respiratory infection, use of ≥ 2 types of vasopressors, and vasopressin use were more frequent among non-survivors. Regarding hydrocortisone timing, the

norepinephrine-equivalent dose at first hydrocortisone administration was significantly higher in non-survivors than in survivors (0.400 [0.275–0.550] vs. 0.300 [0.225–0.475] $\mu\text{g/kg/min}$, $p<0.001$). When analyzed as categorical variables, higher norepinephrine-equivalent doses at first hydrocortisone administration were associated with greater 28-day mortality (both $p<0.001$). In contrast, time from first vasopressor to first hydrocortisone administration, whether analyzed as a continuous or categorical variable, was not associated with mortality ($p=0.613$ and $p=0.719$, respectively). For hydrocortisone dose, hydrocortisone dose was not associated with mortality when analyzed as either a continuous or categorical variable ($p=0.539$ and $p=0.658$, respectively).

In multivariable analyses with each variable of interest entered into separate models (Table 4 and Supplementary Table 4), the norepinephrine-equivalent dose at first hydrocortisone administration was independently associated with increased 28-day mortality (continuous variable: aOR 2.014, 95% CI 1.302–3.114, $p=0.002$; binary ≥ 0.250 $\mu\text{g/kg/min}$: aOR 1.451, 95% CI 1.080–1.949, $p=0.014$; ternary 0.250–0.500 $\mu\text{g/kg/min}$: aOR 1.364, 95% CI 1.004–1.855, $p=0.047$; and ternary >0.500 $\mu\text{g/kg/min}$: aOR 1.688, 95% CI 1.177–2.422, $p=0.005$). Time from first vasopressor to first hydrocortisone administration was also independently associated with increased 28-day mortality (continuous: aOR 1.018, 95% CI 1.003–1.033, $p=0.017$; categorical >12 h: aOR 1.413, 95% CI 1.029–1.941, $p=0.033$).

Hydrocortisone dose was not associated with 28-day mortality when

analyzed as a continuous variable (aOR 1.001, 95% CI 0.999–1.002, $p=0.299$). However, hydrocortisone dose >300 mg/day was independently associated with increased 28-day mortality (aOR 1.577, 95% CI 1.179–2.110, $p=0.002$). These findings remained consistent when the three variables were analyzed simultaneously in a single multivariable model (Supplementary Table 4). Additional analyses showed similar results (Supplementary Table 5). The Hosmer-Lemeshow test indicated good model fit for all models ($p>0.05$).

In subgroup analyses, among patients receiving vasopressin, a higher norepinephrine-equivalent dose, a longer vasopressor-to-hydrocortisone interval, and a hydrocortisone dose >300 mg/day were independently associated with increased 28-day mortality (aOR 1.871, 95% CI 1.137–3.078, $p=0.014$; aOR 1.044, 95% CI 1.018–1.070, $p=0.001$; and aOR 1.540, 95% CI 1.104–2.147, $p=0.011$, respectively; Supplementary Table 6). Among patients not receiving vasopressin, a higher norepinephrine-equivalent dose and a hydrocortisone dose >300 mg/day were independently associated with increased 28-day mortality (aOR 3.171, 95% CI 1.301–7.728, $p=0.011$; and aOR 1.914, 95% CI 1.033–3.546, $p=0.039$, respectively; Supplementary Table 6). Additional analyses showed similar results (Supplementary Table 7).

Exploratory analysis for hydrocortisone timing and dose

For norepinephrine-equivalent dose at first hydrocortisone administration,

restricted cubic spline analysis demonstrated a generally linear association between norepinephrine-equivalent dose and the adjusted predicted probability of 28-day mortality, with a modest increase in risk up to approximately 0.700 $\mu\text{g/kg/min}$, followed by a plateau (Supplementary Figure 3A). RCS analysis with bootstrap resampling yielded a similar pattern, with the lowest adjusted predicted probability observed at 0.040 $\mu\text{g/kg/min}$ (Supplementary Figure 3B). Using this bootstrap-derived cutoff as the reference, the adjusted odds ratio (aOR) curve indicated that the cutoff at which the lower bound of the 95% CI exceeded 1 was 0.449 $\mu\text{g/kg/min}$ (Supplementary Figure 3C). A norepinephrine-equivalent dose $>0.449 \mu\text{g/kg/min}$ was independently associated with increased mortality after adjustment (bootstrap mean aOR 1.52, 95% bootstrap CI 1.17–1.93, $p=0.004$; Supplementary Figure 3D). Additional analyses showed similar results (Supplementary Figure 4).

For the time from first vasopressor initiation to first hydrocortisone administration, RCS analysis showed a generally linear association between this interval and the adjusted predicted probability of 28-day mortality (Supplementary Figure 5A). RCS analysis with bootstrap resampling demonstrated a similar pattern, with the lowest adjusted predicted probability observed at 0.1 h (Supplementary Figure 5B). Using this bootstrap-derived cutoff as the reference, the aOR curve showed that the cutoff at which the lower bound of the 95% CI exceeded 1 was 9.8 h (Supplementary Figure 5C and 5D). Additional analyses showed similar

results (Supplementary Figure 6).

For hydrocortisone dose, both RCS analysis and RCS analysis with bootstrap resampling demonstrated a non-linear relationship between hydrocortisone dose and the adjusted predicted probability of 28-day mortality, with the lowest predicted probability observed at 263.6 mg/day (Supplementary Figures 7A and 7B). Using this bootstrap-derived cutoff as the reference, the aOR curve showed that the cutoff at which the lower bound of the 95% CI exceeded 1 was 312.6 mg/day (Supplementary Figure 7C). A hydrocortisone dose >312.6 mg/day was independently associated with increased 28-day mortality after adjustment (bootstrap mean aOR 1.54, 95% bootstrap CI 1.16-2.02, $p=0.008$; Supplementary Figure 7D).

Additional analyses showed similar results (Supplementary Figure 8).

Sensitivity analysis

Sensitivity analysis using hydrocortisone-equivalent dose, after including patients who received steroids other than hydrocortisone, resulted in 1,601 patients included in the analysis and demonstrated similar findings (Supplementary Table 8). Additional analyses showed similar results (Supplementary Table 9). Another sensitivity analysis using multiple imputation for cases with missing steroid dose and vasopressor dose at initial hydrocortisone administration included 1,631 patients and likewise demonstrated similar results (Supplementary Table 10). Additional analyses showed similar results (Supplementary Table 11).

Discussion

In this multicenter ED-based study of septic shock, steroid administration in the ED was associated with lower 28-day mortality after adjustment for confounders. Importantly, the association between ED steroid administration and 28-day mortality was consistent across multivariable logistic regression, PSM, IPTW, Cox proportional hazards, and time-dependent Cox proportional hazards models. The association between steroids and outcome was observed in subgroups receiving vasopressin, with a statistically significant interaction between steroid administration and vasopressin use. Among patients with septic shock who received hydrocortisone, a lower norepinephrine-equivalent dose at hydrocortisone initiation, a shorter interval from first vasopressor initiation to first hydrocortisone administration, and hydrocortisone dose >300 mg/day were associated with 28-day mortality. Exploratory analyses using RCS provided additional insight into hydrocortisone timing and dose, showing generally linear associations between timing variables and mortality risk, whereas hydrocortisone dose demonstrated a non-linear association. These exploratory analyses identified exploratory higher-risk ranges for hydrocortisone timing and dose, and the overall findings were consistent in sensitivity analyses.

The observed association of steroid administration with lower short-term mortality is consistent with findings from high-quality randomized trials and meta-analyses [8,10,13,16]. In addition, the association was significant

among patients receiving vasopressin, with a clear interaction between vasopressin use and steroid administration. This observation is supported by prior physiologic and clinical studies suggesting that corticosteroids may potentiate the effects of vasopressin in vasodilatory shock [17,20–22,24,34,35]. Glucocorticoids upregulate V1a receptor expression and suppress inducible nitric oxide synthase-mediated nitric oxide production, thereby restoring vasoconstrictor responsiveness in sepsis-induced vasoplegia [36,37]. Given that V1a receptor activation induces intracellular Ca^{2+} mobilization, these effects may enhance vasopressin-mediated signaling pathways [38]. Our findings extend this evidence by demonstrating that this association persists in an ED-based cohort of patients with acute septic shock. However, some studies have not identified a significant interaction between vasopressin and corticosteroids [18]. These heterogeneous results underscore the need for further randomized trials specifically designed to evaluate the interaction between steroids and vasopressin in septic shock.

The Surviving Sepsis Campaign suggests intravenous corticosteroids for patients with septic shock who have an ongoing requirement for vasopressor therapy [2,3]. However, the optimal dose and timing of initiation remain uncertain. Current recommendations largely reflect the inclusion criteria of major ICU-based randomized controlled trials, which defined an ongoing vasopressor requirement as a norepinephrine or epinephrine dose $\geq 0.25 \mu\text{g/kg/min}$ for at least 4 hours to maintain target

mean arterial pressure [2,3,10,11,18]. These criteria were originally designed primarily for trial enrollment and have not been fully validated as dose-response cutoffs in clinical practice. In our study, a longer interval from first vasopressor initiation to first hydrocortisone administration was associated with higher mortality, with an exploratory higher-risk range emerging beyond approximately 9.8 h. This finding suggests that earlier hydrocortisone initiation after vasopressor initiation was associated with lower mortality in this cohort. Although delayed hydrocortisone administration may partly reflect reverse causation and evolving shock severity, these observational data still suggest that substantial delay after shock onset may identify a higher-risk clinical domain that warrants further studies.

The norepinephrine-equivalent dose is another key factor considered when deciding whether to initiate intravenous corticosteroids in the Surviving Sepsis Campaign recommendations [2,3]. We intentionally examined norepinephrine-equivalent dose at first hydrocortisone administration as a clinically relevant initiation-threshold variable. Although a higher norepinephrine-equivalent dose may partly reflect greater shock severity at the time hydrocortisone was started, it also captures the vasopressor requirement at which clinicians chose to initiate hydrocortisone in real-world practice. This distinction is important because uncertainty often arises in patients with prolonged low-dose vasopressor requirements as well as in those with rapidly escalating high-dose vasopressor requirements. In

our cohort, higher norepinephrine-equivalent dose at hydrocortisone initiation was associated with higher mortality, and the exploratory analysis identified a higher-risk range above approximately 0.457 $\mu\text{g/kg/min}$. These findings should not be interpreted as establishing a definitive causal threshold, but they may help define clinically relevant domains for further studies.

The association between hydrocortisone dose and outcome is also clinically relevant because the commonly used range of 200–300 mg/day remains based on limited evidence. In our study, hydrocortisone doses >300 mg/day were associated with higher mortality, and restricted cubic spline analyses suggested a non-linear relationship, with a higher-risk range emerging above approximately 312.6 mg/day. This can be supported by previous studies [12,16]. Because higher doses may also reflect severity, treatment refractoriness, or clinician response to worsening shock, these data should not be interpreted as definitive proof that higher dosing is causally harmful. Nevertheless, they provide observational support for the clinical relevance of moderate-dose hydrocortisone and identify a dose range that merits further validation.

Taken together, the timing-, vasopressor-threshold-, and dose-related findings should be viewed as clinically informative and hypothesis-generating. They do not resolve causality, but they help define real-world domains in which hydrocortisone administration may be associated with outcomes and may inform the design of future randomized trials.

Nevertheless, such thresholds must be prospectively validated in randomized controlled trials before being considered for any form of clinical implementation.

The immune response in sepsis evolves over time, often transitioning from an early hyper-inflammatory phase to a later hypo-inflammatory or immunosuppressed state [39]. Patients with septic shock presenting to the ED are more likely to be in a hyperacute phase, during which excessive inflammation may predominate before the development of immunosuppression. In contrast, patients admitted to the ICU frequently arrive after variable delays, initial resuscitation, and evolving organ dysfunction, conditions that may reflect progression toward a hypo-immune phenotype. This distinction may depend more on the timing of shock recognition and treatment initiation than on the care setting itself. These temporal differences between the ED and ICU suggest that the anti-inflammatory and immunomodulatory effects of corticosteroids may yield greater benefit when initiated during the early hyper-inflammatory phase, such as the hyperacute state encountered in the ED. Individualized and serial assessments of immune status may further help identify patients most likely to benefit from corticosteroid therapy. In light of these potential phase-specific treatment effects, ED-based randomized clinical trials are warranted.

As an exploratory analysis, we additionally evaluated time from ED visit to first hydrocortisone administration and observed a similar directional

association. Nevertheless, we used first vasopressor initiation as the primary anchoring time point because the clinical question concerned corticosteroid initiation after vasopressor initiation. In patients with delayed progression to septic shock, using time from ED visit to hydrocortisone administration may misclassify prompt post-shock hydrocortisone administration as delayed. Therefore, time from first vasopressor initiation to first hydrocortisone administration may provide a more clinically relevant anchor for patients with delayed progression to shock.

This study has several notable strengths. We used an ED-based prospective multicenter septic shock registry and included a large number of patients. Because the cohort was derived from the ED, our findings are particularly applicable to hyperacute and acute-onset septic shock, which is often more severe at presentation. The results add evidence supporting steroid administration in patients with septic shock, even in the ED setting. Moreover, we evaluated hydrocortisone timing and dose as clinically relevant variables in sepsis management. Timing was assessed using both the interval from vasopressor initiation and the vasopressor dose at the time of hydrocortisone initiation. Clinically, uncertainty often arises in scenarios involving prolonged low-dose vasopressor infusion (>24 hours) as well as short-term high-dose vasopressor use (e.g., within 2 hours), and both scenarios were captured in our analysis. We conducted multiple multivariable regression models, subgroup analyses, interaction analyses, and sensitivity analyses, and the consistency of results across these

approaches strengthens the robustness of our findings. In addition, we evaluated non-linear associations after adjustment using restricted cubic spline analyses. Nonparametric bootstrap methods were employed to assess robustness and sampling variability. This methodological approach provides comprehensive information regarding steroid administration strategies. Importantly, by using reference points corresponding to the lowest adjusted predicted probability of mortality in the bootstrap-derived RCS curves, we identified exploratory thresholds that may help define higher-risk domains for future studies.

This study had several limitations. First, because of the observational study design, unmeasured or inadequately captured covariables may have been present. Although multivariable adjustments were performed, residual confounding cannot be excluded. In addition, the analyses identified associations only, and causal relationships cannot be established. The association may partly reflect time-dependent confounding or reverse causation. Although time-dependent Cox models were conducted, this approach does not fully replicate a landmark analysis framework. Therefore, residual time-dependent confounding or reverse causation may remain. Second, the study population consisted exclusively of Asian patients. Genetic polymorphisms affecting steroid metabolism (e.g., CYP3A4/CYP3A5 variants) and host-response variants associated with sepsis susceptibility vary across ethnogeographic populations [40–42]. Therefore, these results cannot be generalized to other racial and ethnic groups, especially non-

Asians. Third, data on steroid duration and tapering strategies were unavailable, indicating an area that requires further investigation. In addition, subsequent administrations of steroids, vasopressors and vasopressin, fluid therapy, or antibiotic management were not assessed in this study. Fourth, steroid timing and dose were evaluated among patients with septic shock who received hydrocortisone. Although sensitivity analyses using hydrocortisone-equivalent doses yielded similar results, only a small proportion of patients received steroids other than hydrocortisone. Therefore, further studies are warranted to evaluate steroid timing and dose across other steroid regimens or combinations. Fifth, the cutoff values were derived from exploratory analyses. These thresholds should be interpreted as conservative indicators of higher-risk domains rather than as rigid clinical cutoffs. Sixth, the study population is derived entirely from Korean EDs. This may limit the applicability to different healthcare systems. Seventh, length of stay, duration or dosing of vasoactive agents were not evaluated as outcomes. Further studies are warranted to evaluate the effect of steroid administration, timing, and dose in these outcomes. Nonetheless, the large sample size, multicenter design, and consistency across analytical models strengthen the overall validity of the conclusions.

Conclusions

In this multicenter ED-based registry, steroid administration in the ED was associated with lower 28-day mortality among patients with septic shock, particularly those receiving vasopressin. Among hydrocortisone-treated

patients, higher norepinephrine-equivalent dose at hydrocortisone initiation, a longer interval from vasopressor initiation to hydrocortisone administration, and hydrocortisone dose >300 mg/day were associated with increased mortality; however, these findings should be interpreted cautiously as observational and hypothesis-generating.

Declaration

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of the Korea University Ansan Hospital (2025AS0150), which waived the requirement for informed consent due to the nature of the observational study.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions:

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Validation: all authors

Formal Analysis: SA, CA, TGS, KK

Investigation: all authors

Data Curation: all authors

Resources: SC, SPC, THL

Writing: SA, CA, TGS, KK

Writing - Review and Editing: all authors

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Supervision: KK, SC, SPC, THL

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Figure legend

Figure 1. Flowchart of study population

Table 1. Baseline characteristics of the study population according to 28-

day mortality

	Survived at day 28 (N=3546)	Died (N=1581)	p-value
Age	70 [61-78]	72 [62-81]	<0.001
Sex			0.130
Men	2108 (59.4%)	976 (61.7%)	
Women	1438 (40.6%)	605 (38.3%)	
SOFA score (max)	9 [7-11]	12 [9-14]	<0.001
APACHE II score	21 [16-27]	26 [20-34]	<0.001
Infection focus*			
Respiratory*	901 (25.4%)	686 (43.4%)	<0.001
Gastrointestinal*	702 (19.8%)	355 (22.5%)	0.033
Hepatobiliary*	935 (26.4%)	255 (16.1%)	<0.001
Genitourinary*	909 (25.6%)	291 (18.4%)	<0.001
Others*	458 (12.9%)	224 (14.2%)	0.240
Comorbidities			
Hypertension	1540 (43.4%)	703 (44.5%)	0.509
Diabetes	1308 (36.9%)	560 (35.4%)	0.329
Cardiac disease	483 (13.6%)	237 (15.0%)	0.208
Stroke	444 (12.5%)	198 (12.5%)	1.000
Chronic lung disease	204 (5.8%)	136 (8.6%)	<0.001
Chronic renal disease	297 (8.4%)	160 (10.1%)	0.049
Chronic liver disease	438 (12.4%)	192 (12.1%)	0.870
Hematologic malignancy	245 (6.9%)	147 (9.3%)	0.004
Metastatic cancer	1044 (29.4%)	554 (35.0%)	<0.001
Clinical data			
Lactate (initial) (mmol/L)	4.1 [2.8-6.0]	5.9 [3.7-9.0]	<0.001
Use of ≥ 2 types of vasopressors	1043 (29.4%)	806 (51.0%)	<0.001
Vasopressin use	944 (26.6%)	708 (44.8%)	<0.001
Steroid administration	1074 (30.3%)	669 (42.3%)	<0.001
Steroid type			<0.001
None	2472 (69.7%)	912 (57.7%)	
Dexamethasone	24 (0.7%)	13 (0.8%)	
Hydrocortisone	1001 (28.2%)	630 (39.8%)	
Methylprednisolone	43 (1.2%)	25 (1.6%)	
Prednisolone	6 (0.2%)	1 (0.1%)	

*Mixed infections are possible.

Table 2. Multivariable regression analysis for steroid administration

	aOR / aHR	95% CI	p-value
Steroid administration (any type of steroid vs. none)			
Multivariable logistic regression			
Model 1	0.752	0.637-0.887	0.001
Model 2	0.796	0.675-0.940	0.007
Multivariable logistic regression after PSM			
Model 1	0.727	0.595-0.889	0.002

Model 2	0.723	0.592–0.884	0.002
Multivariable logistic regression after IPTW			
Model 1	0.706	0.616–0.812	<0.001
Model 2	0.707	0.615–0.812	<0.001
Multivariable Cox proportional hazards model			
Model 1	0.787	0.697–0.889	<0.001
Model 2	0.821	0.724–0.931	0.002
Multivariable time-dependent Cox proportional hazards model			
Model 1	0.802	0.709–0.907	<0.001
Model 2	0.839	0.740–0.951	0.006
Steroid administration (hydrocortisone vs. none)			
Multivariable logistic regression			
Model 1	0.745	0.627–0.884	0.001
Model 2	0.800	0.673–0.950	0.011
Multivariable logistic regression after PSM			
Model 1	0.644	0.520–0.797	<0.001
Model 2	0.643	0.519–0.795	<0.001
Multivariable logistic regression after IPTW			
Model 1	0.695	0.602–0.802	<0.001
Model 2	0.695	0.603–0.802	<0.001
Multivariable Cox proportional hazards model			
Model 1	0.780	0.687–0.885	<0.001
Model 2	0.822	0.722–0.936	0.003
Multivariable time-dependent Cox proportional hazards model			
Model 1	0.794	0.700–0.901	<0.001
Model 2	0.838	0.736–0.954	0.007

aOR>1 indicates higher odds of 28 d mortality. aHR>1 indicates higher hazards of 28 d mortality

Hosmer-Lemeshow test showed $p>0.05$ in all models.

Model 1: sex, admission year, APACHE II score, infection focus, lactate, and use of ≥ 2 types of vasopressors were adjusted.

Model 2: sex, admission year, APACHE II score, infection focus, lactate, and vasopressin use were adjusted.

Table 3. Baseline characteristics of study population for steroid timing and dose according to 28-day survival

	Survived at day 28 (N=935)	Died (N=594)	p-value
Age	69 [61–76]	70 [62–79]	0.023
Sex			0.802
Men	572 (61.2%)	368 (62.0%)	
Women	363 (38.8%)	226 (38.0%)	
SOFA score (max)	11 [8–13]	14 [11–16]	<0.001
APACHE II score	26 [19–32]	33 [25–39]	<0.001
Infection focus*			
Respiratory*	262 (28.0%)	256 (43.1%)	<0.001
GI*	243 (26.0%)	149 (25.1%)	0.738
Hepatobiliary*	220 (23.5%)	94 (15.8%)	<0.001
GU*	200 (21.4%)	97 (16.3%)	0.018
Others*	103 (11.0%)	95 (16.0%)	0.006
Comorbidities			
Hypertension	384 (41.1%)	243 (40.9%)	0.993
Diabetes	332 (35.5%)	195 (32.8%)	0.308
Cardiac disease	125 (13.4%)	98 (16.5%)	0.106
Stroke	102 (10.9%)	70 (11.8%)	0.656
Chronic lung disease	49 (5.2%)	44 (7.4%)	0.106
Chronic renal disease	78 (8.3%)	54 (9.1%)	0.678
Chronic liver disease	124 (13.3%)	70 (11.8%)	0.443
Hematologic malignancy	106 (11.3%)	87 (14.6%)	0.069
Metastatic cancer	330 (35.3%)	238 (40.1%)	0.067
Clinical data			
Lactate (nearest to initial steroid administration) (mmol/L)	4.4 [3.0–6.5]	6.5 [4.2–10.1]	<0.001
Use of ≥ 2 types of vasopressors	683 (73.0%)	500 (84.2%)	<0.001
Epinephrine use	47 (5.0%)	48 (8.1%)	0.021
Dopamine use	6 (0.6%)	13 (2.2%)	0.015
Vasopressin use	663 (70.9%)	463 (77.9%)	0.003
Vasopressor dose at first hydrocortisone administration			
Norepinephrine-equivalent dose ($\mu\text{g/kg/min}$)**	0.300 [0.225–0.475]	0.400 [0.275–0.550]	<0.001
Norepinephrine dose ($\mu\text{g/kg/min}$)	0.274 [0.200–0.400]	0.320 [0.200–0.439]	<0.001
Vasopressin dose (U/min)	0.020 [0.000–0.030]	0.030 [0.000–0.040]	<0.001
Norepinephrine-equivalent dose ($\mu\text{g/kg/min}$) as categorical variable (<0.250 $\mu\text{g/kg/min}$, ≥ 0.250 $\mu\text{g/kg/min}$)**			<0.001
Norepinephrine-equivalent dose <0.250 $\mu\text{g/kg/min}$	267 (28.6%)	101 (17.0%)	
Norepinephrine-equivalent dose ≥ 0.250 $\mu\text{g/kg/min}$	668 (71.4%)	493 (83.0%)	

Norepinephrine-equivalent dose ($\mu\text{g/kg/min}$) as categorical variable ($<0.250 \mu\text{g/kg/min}$, $0.250\text{--}0.500 \mu\text{g/kg/min}$, $>0.500 \mu\text{g/kg/min}$)**			<0.001
Norepinephrine-equivalent dose $<0.25 \mu\text{g/kg/min}$	267 (28.6%)	101 (17.0%)	
Norepinephrine-equivalent dose $0.250\text{--}0.500 \mu\text{g/kg/min}$	506 (54.1%)	325 (54.7%)	
Norepinephrine-equivalent dose $>0.500 \mu\text{g/kg/min}$	162 (17.3%)	168 (28.3%)	
Time from first vasopressor to first hydrocortisone administration			
Vasopressor to hydrocortisone time (h)	2.7 [1.2–6.0]	2.8 [1.2–6.4]	0.613
Vasopressor to hydrocortisone time as categorical variable ($<6 \text{ h}$, $6\text{--}12 \text{ h}$, $>12 \text{ h}$)			0.719
Vasopressor to hydrocortisone time $<6 \text{ h}$	698 (74.7%)	433 (72.9%)	
Vasopressor to hydrocortisone time $6\text{--}12 \text{ h}$	149 (15.9%)	99 (16.7%)	
Vasopressor to hydrocortisone time $>12 \text{ h}$	88 (9.4%)	62 (10.4%)	
Time from ED visit to first hydrocortisone administration			
ED visit to hydrocortisone time (h)	5.6 [2.9–9.4]	5.5 [2.6–9.7]	0.797
Hydrocortisone dose			
Hydrocortisone dose (mg/day)	250 [200–300.0]	250 [200–300]	0.539
Hydrocortisone dose as categorical variable ($<200 \text{ mg/day}$, $200\text{--}300 \text{ mg/day}$, $>300 \text{ mg/day}$)			0.658
Hydrocortisone dose $<200 \text{ mg/day}$	80 (8.6%)	56 (9.4%)	
Hydrocortisone dose $200\text{--}300 \text{ mg/day}$	650 (69.5%)	400 (67.3%)	
Hydrocortisone dose $>300 \text{ mg/day}$	205 (21.9%)	138 (23.2%)	

*Mixed infections are possible.

** Norepinephrine-equivalent dose ($\mu\text{g/kg/min}$) = Norepinephrine dose ($\mu\text{g/kg/min}$) + epinephrine dose ($\mu\text{g/kg/min}$) + $1/100 \times$ dopamine dose ($\mu\text{g/kg/min}$) + $0.06 \times$ phenylephrine dose ($\mu\text{g/kg/min}$) + $2.5 \times$ vasopressin dose (U/min) + $0.0025 \times$ angiotensin II dose (ng/kg/min) + $10 \times$ terlipressin dose ($\mu\text{g/kg/min}$) + $0.2 \times$ methylene blue dose (mg/kg/h) + $1/8 \times$ metaraminol dose ($\mu\text{g/kg/min}$) + $0.02 \times$ hydroxocobalamin dose (g) + $0.4 \times$ midodrine dose ($\mu\text{g/kg/min}$)

Table 4. Multivariable logistic regression analysis for steroid timing and dose

	aOR	95% CI	p-value
Norepinephrine-equivalent dose at first hydrocortisone administration ($\mu\text{g/kg/min}$)	2.014	1.302–3.114	0.002
Time from first vasopressor to first hydrocortisone administration (h)	1.018	1.003–1.033	0.017
Hydrocortisone dose			

Hydrocortisone dose <200 mg/day	1.370	0.901-2.086	0.141
Hydrocortisone dose 200-300 mg/day	reference		
Hydrocortisone dose >300 mg/day	1.577	1.179-2.110	0.002

aOR>1 indicates higher odds of 28 d mortality

Each variable of interest was adjusted to a separate multivariable model (primary model)*

Hosmer-Lemeshow test showed $p>0.05$ in all models.

*Sex, admission year, APACHE II score, infection focus, lactate (nearest to initial steroid administration), and use of ≥ 2 types of vasopressors were adjusted.

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