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Original Article

Effect of timing of norepinephrine administration on prognosis of patients with septic shock: A prospective cohort study

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ABSTRACT

Background: Sepsis and septic shock are major healthcare problems worldwide, associated with substantial mortality. Early administration of norepinephrine in septic shock patients has been associated with an increased survival rate, but the timing from septic shock to norepinephrine initiation is controversial. This study examined the associations between the timing of initial norepinephrine administration and clinical outcomes in adult patients with septic shock.

Methods: This prospective cohort study was conducted from September 2021 to June 2022 in an intensive care unit (ICU) of a tertiary general hospital. All enrolled patients were divided into early and late norepinephrine groups according to whether the time from the onset of septic shock to the first application of norepinephrine was >1 h. The primary outcome was 28-day mortality. Secondary outcomes included ICU length of stay (LOS), hospital LOS, time to achieve a mean arterial pressure (MAP) ≥65 mmHg, 24-hour infusion volume, 6-hour Lac clearance, mechanical ventilation days, and continuous renal replacement therapy (CRRT)ratio. Multivariable logistic regression analysis was used to evaluate the independent risk factors for 28-day mortality.

Results: This study enrolled 120 patients, including 42 patients (35.0%) and 78 patients (65.0%) in the early and late norepinephrine groups, respectively. The 28-day mortality was lower in the early group than in the late group (28.6% *vs.* 47.4%, *P*=0.045). The median time to achieve MAP ≥65 mmHg was shorter in the early group than in the late group (1.0 h *vs.* 1.5 h, *P*=0.010). The median 24-hour intravenous fluids volume in the early group was lower than that in the late group (40.7% *vs.* 14.9%, *P*=0.030). The median 6-hour lactate (Lac) clearance rate in the early group was higher than that in the late group (40.7% *vs.* 14.9%, *P*=0.009). There were no significant differences between early and late groups by ICU LOS (*P*=0.748), hospital LOS (*P*=0.369), mechanical ventilation time (*P*=0.128), and CRRT ratio (*P*=0.637). The independent risk factors for 28-day mortality included being male (odds ratio [OR]=3.288, 95% confidence interval [CI]: 1.236 to 8.745, *P* = 0.017), time to norepinephrine initiation >1 h (OR=4.564, 95% CI: 1.382 to 15.079, *P* = 0.013), and time to achieve MAP ≥65 mmHg (OR=1.800, 95% CI: 1.171 to 2.767, *P* = 0.007).

Conclusions: Norepinephrine initiation ≤1 h is associated with lower 28-day mortality in patients with septic shock. Early norepinephrine administration is also associated with a shorter time to achieve MAP ≥65 mmHg, lower 24-hour intravenous fluids volume, and higher 6-hour Lac clearance rate. Being male, time to achieve MAP ≥65 mmHg, and norepinephrine initiation >1 h are independent risk factors for 28-day mortality.

Trial registration Chinese Clinical Trial Registry Identifier: ChiCTR2100044071.

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is characterized by sepsis with persistent hypotension requiring vasoactive medications to maintain a mean arterial pressure (MAP) ≥65 mmHg and serum lactate (Lac) level >2 mmol/L despite adequate fluid resuscitation.[1] Sepsis and septic shock are major healthcare problems, affecting millions of people worldwide each year and resulting in between one in six and one in three deaths.[2–4] Early identification and appropriate management within the first few hours of septic shock can significantly improve clinical outcomes.

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Fluid resuscitation is widely regarded as the first line of hemodynamic resuscitation for septic shock.[5] However, severe hypotension caused by sepsis results not only from relative or absolute hypovolemia but also from vasoplegia, which requires vasopressor support. Thus, fluid resuscitation alone is insufficient to increase peripheral perfusion pressure in most patients with septic shock.[6] In addition, extracellular fluid overload may lead to tissue edema and increased mortality.[7–9] Therefore, early use of vasoactive drugs to promote hemodynamic stability is crucial in managing septic shock.[10] Norepinephrine is both an α1- and β1-agonist and can increase vascular tone and contractility.[11] Recent guidelines recommend norepinephrine as a first-line vasopressor for septic shock treatment.[12] However, the timing of vasopressor treatment appears to be more critical than the specific drug.[13]

Several studies suggest that early administration of norepinephrine in septic shock patients may be associated with improved survival rates.[14–20] However, the timing from septic shock to norepinephrine initiation is controversial, with studies defining early initiation differently, from 2 h to 6 h or even longer. In addition, uncertainties persist regarding the effect of the timing of norepinephrine administration on other clinical outcomes in patients with septic shock, including length of hospital stay, mechanical ventilation time, and organ function. Hence, this study aimed to examine the relationship between the timing of initial norepinephrine administration and clinical outcomes in patients with septic shock.

Methods

Study population

This study was conducted from September 2021 to June 2022 in the intensive care unit (ICU) of the First Hospital of Jilin University in Changchun, China, a tertiary general hospital. Adult patients diagnosed with septic shock according to The Third International Consensus definitions[1] for sepsis and septic shock (Sepsis-3) were prospectively included. This study was approved by the Ethics Committee of the First Hospital of Jilin University (01.29.2021, 20K099–002) and registered in the Chinese Clinical Trial Registry (ChiCTR2100044071).

All enrolled patients received norepinephrine (the only vasoactive agent) to maintain a target MAP ≥65 mmHg. Triggers to start norepinephrine infusion included low diastolic arterial pressure (DAP <40 mmHg) and very low MAP (MAP <60 mmHg). According to the Surviving Sepsis Campaign Guidelines,[12] broad-spectrum antibiotics were administered within the first hour, and 30 mL/kg of sodium bicarbonate Ringer solution was used for initial volume resuscitation.

The inclusion criteria were: (1) adults (≥18 years old); (2) patients with septic shock; (3) use of norepinephrine as the only vasoactive drug to maintain target MAP ≥65 mmHg; (4) sodium bicarbonate Ringer solution (30 mL/kg) was used for initial volume resuscitation. The exclusion criteria were: (1) pregnant or lactating women; (2) patients with end-stage renal disease; (3) patients with incomplete information; (4) patients enrolled in other trials; (5) other reasons that the researchers considered inappropriate to participate in the study.

Patients with septic shock were identified by clinical manifestations of sepsis with persistent hypotension requiring vasoactive medications to maintain MAP ≥65 mmHg and serum Lac level >2 mmol/L despite adequate fluid resuscitation.[1] All enrolled patients were classified into early or late norepinephrine groups based on whether norepinephrine was administered ≤1 h or >1 h of the onset of septic shock, respectively. In this study, early norepinephrine was defined as the administration of norepinephrine within one hour of the onset of septic shock. The flowchart for patient inclusion is presented in (Figure 1).

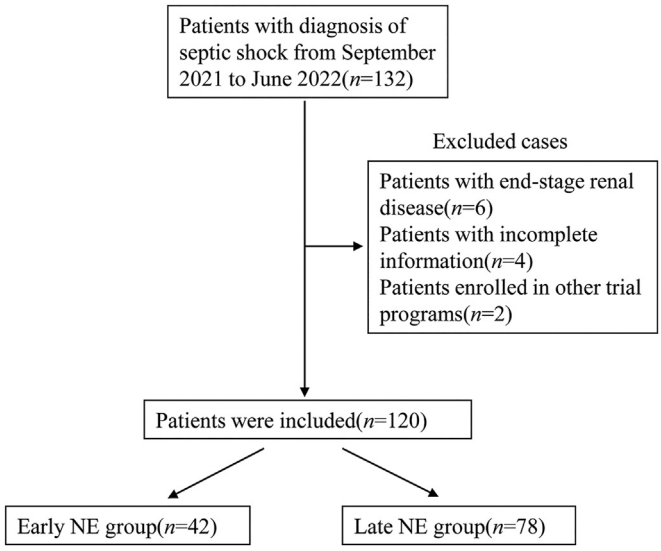

Figure 1. Flowchart for patients inclusion. NE: Norepinephrine.

Data collection

Data was collected on age, sex, body weight, complications, the Acute Physiology and Chronic Health Evaluation (APACHE) II score based on the worst values obtained within 24 h after the onset of septic shock, Sequential Organ Failure Assessment (SOFA) score, past medical history, and site of infection. In addition, procalcitonin (PCT), white blood cells (WBC), platelets (PLT), creatinine (CRE), blood urea nitrogen (BUN), liver function, and Lac were also collected. Furthermore, We also collected the time to achieve MAP ≥65 mmHg, 24-hour infusion volume (including crystalloid, colloid, and blood products) after septic shock, 6-hour Lac clearance, continuous renal replacement therapy (CRRT) ratio, mechanical ventilation days, length of ICU stay, length of hospital stay, and 28-day survival. The time to achieve MAP ≥65 mmHg was defined as the time from shock onset to sustained MAP ≥65 mmHg. Six-hour Lac clearance was calculated as follows: (initial Lac concentration – 6-hour Lac concentration)/initial Lac concentration × 100%.

Primary and secondary outcomes

The primary outcome was 28-day mortality. Secondary outcomes included ICU length of stay (LOS), hospital LOS, time to achieve MAP ≥65 mmHg, 24-hour infusion volume, 6-hour Lac clearance, mechanical ventilation days, and CRRT ratio.

Statistical analysis

Data were analyzed using SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). We evaluated the normality of dif-

ferent dependent variables in relation to their independent variables. A variable was considered normally distributed if the *z*-value of skewness and kurtosis was between −1.96 and +1.96[21] and the Shapiro–Wilk's test had a *P*-value ≥0.05.[22,23] Most variables were found to be non-normally distributed. Hence, continuous variables were expressed as median (interquartile range). Categorical variables were expressed as frequency and proportion.

The non-parametric Mann–Whitney *U* test was used to compare quantitative variables between two groups.[24] Categorical variables were compared using the chi-squared or Fisher's exact test.[25] We used the Kaplan–Meier survival model and Log Rank test to compare 28-day survival rate between two groups. A two-sided *P*-value <0.05 was considered to be statistically significant.

Risk factors for 28-day mortality

Patients were categorized into a 28-day survival group and a 28-day non-survival group based on their survival at 28 days. We performed univariate and multivariable analyses to identify risk factors for 28-day mortality in patients with septic shock. The multivariable logistic regression analysis included parameters with *P*-values <0.1 in univariate analyses.

In addition, multivariable logistic regression analysis was used to examine the risk factors of 28-day mortality in patients with septic shock,[26] and the results are reported as odds ratios (OR) of death with their corresponding 95% confidence intervals (CIs). Variable selection was based on the *P*-values from univariate analyses.

Results

Cohort characteristics

A total of 132 patients were screened for this study based on the number of beds in the ward and the research period. After excluding patients with missing data, 120 eligible patients were continuously included to minimize bias: 42 patients (35.0%) and 78 (65.0%) patients were classified into the early and late norepinephrine initiation groups, respectively. Table 1 summarizes the baseline characteristics of the study participants.

There were no significant differences between the early and late groups with respect to sex, disease severity score, past medical history, organ function, and site of infection. The baseline data of the two groups of patients were matched.

Primary and secondary outcomes

The clinical outcomes of the two groups are shown in (Table 2). The 28-day mortality of the early norepinephrine group (28.6%) was lower than that in the late group (47.4%) (*P*=0.045). The total 28-day mortality of all enrolled patients was 40.8% (49/120). Kaplan–Meier survival analysis showed that the 28-day survival rate of the early norepinephrine group was higher than that of the late norepinephrine group (*P*=0.049) (Figure 2).

The time to achieve MAP ≥65 mmHg in the early group was shorter compared to the late group (1.0 h *vs.* 1.5 h, *P*=0.010). The 24-hour intravenous fluids volume was also lower in the early group than in the late group (3605.00 mL *vs.* 3930.50 mL, *P*=0.030). In addition, the 6-hour Lac clearance rate in the early group was higher than in the late group (40.7% *vs.* 14.9%, *P*=0.009). There were no significant differences observed between the early and late groups with respect to ICU LOS (*P*=0.748), hospital LOS (*P*=0.369), mechanical ventilation days (*P*=0.128), and CRRT ratio (*P*=0.637).

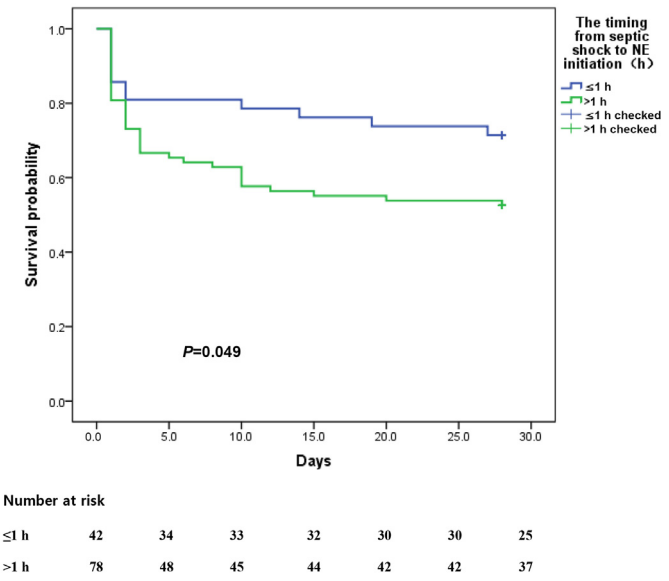

Figure 2. The Kaplan–Meier curve of 28-day survival rate. NE: Norepinephrine.

Univariate analysis

Patients were divided into a 28-day survival (*n*=71) and non-survival group (*n*=49) based on survival at 28 days. The clinical characteristics of the two groups are shown in (Table 3). The male proportion in the survival group was lower compared to the non-survival group (59.4% *vs.* 73.5%, *P*=0.039). The proportion of patients who received initial norepinephrine administration ≤1 h in the survival group was higher than that in the non-survival group (42.3% *vs.* 24.5%, *P*=0.045). The median time to achieve MAP ≥65 mmHg was shorter in the survival group compared to the non-survival group (1 h *vs.* 2 h, *P* <0.001). The 6-hour Lac clearance rate was higher in the survival group compared to the non-survival group (33.0% *vs.* 15.0%, *P*=0.031). There were no significant differences between the survival and non-survival groups with respect to 24-hour intravenous fluids volume, age, body weight, APACHE II score, SOFA score, PCT, and WBC.

Logistic regression analysis

Multivariable logistic regression analysis showed that being male (OR=3.288, 95% CI: 1.236 to 8.745, *P*=0.017), time to initial norepinephrine administration >1 h (OR=4.564, 95% CI: 1.382 to 15.079, *P*=0.013), and time to achieve MAP ≥65 mmHg (OR=1.800, 95% CI: 1.171 to 2.767, *P*=0.007) were independent risk factors for 28-day mortality. By contrast, 6-hour Lac clearance rate (OR=0.431, 95% CI: 0.155to 1.198, *P*=0.107) was not a risk factor for 28-day mortality (Table 4).

Table 1
The baseline characteristics of included patients grouped by NE administration time.

Characteristic	Early NE group (*n*=42)	Late NE group (*n*=78)	*P*-value
Sex (male))	27 (64.3)	58 (74.4)	0.247
Age (years)	67 (53 – 74)	68 (57 – 76)	0.498
Weight (kg)	65.0 (56.5 – 70.0)	65.5 (57.5 – 70.0)	0.807
APACHE II	18 (16 – 20)	19 (18 – 20)	0.137
SOFA	10 (10 – 13)	12 (10 – 14)	0.262
Past medical history			
Hypertension	13 (31.0)	21 (26.9)	0.640
Diabetes mellitus	9 (21.4)	13 (16.7)	0.413
Coronary artery disease	2 (4.8)	7 (9.0)	0.643
Atrial fibrillation	0 (0)	1 (1.3)	0.461
Cerebral infarction/hemorrhage	2 (4.8)	1 (1.3)	0.581
Tuberculosis	0 (0)	1 (1.3)	0.461
Cancer	2 (4.8)	4 (5.1)	0.930
Chronic kidney disease	1 (2.4)	0 (0)	0.752
PCT (ng/mL)	6.70 (1.80 – 26.29)	14.29 (2.41 – 62.43)	0.161
WBC ($\times 10^9$/L)	11.95 (5.37 – 15.62)	9.99 (4.54 – 17.73)	0.976
PLT ($\times 10^9$/L)	171.00 (87.25– 247.25)	143.00 (67.25 – 219.50)	0.159
CRE (μmol/L)	82.55 (59.35–181.40)	131.95 (86.63–185.98)	0.057
BUN (mmol/L)	9.48 (6.81 – 14.32)	11.02 (7.65 – 17.56)	0.134
AST (U/L)	35.55 (20.48–73.02)	39.95 (22.15–68.02)	0.658
ALT (U/L)	22.85 (10.08–40.23)	21.1 (13.35 – 35.73)	0.845
TBIL (μmol/L)	18.00 (12.50 – 25.75)	18.20 (12.95 – 35.10)	0.379
Lac (mmol/L)	2.30 (2.00 – 3.43)	2.70 (2.00 – 6.40)	0.137
Mechanical ventilation	31 (73.8)	66 (84.6)	0.151
Site of infection			
Pulmonary	10 (23.8)	27 (34.6)	0.221
Genitourinary	5 (11.9)	3 (3.9)	0.192
Intra-abdominal	23 (54.8)	41 (52.6)	0.818
Skin/soft tissue infection	4 (9.5)	4 (5.1)	0.591
Blood	0 (0)	2 (2.6)	0.765
Central nervous system	0 (0)	1 (1.3)	0.461

Data are expressed as *n* (%) or median (interquartile range).
ALT: Alanine aminotransferase; APACHE II: Acute Physiology and Chronic Health Evaluation II; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CRE: Creatinine; Lac: Lactate; NE: Norepinephrine; PCT: Procalcitonin; PLT: Platelet; SOFA: Sequential Organ Failure Assessment; TBIL: Total bilirubin; WBC: White blood cells.

Table 2
The clinical outcomes of included patients grouped by NE administration time.

Clinical outcomes	Early NE group (*n*=42)	Late NE group (*n*=78)	*P*-value
28-day mortality	12 (28.6)	37 (47.4)	0.045
ICU LOS (day)	5.5 (2.0 – 10.0)	6.0 (2.0 – 12.5)	0.748
Hospital LOS (day)	12.50 (5.75 – 29.75)	11.00 (5.00 – 19.00)	0.369
Time to achieved MAP ≥65 mmHg (h)	1.00 (0.95 – 2.00)	1.50 (1.00 – 2.00)	0.010
24-hour infusion volume (mL)	3605.00 (2593.00–4488.75)	3930.50 (3410.75–5102.50)	0.030
6-hour Lac clearance (%)	40.7 (13.4 – 55.2)	14.9 (–33.2 – 45.6)	0.009
Mechanical ventilation time (day)	2 (1.00 – 5.00)	2 (1.00 – 9.00)	0.128
CRRT ratio	2 (4.8)	7 (9.0)	0.637

Data are expressed as *n* (%), median (interquartile range).
CRRT: Continuous renal replacement therapy; ICU: Intensive care unit; Lac: Lactate; LO: Length of stay; MAP: Mean arterial pressure; NE: Norepinephrine.

Discussion

This prospective cohort study indicated that initial norepinephrine administration ≤1 h was associated with lower 28-day mortality in patients with septic shock. Kaplan–Meier survival analysis showed that the 28-day survival rate was higher in the early norepinephrine group compared to the late norepinephrine group. In addition, multivariable logistic regression analysis identified initial norepinephrine administration >1 h as an independent risk factor for 28-day mortality. These findings suggest that early administration of norepinephrine may reduce mortality in ICU patients with septic shock. Hence, delaying norepinephrine administration will increase mortality in patients with septic shock.[14] The 1-hour Bundle supported by the Surviving Sepsis Campaign recommends starting vasopressors within the first hour of resuscitation if initial fluid resuscitation does not restore minimum MAP.[27] Indeed, norepinephrine infusion can be safely started before ICU admission, even in intermediate care without intensive monitoring.[28]

Early norepinephrine administration was associated with a shorter time to achieve MAP ≥65 mmHg, reduced 24-hour intravenous fluids volume, and higher 6-hour Lac clearance rate. Early norepinephrine initiation was also associated with a lower resuscitation fluid volume and fluid accumulation and a shorter duration of hypotension. In addition, early norepinephrine administration was significantly associated with increased shock control by 6 h.[29] Early initiation of norepinephrine, even before the completion of a predetermined amount of fluid resuscitation, appears to be a safe intervention with potentially beneficial effects on clinical outcomes.[16] Septic shock, defined in part

Table 3
The clinical characteristics of included patients according to 28-day survival status.

Characteristic	28-day survival (*n*=71)	28-day non-survival (*n*=49)	*P*-value
Sex (male)	39 (54.9)	36 (73.5)	0.039
Age (years)	68 (57 – 76)	67 (54 – 73)	0.400
Weight (kg)	65 (55 – 70)	70 (60 – 70)	0.149
APACHE II	18 (16 – 20)	19 (16 – 20)	0.724
SOFA	12 (10 – 13)	12 (10 – 13)	0.798
PCT (ng/mL)	7.05 (2.10 – 35.89)	13.6 (2.70 – 83.19)	0.185
WBC ($\times 10^9$/L)	10.93 (4.92–15.89)	9.25 (4.54 – 19.20)	0.850
PLT ($\times 10^9$/L)	142.00 (75.00– 233.00)	179.00 (81.50 – 243.00)	0.343
CRE (μmol/L)	105.00 (65.50– 192.80)	130.50 (78.60– 171.50)	0.473
BUN (mmol/L)	11.60 (7.42–15.44)	9.88 (7.27– 17.91)	0.677
AST (U/L)	19.50 (11.00 – 36.40)	24.6 (13.60– 38.35)	0.377
ALT (U/L)	36.20 (20.70–71.10)	40.5 (23.15– 60.70)	0.837
Lac (mmol/L)	2.70 (2.00 – 4.20)	2.40 (2.00 – 4.75)	0.618
Time to initial NE administration ≤1 h	30 (42.3)	12 (24.5)	0.045
Time to achieved MAP ≥65 mmHg (h)	1 (1 – 2)	2 (1–3)	<0.001
6-hour Lac clearance (%)	33.0 (10.0– 52.2)	15.0 (−76.8– 48.1)	0.031
Volume of intravenous fluids within 24 h (mL)	3652.0 (3051.0– 4680.0)	3950.0 (3347.5–5469.5)	0.162

Data are expressed as *n* (%) or median (interquartile range).
Non-parametric test (Mann–Whitney *U* test) was used for comparison between two groups with regard to quantitative variables. Categorical variables were compared using the chi-squared test.
ALT: Alanine aminotransferase; APACHE II: Acute Physiology and Chronic Health Evaluation II; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CRE: Creatinine; Lac: Lactate; MAP: Mean arterial pressure; NE: Norepinephrine; PCT: Procalcitonin; PLT: Platelet; SOFA: Sequential Organ Failure Assessment; WBC: White blood cells.

Table 4
Multivariable logistic regression analysis of independent risk factors for 28-day mortality.

Variable	OR	95% CI	*P*-value
Male	3.288	1.236 to 8.745	0.017
Time to initial NE administration >1 h	4.564	1.382 to 15.079	0.013
Time to achieved MAP ≥65 mmHg	1.800	1.171 to 2.767	0.007
6-hour Lac clearance	0.431	0.155 to 1.198	0.107

CI: Confidence interval; Lac: Lactate; MAP: Mean arterial pressure; NE: Norepinephrine; OR: Odds ratio.

by persistent hypotension, is a significant predictor of increased mortality in septic states.[30,31] At least two retrospective studies on septic shock in humans have shown that mortality increases with the severity and duration of hypotension.[32,33] Varpula and colleagues demonstrated in 111 patients with septic shock that the duration of MAP <65 mmHg during the first 48 h was a strong predictor of mortality.[31] Generally, 24-hour Lac clearance is a better predictor of mortality and duration of vasopressor use.[34] Lac clearance is a better determinant of effective management in sepsis and septic shock, with early Lac clearance associated with better clinical outcomes in septic patients.[35]

Although considered a “first-line” intervention, norepinephrine support is usually used as a rescue therapy when initial fluid therapy fails to correct hypotension or when arterial pressure is insufficient to ensure adequate tissue perfusion.[5] Early initiation of vasopressor support may have several potential beneficial effects. Early norepinephrine administration could (1) correct hypotension faster and prevent prolonged severe hypotension; (2) increase cardiac output through several mechanisms; (3) recruit microvessels and improve microcirculation in severe hypotension by increasing organ perfusion pressure; (4) prevent harmful fluid overload. There is widespread concern that aggressive early fluid resuscitation in patients with septic shock (regardless of whether it is essential for stabilization) may lead to detrimental increases in tissue edema. Early norepinephrine administration is recommended to achieve the initial MAP goal of 65 mmHg faster and to reduce the risk of fluid overload[36]; and (5) improve patients’ outcomes.[37] DAP, as a marker of vascular tone, could be used to identify patients who urgently need norepinephrine.[38] The optimal MAP target should be individualized since it depends on several factors such as history of chronic hypertension, values of central venous pressure, and intra-abdominal pressure (IAP).[39]

Logistic regression analysis showed that time to achieve MAP ≥65 mmHg, time to initial norepinephrine administration >1 h, and being male were independent risk factors for 28-day mortality. However, the variables in the multivariable model may be affected by multicollinearity, as the time to achieve MAP ≥65 mmHg is closely related to the norepinephrine administration time. Early norepinephrine administration can increase MAP, shorten the duration of hypotension and, therefore, may improve vital organ perfusion and decrease serum Lac levels.[19] Studies have shown that prehospital norepinephrine infusion to attain a MAP >65 mmHg is associated with lower 30-day mortality in patients with septic shock cared for by a mobile ICU in the prehospital setting. Previous hypertension history should be considered from the prehospital stage of septic shock resuscitation to determine the optimal MAP target.[40] Early administration of norepinephrine during shock may be justified in patients with profound vasoplegia and at high risk of fluid overload, along with a personalized fluid administration strategy.[41] This study also found that being male was associated with higher 28-day mortality. This result was consistent with a previous retrospective cohort study of 1,064,790 patients with severe sepsis and septic shock.[42]

This study had several limitations. First, this was a single-center prospective study, although this is based on comprehensive and high-quality data. Second, the number of patients in the early group was significantly lower than that in the late group, and this imbalance may reduce the efficiency of the statistical analysis. Third, the one-hour window is quite short and could be affected by the time point chosen for the onset of shock, potentially leading to allocation bias in both groups. Fourth, the sample size of this study population was relatively small. Therefore, large multicenter prospective cohort studies are needed to validate whether early norepinephrine administration is associated with decreased mortality and other improved clinical outcomes in patients with septic shock.

Conclusions

Time to initial norepinephrine administration ≤1 h is associated with lower 28-day mortality in patients with septic shock. The early group has a shorter time to achieve MAP ≥65 mmHg, lower 24-hour intravenous fluid volume, and 6-hour Lac clearance rate. Male, time to achieve MAP ≥65 mmHg, and time to initial norepinephrine administration >1 h are independent risk factors for 28-day mortality. Further, large-scale studies are needed to validate these results.

CRediT Authorship Contribution Statement

Yuting Li: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Deyou Zhang:** Investigation, Data curation. **Hongxiang Li:** Investigation, Formal analysis, Data curation. **Youquan Wang:** Software, Methodology. **Dong Zhang:** Writing – review & editing, Visualization, Validation, Supervision, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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Ethics Statement

Our study has been approved by the Ethics Committee of the First Hospital of Jilin University (01.29.2021, 20K099–002). The informed consent was obtained according to the national regulation from all participants prior to inclusion. The study was performed in accordance with the 2008 Declaration of Helsinki and its later amendments.

Conflict of Interests

The authors declare that they have no competing interests.

Data Availability

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

References

[1] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315(8):801–10. doi:10.1001/jama.2016.0287.
[2] Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med 2016;193(3):259–72. doi:10.1164/rccm.201504-0781OC.
[3] Fleischmann-Struzek C, Mellhammar L, Rose N, Cassini A, Rudd KE, Schlattmann P, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. Intensive Care Med 2020;46(8):1552–62. doi:10.1007/s00134-020-06151-x.
[4] Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyna TJ, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. JAMA 2017;318(13):1241–9. doi:10.1001/jama.2017.13836.
[5] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43(3):304–77. doi:10.1007/s00134-017-4683-6.
[6] Hamzaoui O, Georger JF, Monnet X, Ksouri H, Maizel J, Richard C, et al. Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension. Crit Care 2010;14(4):R142. doi:10.1186/cc9207.
[7] Acheampong A, Vincent JL. A positive fluid balance is an independent prognostic factor in patients with sepsis. Crit Care 2015;19(1):251. doi:10.1186/s13054-015-0970-1.
[8] Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med 2011;39(2):259–65. doi:10.1097/CCM.0b013e3181feeb15.
[9] Marik PE, Linde-Zwirble WT, Bittner EA, Sahatjian J, Hansell D. Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database. Intensive Care Med 2017;43(5):625–32. doi:10.1007/s00134-016-4675-y.
[10] Annane D, Ouanes-Besbes L, de Backer D, DU B, Gordon AC, Hernández G, et al. A global perspective on vasoactive agents in shock. Intensive Care Med 2018;44(6):833–46. doi:10.1007/s00134-018-5242-5.
[11] Colling KP, Banton KL, Beilman GJ. Vasopressors in sepsis. Surg Infect (Larchmt) 2018;19(2):202–7. doi:10.1089/sur.2017.255.
[12] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47(11):1181–247. doi:10.1007/s00134-021-06506-y.
[13] Parrillo JE. Septic shock-vasopressin, norepinephrine, and urgency. N Engl J Med 2008;358(9):954–6. doi:10.1056/NEJMe0800245.
[14] Alshahrani MS, Alatigue R. Association between early administration of norepinephrine in septic shock and survival. Open Access Emerg Med 2021;13:143–50. doi:10.2147/OAEM.S298315.
[15] Beck V, Chateau D, Bryson GL, Pisipati A, Zanotti S, Parrillo JE, et al. Timing of vasopressor initiation and mortality in septic shock: a cohort study. Crit Care 2014;18(3):R97. doi:10.1186/cc13868.
[16] Ospina-Tascón GA, Hernandez G, Alvarez I, Calderón-Tapia LE, Manzano-Nunez R, Sánchez-Ortiz AI, et al. Effects of very early start of norepinephrine in patients with septic shock: a propensity score-based analysis. Crit Care 2020;24(1):52. doi:10.1186/s13054-020-2756-3.
[17] Elbouhy MA, Soliman M, Gaber A, Taema KM, Abdel-Aziz A. Early use of norepinephrine improves survival in septic shock: earlier than early. Arch Med Res 2019;50(6):325–32. doi:10.1016/j.arcmed.2019.10.003.
[18] Xu F, Zhong R, Shi S, Zeng Y, Tang Z. Early initiation of norepinephrine in patients with septic shock: a propensity score-based analysis. Am J Emerg Med 2022;54:287–96. doi:10.1016/j.ajem.2022.01.063.
[19] Bai X, Yu W, Ji W, Lin Z, Tan S, Duan K, et al. Early versus delayed administration of norepinephrine in patients with septic shock. Crit Care 2014;18(5):532. doi:10.1186/s13054-014-0532-y.
[20] Colon Hidalgo D, Patel J, Masic D, Park D, Rech MA. Delayed vasopressor initiation is associated with increased mortality in patients with septic shock. J Crit Care 2020;55:145–8. doi:10.1016/j.jcrc.2019.11.004.
[21] Doane DP, Seward LE. Measuring skewness: a forgotten statistic. J Stat Educ 2011;19:1. doi:10.1080/10691898.2011.11889611.
[22] Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples). Biometrika 1965;52:591. doi:10.1093/biomet/52.3-4.591.
[23] Razali NM, Wah YB. Power comparisons of Shapiro–Wilk, Kolmogorov–Smirnov, Lilliefors and Anderson–Darling tests. J Stat Model Anal 2011;2:21.
[24] Rosner B, Grove D. Use of the Mann–Whitney *U test* for clustered data. Stat Med 1999;18(11):1387–400. doi:10.1002/(sici)1097-0258(19990615)18:11<1387:aid-sim126>3.0.co;2-v.
[25] Kim HY. Statistical notes for clinical researchers: chi-squared test and Fisher's exact test. Restor Dent Endod 2017;42(2):152–5. doi:10.5395/rde.2017.42.2.152.
[26] Ely JW, Dawson JD, Mehr DR, Burns TL. Understanding logistic regression analysis through example. Fam Med 1996;28(2):134–40.
[27] Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Intensive Care Med 2018;44(6):925–8. doi:10.1007/s00134-018-5085-0.
[28] Hallengren M, Åstrand P, Eksborg S, Barle H, Frostell C. Septic shock and the use of norepinephrine in an intermediate care unit: mortality and adverse events. PLoS ONE 2017;12(8):e0183073. doi:10.1371/journal.pone.0183073.

[29] Permpikul C, Tongyoo S, Viarasilpa T, Trainarongsakul T, Chakorn T, Udompanturak S. Early use of norepinephrine in septic shock resuscitation (CENSER). A randomized trial. Am J Respir Crit Care Med 2019;199(9):1097–105. doi:10.1164/rccm.201806-1034OC.
[30] Vallés J, Rello J, Ochagavía A, Garnacho J, Alcalá MA. Community-acquired bloodstream infection in critically ill adult patients: impact of shock and inappropriate antibiotic therapy on survival. Chest 2003;123(5):1615–24. doi:10.1378/chest.123.5.1615.
[31] Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. JAMA 1995;273(2):117–23. doi:10.1001/jama.1995.03520260039030.
[32] Varpula M, Tallgren M, Saukkonen K, Voipio-Pulkki LM, Pettilä V. Hemodynamic variables related to outcome in septic shock. Intensive Care Med 2005;31(8):1066–71. doi:10.1007/s00134-005-2688-z.
[33] Dünser MW, Takala J, Ulmer H, Mayr VD, Luckner G, Jochberger S, et al. Arterial blood pressure during early sepsis and outcome. Intensive Care Med 2009;35(7):1225–33. doi:10.1007/s00134-009-1427-2.
[34] Shadvar K, Nader-Djalal N, Vahed N, Sanaie S, Iranpour A, Mahmoodpoor A, et al. Comparison of lactate/albumin ratio to lactate and lactate clearance for predicting outcomes in patients with septic shock admitted to intensive care unit: an observational study. Sci Rep 2022;12(1):13047. doi:10.1038/s41598-022-14764-z.
[35] Rehman F, Zafar SB, Aziz A, Aziz A, Memon PS, Ejaz T, et al. Early lactate clearance as a determinant of survival in patients with sepsis: findings from a low-resource country. J Crit Care Med (Targu Mures) 2023;9(1):30–8. doi:10.2478/jccm-2023-0005.
[36] Scheeren TWL, Bakker J, De Backer D, Annane D, Asfar P, Boerma EC, et al. Current use of vasopressors in septic shock. Ann Intensive Care 2019;9(1):20. doi:10.1186/s13613-019-0498-7.
[37] Shi R, Hamzaoui O, De Vita N, Monnet X, Teboul JL. Vasopressors in septic shock: which, when, and how much? Ann Transl Med 2020;8(12):794. doi:10.21037/atm.2020.04.24.
[38] Hamzaoui O, Teboul JL. Importance of diastolic arterial pressure in septic shock: PRO. J Crit Care 2019;51:238–40. doi:10.1016/j.jcrc.2018.10.032.
[39] Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med 2014;40(12):1795–815. doi:10.1007/s00134-014-3525-z.
[40] Jouffroy R, Hajjar A, Gilbert B, Tourtier JP, Bloch-Laine E, Ecollan P, et al. Prehospital norepinephrine administration reduces 30-day mortality among septic shock patients. BMC Infect Dis 2022;22(1):345. doi:10.1186/s12879-022-07337-y.
[41] De Backer D, Cecconi M, Chew MS, Hajjar L, Monnet X, Ospina-Tascón GA, et al. A plea for personalization of the hemodynamic management of septic shock. Crit Care 2022;26(1):372. doi:10.1186/s13054-022-04255-y.
[42] Cerceo E, Rachoin JS, Gaughan J, Weisberg L. Association of gender, age, and race on renal outcomes and mortality in patients with severe sepsis and septic shock. J Crit Care 2021;61:52–6. doi:10.1016/j.jcrc.2020.10.007.