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Effect of norepinephrine initiation timing on mortality in septic shock: a multicenter cohort study

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Abstract

Background This study aims to investigate the association between timing of norepinephrine (NE) initiation and mortality in septic shock.

Methods We conducted a retrospective study using data from a multicenter database. Adult patients with septic shock presenting to the emergency departments, who showed initial hypotension and received NE, were included. We performed multivariable regression analysis to evaluate the association between norepinephrine timing and 28-day mortality, with stratifying according to the Sepsis-3 shock definition and vasopressor requirement risk assessed by the diastolic shock index and lactate levels.

Results A total of 4,456 patients were included. In the non-Sepsis-3 shock group, no significant association was found between the timing of NE administration and 28-day mortality. However, in the Sepsis-3 shock group, a significant association was observed, with each hourly delay in NE administration increasing the risk of 28-day mortality (aOR for hourly delay: 1.07, 95% CI: 1.02–1.13, $P=0.002$). Compared to the > 6-hour group, the aOR for 28-day high vasopressor requirement risk. mortality was 0.54 (95% CI: 0.35–0.81, $P=0.003$) for norepinephrine administration within 1 h and 0.63 (95% CI: 0.42–0.95, $P=0.025$) for the 1–3 h group. In the high-vasopressor requirement risk, hourly delay in NE administration was also associated with an increased risk of 28-day mortality (aOR for hourly delay: 1.07, 95% CI: 1.00-1.13, $P=0.027$). Compared to the > 6-hour group, the aOR for 28-day mortality was 0.53 (95% CI: 0.33–0.86, $P=0.010$) for within 1 h group.

Conclusions Early NE administration was associated with decreased 28-day mortality in patients who met the Sepsis-3 septic shock criteria and who had high vasopressor requirement risk.

Keywords Septic shock, Sepsis, Vasopressor, Norepinephrine

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Background

Sepsis, a life-threatening condition characterized by organ dysfunction resulting from a dysregulated host response to infection, carries a significant mortality risk [1, 2]. In cases progressing to septic shock which is characterized by profound circulatory and cellular/metabolic presents numerous challenges, In cases progressing to septic shock which is characterized by profound circulatory and cellular/metabolic presents numerous challenges, with mortality rates ranging from 30% to 50% [3, 4]. In septic shock, timely resuscitation and hemodynamic stabilization are critical for improving patient outcomes [5].

Vasopressor administration with initial fluid resuscitation is a main intervention to correct hypotension and maintain organ perfusion in septic shock [6]. The Surviving Sepsis Campaign (SSC) guidelines recommend administering at least 30 ml/kg of intravenous crystalloid fluid and applying norepinephrine (NE) as a first-line vasopressor to initially target a MAP of 65 mmHg for patients with septic shock [5]. However, despite these guideline recommendations, optimal vasopressor strategies remain an active area of research with unanswered questions regarding timing, combinations, and individualization of therapy [7].

Early NE administration, which is included in the SSC 1-hour bundle, may have beneficial effects on maintaining blood pressure, cardiac output, and tissue perfusion [8–10]. However, the association between the timing of NE initiation and mortality remains controversial. One previous meta-analysis showed that early NE administration was associated with improved survival [11]. However, in a most recent meta-analysis including more studies, early NE administration was not associated with a significant reduction in mortality [12]. In this study, possible mortality reduction was observed in studies without fluid restriction interventions. The heterogeneous results observed across different studies of sepsis interventions including vasopressors may be attributed to the inherent heterogeneity including disease severity of the patient population [13–16].

The aim of this study was to investigate the association between the timing of NE administration and mortality in patients with septic shock, stratified by the Sepsis-3 septic shock definition, which represents a more severe subset of patients [17, 18]. We also analyzed this relationship according to predicted vasopressor requirements using diastolic shock index (DSI) and lactate levels of initial presentation in emergency departments (EDs) [9]. By stratifying patients according to these criteria, we aimed to better characterize the impact of NE timing and identify subgroups who might derive greater therapeutic benefit from early NE administration.

Method

Study design and population

We conducted a retrospective study using data from a multicenter septic shock registry by the Korean Shock Society (KoSS) from October 2015 to December 2023 [19]. The KoSS web-based septic shock registry, which currently includes 21 teaching hospital EDs in Korea, has been prospectively collecting predetermined data pertaining to patients with septic shock who visited the EDs.

The KoSS septic shock registry included adult patients with suspected or confirmed infections who present to EDs with evidence of refractory hypotension or hypoperfusion [20, 21]. Refractory hypotension is characterized by persistent low blood pressure despite fluid administration, or the necessity for vasopressors after fluid resuscitation. Hypoperfusion is identified by serum lactate levels equal to or greater than 4 mmol/L. As the implementation of the KoSS registry began before the publication of the Sepsis-3 criteria, the inclusion strategy was based on the concept of refractory sepsis-induced hypotension or tissue hypoperfusion described in the 2012 Surviving Sepsis Campaign (SSC) guidelines, in which a serum lactate level ≥ 4 mmol/L was used as a marker of hypoperfusion [22]. In the registry database, patients presenting with initial systolic blood pressure (BP) below 90 mmHg or mean arterial pressure below 65 mmHg on ED arrival and receiving NE as first-line therapy within 12 h were included in this study. Patients with missing lactate values or unknown 28-day mortality were excluded.

The patients were divided into two groups based on whether they met the Sepsis-3 septic shock criteria (Sepsis-3 shock group vs. non-sepsis-3 shock group), defined by persistent hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) ≥ 65 mmHg and having serum lactate > 2 mmol/L despite adequate volume resuscitation [17].

Patients were also categorized as high-risk for vasopressor requirement by the vasopressor prediction score using the DSI and lactate levels [9]. The DSI is calculated by dividing the heart rate by the diastolic BP. This score ranges from 0 to 2 points, with 1 point assigned if the DSI is 2.0 or higher, and another point if lactate levels are 2.5 mmol/L or higher. Patients are categorized as high-vasopressor risk if they score 2 points, while those who do not meet both criteria are considered as low-vasopressor risk. Early NE administration was defined as NE administration within 1 h of ED arrival.

Data collection and outcome

All data were collected anonymously using standardized web-based report forms by research coordinators or clinicians at each participating hospital. Data were centrally reviewed at the coordinating hospital to control quality of data. For this study, the following patients' demographic and clinical data were retrieved from the KoSS registry: age, sex, initial vital signs, suspected infection source, comorbidities, result of blood culture, lactate levels, the Sequential Organ Failure Assessment (SOFA) score, mechanical ventilation, renal replacement therapy, the timing of NE and antibiotic administration and survival data. The times of ED arrival and the administration of NE and antibiotics were obtained from the electronic medical record as time stamps recorded in minute increments. For each patient, we calculated time-to-NE and time-to-antibiotics as the minute-level difference between these time points and then converted these values into hours for inclusion in the statistical models. Since we included only patients who were hypotensive upon ED arrival, this duration corresponds to the time from initial hypotension to NE administration. We analyzed complete cases without performing imputation for missing data. The primary outcome of this study was 28-day mortality.

Statistical analysis

Continuous variables are reported as mean and standard deviation (SD) and categorical variables as frequencies and proportions. We used two sample t tests to compare the means of the groups and the $\chi 2$ test for categorical variables.

The correlation between the time to NE administration and lactate levels or SOFA scores was evaluated using linear regression analysis, and fitted plots was generated. We performed univariable regression analysis and multivariable regression analysis to evaluate the association between NE timing and 28-day mortality adjusting age, the SOFA score, lactate levels, initial DSI, suspected infection source, and antibiotic administration within 1 h of ED arrival with stratifying according to the Sepsis-3 shock definition and vasopressor requirement risk. Time to NE administration was included in the models either as a linear continuous variable (per 1-hour increase) or as a categorical variable divided into the following intervals: within 1 h, 1–3 h, 3–6 h, and more than 6 h from ED arrival. We employed a restricted cubic spline curve to explore the trend, including potential non-linear patterns, in the relationship between the adjusted odds ratio (aOR) and time-to-NE. Statistical significance was defined as a two-tailed p-value < 0.05. Statistical analysis was performed using R version 4.3.3.

Study approval

This study was approved by the Institutional Review Boards of Samsung Medical Center (2024-02-270). The need for informed consent to participate was waived by the IRB of Samsung Medical Center. All research was performed in accordance with relevant guidelines/regulations and adhered to the Declaration of Helsinki.

Results

Study population

We assessed the eligibility of 10,376 adult patients in septic shock registry from October 2015 to December 2023 (Fig. 1). Patients who did not receive NE as the first-line vasopressor, those who received the first vasopressor more than 12 h after emergency department arrival,

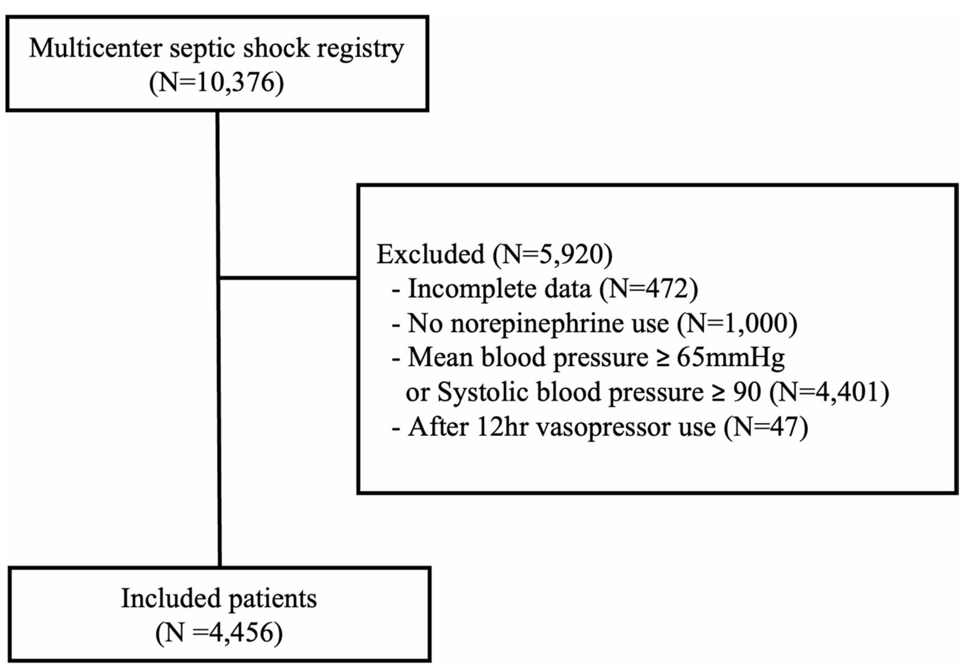

Fig. 1 Flow chart of study population. Excluded for incomplete data: 75 missing lactate values and 397 missing 28-day mortality status

patients with an initial mean arterial pressure ≥ 65 mmHg or systolic blood pressure ≥ 90 mmHg, and those with insufficient data including 75 missing lactate values and 397 missing 28-day mortality status were excluded from the study. A total of 4,456 patients were included in the study.

Comparisons between early NE group vs. late NE group

The baseline characteristics are shown in Table 1. In the overall study population ($N = 4{,}456$), the mean age was 68.1 ± 13.0 years, and 58.1% were male. The overall 28-day mortality in the study population was 24.9%. Among them, 1,191 patients (26.7%) received NE within 1 h of ED arrival and were categorized as the early NE group. The early NE group had higher lactate levels (5.2 ± 3.8 mmol/L vs. 3.8 ± 3.0 mmol/L, $P < 0.001$), SOFA scores (8.0 ± 3.3 vs. 6.2 ± 3.1, $P < 0.001$), and DSI (2.6 ± 1.1 vs. 2.3 ± 0.7, $P < 0.001$). The mean time to norepinephrine administration was 0.5 ± 0.3 h for the Early group and 2.8 ± 1.9 h for the late NE group. Time to NE showed negative correlation with lactate levels and SOFA score (Supplementary Fig. 1A and 1B). The proportion of patients with Sepsis-3 septic shock was significantly higher in the early NE group (77.9% vs. 58.0%, $p < 0.001$). Mortality was also significantly higher in the early NE group (31.6% vs. 22.5%, $p < 0.001$).

Comparisons according to the Sepsis-3 shock definition and the vasopressor requirement risk score

The Sepsis-3 shock group consisted of 2821 patients (63.3%), while the non-Sepsis-3 group included 1635 patients (36.7%) (Supplementary Table 1). Among the Sepsis-3 shock group, 28-day mortality was 32.1%, compared to 12.6% in the non-Sepsis-3 group ($P < 0{,}001$).

Table 1 Baseline characteristics

Characteristic	Overall (*N* = 4456)	Early group (< 1 h, *N* = 1191)	Late group (≥ 1 h, *N* = 3265)	*p*
Age(yr)	68.1 ± 13.0	69.4 ± 12.7	67.6 ± 13.1	< 0.001
Male sex	2591(58.1%)	719 (60.4%)	1872 (57.3%)	0.075
Vital sign at ED arrival				
Systolic pressure (mmHg)	75.5 ± 11.5	70.7 ± 12.9	77.2 ± 10.4	< 0.001
Diastolic pressure (mmHg)	46.8 ± 8.9	43.3 ± 9.5	48.1 ± 8.2	< 0.001
Heart rate (/min)	106.1 ± 24.8	105.6 ± 25.5	106.3 ± 24.6	0.381
Respiratory rate (/min) *	21.4 ± 5.2	22.4 ± 5.9	21.0 ± 4.8	< 0.001
Body temperature*	37.3 ± 1.3	37.1 ± 1.3	37.4 ± 1.3	< 0.001
Suspected infection source				
Respiratory infection	1274 (28.6%)	427 (35.9%)	847 (25.9%)	< 0.001
Urinary tract infection	1143 (25.7%)	336 (28.2%)	807 (24.7%)	0.002
Intraabdominal infection	1872 (42.0%)	440 (36.9%)	1432 (43.9%)	< 0.001
Other or unknown	761 (17.1%)	190 (16.0%)	571 (17.5%)	0.246
Comorbidity				
HTN	1834 (41.2%)	511 (42.9%)	1323 (40.5%)	0.162
DM	1396 (31.3%)	410 (34.4%)	986 (30.2%)	0.008
Cardiac disease	640 (14.4%)	191 (16.0%)	449 (13.8%)	0.061
Chronic lung disease	307 (6.9%)	81 (6.8%)	226 (6.9%)	0.941
Chronic renal disease	451 (10.1%)	142 (11.9%)	309 (9.5%)	0.019
Chronic liver disease	477 (10.7%)	120 (10.1%)	357 (10.9%)	0.444
Cerebrovascular disease	528 (11.8%)	192 (16.1%)	336 (10.3%)	< 0.001
Positive blood culture	2001 (44.9%)	532 (44.7%)	1469 (45.0%)	0.874
Lactate (mmol/L)	4.2 ± 3.3	5.2 ± 3.8	3.8 ± 3.0	< 0.001
SOFA score	6.7 ± 3.2	8.0 ± 3.3	6.2 ± 3.1	< 0.001
DSI	2.4 ± 0.8	2.6 ± 1.1	2.3 ± 0.7	< 0.001
Septic shock (Sepsis-3)	2,821 (63.3)	928 (77.9%)	1893 (58.0%)	< 0.001
Mechanical ventilation	1202 (27.0%)	483 (40.6%)	719 (22.0%)	< 0.001
Renal replacement therapy	753 (16.9%)	305 (25.6%)	448 (13.7%)	< 0.001
Antibiotics administered within 1 h	880(19.7%)	332(27.9%)	548(16.8%)	< 0.001
2nd vasopressor use	1328 (29.8%)	561 (47.1%)	767 (23.5%)	< 0.001
Time to norepinephrine use from ED arrival (hour)	2.2 ± 1.9	0.5 ± 0.3	2.8 ± 1.9	< 0.001
28-Day mortality	1111(24.9%)	376 (31.6%)	735 (22.5%)	< 0.001

ED Emergency Department, *HTN* Hypertension, *DM* Diabetes mellitus, *SOFA* Sequential Organ Failure Assessment, *DSI* Diastolic Shock Index

*Except for one missing respiratory rate and one missing body temperature, no additional missing data were identified

Overall, the Sepsis-3 shock group demonstrated higher severity. The mean time to NE administration was 2.2 ± 1.9 h, and NE was administered more rapidly in the Sepsis-3 shock group compared to the non-Sepsis-3 group (2.0 ± 1.9 h vs. 2.6 ± 2.0 h, $P < 0.001$). The distributions of NE administration are shown in Supplementary Fig. 2.

According to the vasopressor requirement risk score, the high-vasopressor risk group consisted of 2055 patients (46.1%), while the low-vasopressor risk group included 2401 patients (53.9%) (Supplementary Table 2). The comparison between high- and low-vasopressor risk groups showed a similar trend to the differences observed based on the presence of Sepsis-3 septic shock. The high-vasopressor risk group demonstrated significantly higher severity and 28-day mortality.

Effect of NE administration timing on mortality

In the unadjusted analysis, hourly delay in NE administration was associated with decreased risk of 28-day mortality in the non-Sepsis-3 shock group (odds ratio [OR] for hourly delay: 0.91, 95% CI: 0.84–0.99, $P = 0.03$). On the contrary, no significant association was found in Sepsis-3 shock group (Table 2). In the multivariable analysis, no significant association was found between the timing of NE administration and 28-day mortality in the non-Sepsis-3 shock group, (aOR for hourly delay: 0.96, 95% CI: 0.88–1.04, $P = 0.37$). However, in the Sepsis-3 shock group, a significant association was observed, with each hourly delay in NE administration increasing the risk of 28-day mortality (aOR for hourly delay: 1.07, 95% CI: 1.02–1.13, $P = 0.002$). Compared to the > 6-hour group, the aOR for 28-day mortality was 0.54 (95% CI: 0.35–0.81, $P = 0.003$) for NE administration within 1 h and 0.63 (95% CI: 0.42–0.95, $P = 0.025$) for the 1–3 h group. When using either the 1–3 h interval (aOR 0.85, 95% CI: 0.69–1.03, $P = 0.103$) or the 3–6 h interval (aOR 0.78, 95% CI: 0.59–1.03, $P = 0.07$) as reference points in the Sepsis-3 shock group, the association between NE administration within 1 h and reduced mortality did not reach statistical significance.

The high-vasopressor risk group also demonstrated a similar trend. Each hourly delay in NE administration was associated with an increased risk of 28-day mortality (aOR for hourly delay: 1.07, 95% CI: 1.00-1.13, $P = 0.027$) (Table 3). Compared to the > 6-hour group, the aOR for 28-day mortality was 0.53 (95% CI: 0.33–0.86, $P = 0.010$) for within 1 h group and 0.63 (95% CI: 0.40–1.01, $P = 0.056$) for the 1–3 h group. Similar results were observed, where using either the 1–3 h interval (aOR 0.84, 95% CI: 0.66–1.06, $P = 0.140$) or the 3–6 h interval (aOR 0.85, 95% CI: 0.60–1.17, $P = 0.294$) as reference points, the association between early NE administration within 1 h and mortality reduction did not achieve statistical significance.

When analyzing the spline curves illustrating aOR for 28-day mortality according to NE initiation time, the Sepsis-3 shock group revealed an increasing trend in the aOR over the time to NE administration (Fig. 2). Also, High risk vasopressor prediction score group showed similarly pattern (Supplementary Fig. 3).

In additional subgroup analyses, each hourly delay in norepinephrine initiation remained independently associated with higher 28-day mortality among patients with lactate ≥ 4 mmol/L (aOR = 1.07; 95% CI 1.01–1.13; $P = 0.025$) and those with a DSI ≥ 2.2 (aOR = 1.07; 95% CI 1.01–1.13; $P = 0.016$). In contrast, no significant association was observed in patients with lactate < 4 mmol/L or DSI < 2.2 (Supplementary Table 3).

Table 2 Multivariable logistic regression for the effect of the timing of norepinephrine administration from initial hypotension on 28-day mortality according to the Sepsis-3 shock

Group	Unadjusted OR	95% CI	*p*	Adjusted OR	95% CI	*p*
Non-Sepsis-3 shock group						
Hourly delay of norepinephrine administration	0.91	0.84–0.99	0.029	0.96	0.88–1.04	0.319
Timing of norepinephrine administration (hr)						
> 6 h	Reference			Reference		
3–6 h	0.94	0.49–1.94	0.869	0.93	0.47–1.98	0.848
1–3 h	1.23	0.68–2.43	0.514	1.13	0.60–2.28	0.718
< 1 h	1.75	0.92–3.60	0.104	1.31	0.65–2.79	0.461
Sepsis-3 shock group						
Hourly delay of norepinephrine administration	0.98	0.93–1.02	0.332	1.07	1.02–1.13	0.002
Timing of norepinephrine administration (hr)						
> 6 h	Reference			Reference		
3–6 h	0.69	0.46–1.04	0.071	0.69	0.44–1.07	0.095
1–3 h	0.73	0.51–1.07	0.099	0.63	0.42–0.95	0.025
< 1 h	0.94	0.65–1.38	0.003	0.54	0.35–0.82	0.003

Table 3 Multivariable logistic regression for the effect of the timing of norepinephrine administration from initial hypotension on 28-day mortality according to the vasopressor requirement risk

Group	Unadjusted OR	95% CI	*p*	Adjusted OR	95% CI	*p*
Low-vasopressor risk group						
Hourly delay of norepinephrine administration	0.93	0.88–0.99	0.015	1.01	0.95–1.07	0.812
Timing of norepinephrine administration (hr)						
> 6 h	Reference			Reference		
3–6 h	0.94	0.58–1.57	0.801	0.96	0.57–1.65	0.878
1–3 h	1.08	0.69–1.75	0.750	0.96	0.60–1.60	0.872
< 1 h	1.59	1.00-2.64	0.059	0.97	0.58–1.67	0.918
High-vasopressor risk group						
Hourly delay of norepinephrine administration	0.96	0.91–1.01	0.143	1.07	1.01–1.13	0.027
Timing of norepinephrine administration (hr)						
> 6 h	Reference			Reference		
3–6 h	0.64	0.40–1.04	0.068	0.63	0.37–1.07	0.083
1–3 h	0.74	0.48–1.14	0.166	0.63	0.40–1.02	0.056
< 1 h	0.98	0.63–1.52	0.915	0.53	0.33–0.86	0.010

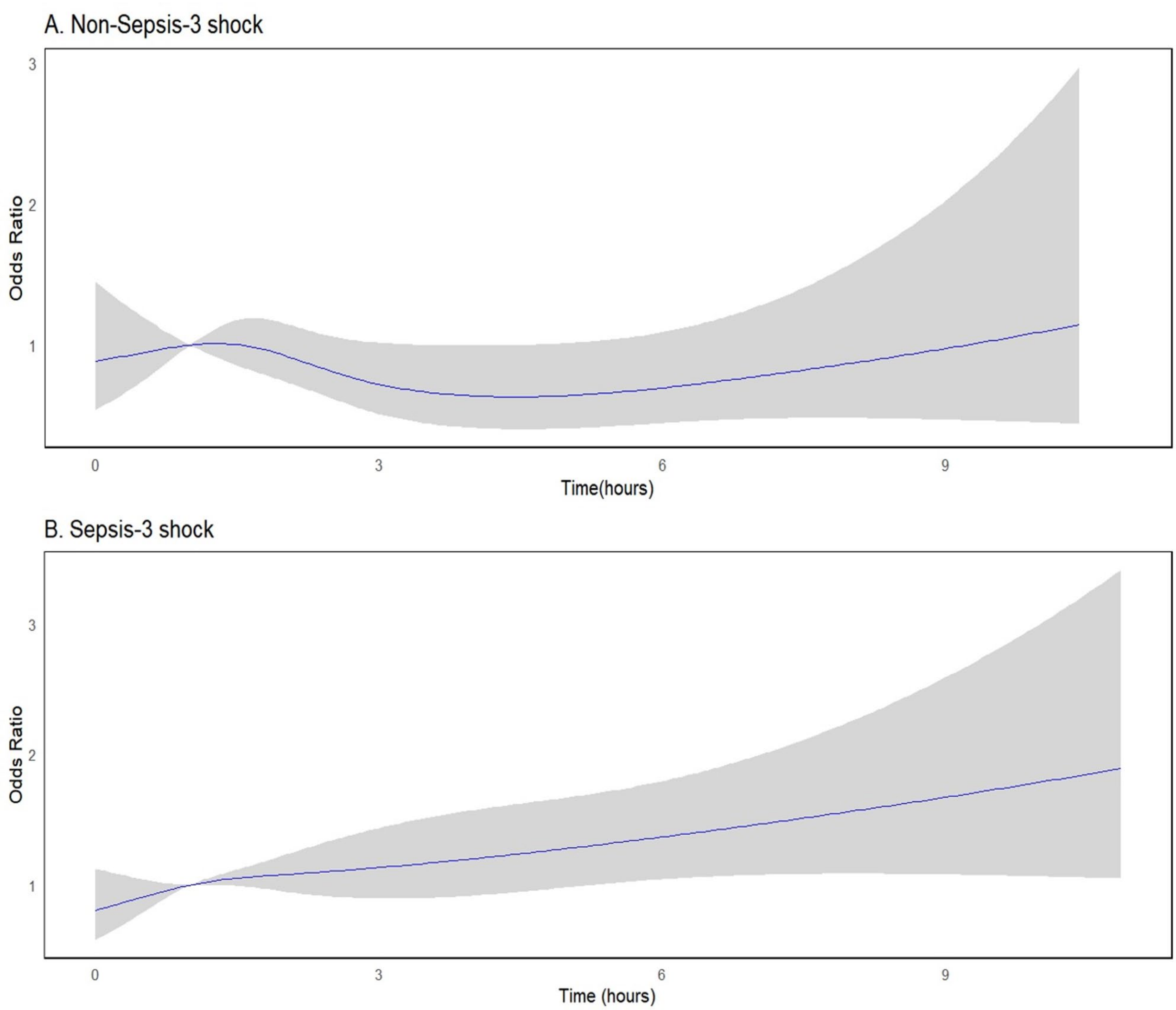

Fig. 2 Spline curves showing adjusted odds ratios for 28-day mortality by norepinephrine initiation time

Discussion

In this study, we investigated the relationship between norepinephrine NE administration timing and 28-day mortality among initially hypotensive patients in the EDs. Our analysis revealed a significant association between early NE administration and improved survival, particularly in patients meeting the Sepsis-3 shock criteria and those classified as high-vasopressor risk based on the DSI and lactate levels. Our study suggests that the relationship between NE administration timing and outcomes might vary depending on disease severity and more severe cases could benefit from earlier administration of norepinephrine.

The impact of early NE administration on survival in septic shock patients has shown heterogeneous results across various studies [9, 11–13, 16, 23–31]. This variability might be attributed to the diverse characteristics of patient populations, including differences in baseline severity of illness and comorbidities, study designs, timing of NE administration, fluid resuscitation, and other concurrent interventions. Some studies suggest that early NE administration can improve outcomes by stabilizing hemodynamics, reducing the duration of hypotension, and achieving faster hemodynamic stabilization [23, 29, 31]. However, other studies indicate that initiating NE too early may increase mortality [16]. In some observational studies including this study, the early administration group included patients with higher severity of illness, which can confound results and lead to biased interpretations of the impact on survival. This indicates that patient heterogeneity and the severity of illness are critical factors that may impact the observed outcomes.

Current research indicates that the effectiveness of treatments for sepsis and septic shock can vary significantly based on patient characteristics and clinical subtypes [32–35]. For instance, recent observational studies showed that timely administration of antibiotics improved outcomes in patients with septic shock [32, 33]. However, the positive association between early antibiotic administration and improved outcomes was less evident in patients with sepsis without shock. The findings align with these SSC guidelines recommending that antibiotics be administered within one hour for patients experiencing shock and prioritizing a rapid assessment for those with potential sepsis but without shock [5]. Our findings parallel the concept of targeted intervention timing in sepsis care, similar to the evidence for early antibiotic administration.

The Sepsis-3 shock criteria can only be confirmed after vasopressor initiation as it requires persistent hypotension requiring vasopressors with elevated lactate. Considering the present findings, it could be a practical approach early NE administration may be considered particularly in sepsis-induced hypotension and elevated lactate levels. Furthermore, our results indicate that patients with both high DSI and elevated lactate levels are more likely to require vasopressors and may derive benefit from early NE administration, as demonstrated by improved mortality outcomes in this high-vasopressor risk group. These findings provide a potential risk-stratification strategy for identifying patients who might benefit from early vasopressor support. These observations require validation through prospective studies and clinical trials to establish definitive treatment protocols.

In patients not meeting the Sepsis-3 criteria or patients with low-vasopressor risk, we found no clear link between NE timing and 28-day mortality. This suggests that for less severe cases, other factors may play a more significant role in determining outcomes. Also, because the mortality was relatively low, the significant effect could not be observed due to the limited sample size. In less severe cases, clinicians may consider a balanced approach, potentially prioritizing fluid resuscitation and infection control in these patients.

Our study has several limitations that should be considered when interpreting the results. First, due to its retrospective design, we cannot establish a causal relationship between early NE administration and mortality outcomes, and unmeasured confounding factors might have influenced the results [36]. The timing of NE administration could have been affected by various clinical factors, including physician preference, institutional protocols, and resource availability. Second, although we adjusted for multiple variables in our analysis, we could not account for the timing and volume of fluid administration before NE initiation, which might have impacted patient outcomes. Additionally, our study has a limitation the generalizability of our findings to other healthcare settings or populations. Furthermore, the risk stratification score using DSI and lactate levels was initially developed and validated in a single-center study, requiring further external validation. Also, these markers might not fully capture the complex pathophysiology of septic shock.

Conclusion

Among adult ED patients with sepsis patients requiring vasopressor, early NE administration was associated with decreased 28-day mortality in patients who met the Sepsis-3 septic shock criteria and who had high vasopressor requirement risk based on DSI and lactate levels. Our findings suggest that risk stratification could help identify patients who might benefit from early vasopressor support.

Abbreviations

aOR Adjusted Odds Ratio
BP Blood Pressure
CI Confidence Interval

DSI	Diastolic Shock Index
ED	Emergency Department
KoSS	Korean Shock Society
MAP	Mean Arterial Pressure
MV	Mechanical Ventilation
NE	Norepinephrine
OR	Odds Ratio
RRT	Renal Replacement Therapy
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment
SSC	Surviving Sepsis Campaign

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-026-03638-w.

Supplementary Material 1.

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Clinical trial number

Not applicable

Authors' contributions

All authors made a substantial contribution to the concept and design of the manuscript.Conceptualization: JWC, TGSMethodology: all authorsValidation: all authorsFormal Analysis: JWC, TGSInvestigation: all authorsData Curation: all authorsResources: SC, SPC, THLWriting: JWC, TGSWriting – Review and Editing: all authorsVisualization: JWCSupervision: KK, SC, SPC, THLFunding acquisition: TGSAll authors have read and granted final approval of the version of the manuscript to be published.

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Data availability

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

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Boards of Samsung Medical Center (2024-02-270). The need for informed consent to participate was waived by the IRB of Samsung Medical Center. All research was performed in accordance with relevant guidelines/regulations and adhered to the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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