Critical Care

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Adjunctive terlipressin versus placebo in the treatment of refractory septic shock: a randomized, placebo-controlled trial

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Abstract

Background Terlipressin's role as an adjunctive vasopressor in septic shock remains controversial. We aimed to evaluate the efficacy of terlipressin versus placebo as an additional vasopressor in refractory septic shock.

Methods We conducted a single-center, prospective, double-blind, randomized controlled trial in a medical intensive care unit. Adult patients with septic shock requiring norepinephrine > 0.2 mcg/kg/min or epinephrine were randomly assigned (1:1) to receive terlipressin or placebo. The primary outcome was the proportion of patients achieving mean arterial pressure ≥ 65 mmHg with total catecholamine equivalent dose below 0.2 mcg/kg/min at 6 h after randomization.

Results A total of 130 patients were enrolled: 66 in the terlipressin group and 64 in the placebo group. Baseline characteristics were comparable. The median (interquartile range) baseline norepinephrine equivalent dose was 0.39 (0.29 – 0.73) mcg/kg/min for terlipressin versus 0.39 (0.27 – 0.62) mcg/kg/min for placebo. Pneumonia (57.6% vs 48.4%) and intra-abdominal infection (21.2% vs 23.4%) were the most common etiologies in the terlipressin and placebo arms, respectively. Significantly more patients met the primary outcome with terlipressin than with placebo (22.7% vs 9.4%; relative risk [RR] = 1.53, 95% confidence interval [CI] = 1.09–2.14; $P = 0.039$). The 28-day mortality was 60.6% in the terlipressin group versus 64.1% in the placebo group (RR = 0.93, 95% CI = 0.66–1.31; $P = 0.68$). Digital ischemia occurred in 28.8% versus 27.4% ($P = 0.86$).

Conclusions Among patients with refractory septic shock, adjunctive terlipressin reduced the proportion of patients requiring high-dose catecholamines at 6 h, without significantly altering mortality or digital ischemia risk.

Trial registration Clinicaltrials.gov (NCT 04339868). The registration date was April 7, 2020.

Keywords Refractory, Septic shock, Terlipressin, Vasopressor

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Background

Septic shock is a clinical syndrome of circulatory failure caused by a dysregulated host response to infection. This response leads to inadequate tissue perfusion, which contributes to multiple organ dysfunction and is associated with a high mortality rate [1]. Key features of septic shock include hypotension with inadequate tissue perfusion. The main hemodynamic disturbance in septic shock consists of decreased systemic vascular resistance, vascular leakage, and myocardial dysfunction [2]. Management of septic shock includes eliminating the source of infection, providing fluid resuscitation, and administering vasopressors to rapidly restore blood pressure and maintain tissue perfusion [3, 4].

Current septic shock guidelines recommend starting norepinephrine, a catecholamine with potent alpha-1 and weaker beta-1 adrenergic receptor stimulation, as the first-line vasopressor of choice [3]. Early norepinephrine administration (within the first hour of septic shock resuscitation) is advised alongside fluid resuscitation [5, 6]. Alpha-1 receptor stimulation increases vascular tone and blood pressure, whereas beta-1 receptor stimulation enhances heart rate, cardiac contractility, and cardiac output. In refractory septic shock patients whose hemodynamics do not respond to a high norepinephrine dose, adding either epinephrine or vasopressin can improve blood pressure. Although the exact norepinephrine threshold for adding a second vasopressor is unclear, current guidelines suggest introducing a second agent when a patient requires an norepinephrine infusion of 0.25 mcg/kg/min or higher [3]. Excessive adrenergic receptor stimulation can cause serious complications, including cardiac arrhythmias, acute myocardial ischemia, severe metabolic acidosis, and bowel ischemia [7, 10].

An alternative vasopressor that acts via a non-adrenergic receptor pathway has emerged as a potentially synergistic approach to improving blood pressure while minimizing the risk of excessive adrenergic stimulation [11]. Vasopressin, a peptide hormone produced in the hypothalamus and stored in the posterior pituitary gland, is released during shock. Vasopressin binds to multiple vasopressin receptors: activation of V1 receptors causes vascular smooth muscle contraction and increases arterial pressure, whereas V2 receptor activation promotes free water reabsorption in the distal convoluted tubule [12]. Terlipressin, a vasopressin analog with a longer half-life (6 h) and higher selectivity for V1 receptors, is another potential option [13]. Current septic shock guidelines recommend combining vasopressin with norepinephrine when patients do not achieve adequate mean arterial pressure despite high norepinephrine doses. However, data on combining terlipressin with norepinephrine in refractory septic shock are limited. We conducted this study to evaluate the efficacy of adding terlipressin as a second vasopressor in septic shock patients who have inadequate tissue perfusion despite high-dose norepinephrine.

Methods

Study design

This was a prospective, single-center, double-blind, 1:1 randomized controlled trial. It enrolled adult septic shock patients to evaluate the effect of adding terlipressin to a catecholamine vasopressor regimen, compared with a catecholamine-only vasopressor strategy. The trial took place in the medical intensive care unit (ICU) of Siriraj Hospital, Mahidol University, Bangkok, Thailand, between April 9, 2020, and January 31, 2024. It was approved by the Siriraj Hospital Ethics Committee, Mahidol University (reference: Si 049/2020) and registered at Clinicaltrials.gov (NCT 04339868), the registration date was April 7, 2020. All participant screening and enrollment procedures were performed by the coinvestigators (Fig. 1). Written informed consent was obtained from each patient or from next of kin or legal guardians when the patient was unable to consent.

The principal investigator and a statistician, both blinded to the patient's treatment group, analyzed the outcomes. This research was supported by the Siriraj Research Fund, Faculty of Medicine Siriraj Hospital, Mahidol University (grant number: R016433013). The funder played no role in the study design, data analysis, or outcome assessment. The full study protocol has been published elsewhere [14]. The reporting of this study adheres to the CONSORT (Consolidated Standards of Reporting Trials) guidelines [15].

Study participants

We screened all patients aged 18 years or older who were admitted to the medical ICU with septic shock, as defined by the SEPSIS-III criteria [16]. Patients were eligible if they had persistent hypotension requiring norepinephrine doses above 0.2 mcg/kg/min—or norepinephrine combined with epinephrine—to maintain a mean arterial blood pressure (MAP) of at least 65 mmHg. They also had to have a serum lactate level higher than 2 mmol/L (18 mg/dL), despite adequate fluid resuscitation. Adequate fluid resuscitation was defined as receiving an initial fluid volume of at least 30 ml/kg, plus evidence of a lack of fluid responsiveness in at least one fluid-responsiveness test. These tests included a central venous pressure > 12 mmHg; a pulmonary artery occlusive pressure > 18 mmHg; a negative passive leg-raising test (cardiac output increase < 15%); an inferior vena cava collapsibility index < 40% in spontaneously breathing patients or inferior vena cava distensibility index < 18%

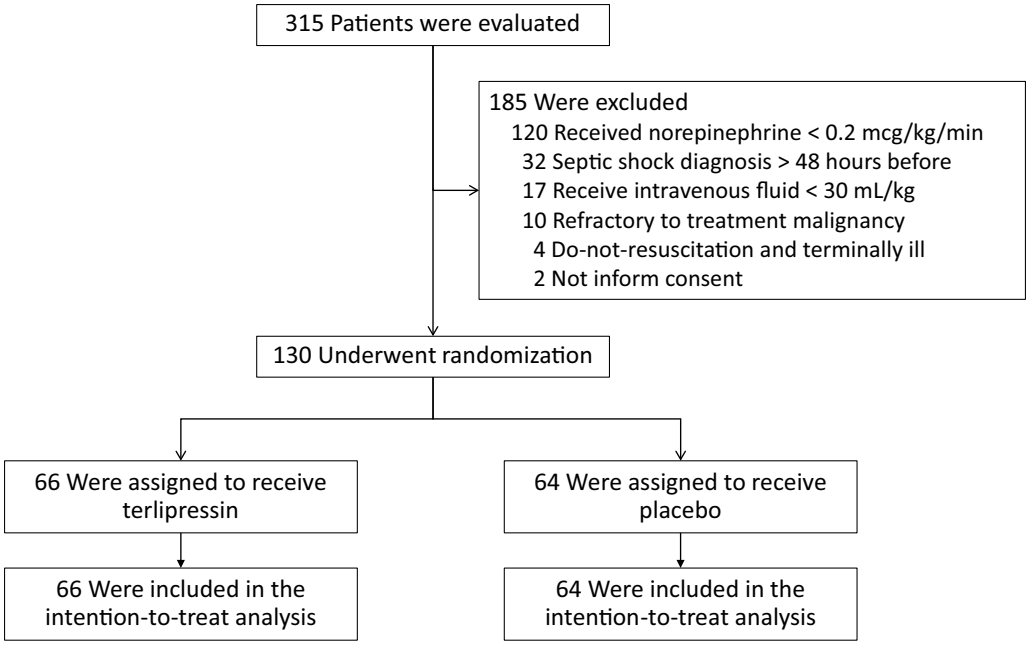


Fig. 1 CONSORT flow diagram of patient screening, enrollment, randomization, and analysis

in mechanically ventilated patients; or a pulse pressure variation < 15% [17].

We excluded patients who had been in septic shock for more than 48 h before inclusion, those with a do-not-resuscitate plan, pregnant patients, patients with chronic kidney disease stage V but no renal replacement therapy, patients with Child – Turcotte – Pugh class C chronic liver disease, or those in cardiogenic shock (cardiac index < 2.2 L/min/m^2 and pulmonary artery occlusive pressure ≥ 18 mmHg). We also excluded patients with decompensated heart failure, left ventricular ejection fraction < 35%, acute coronary syndrome, severe valvular heart disease, life-threatening arrhythmias (ventricular fibrillation or ventricular tachycardia) before inclusion, suspected or confirmed mesenteric ischemia, systemic sclerosis with Raynaud's phenomenon, or peripheral arterial disease. Lastly, we excluded any patient who declined to provide informed consent.

Randomization and interventions

After enrollment, patients were randomly assigned in a 1:1 ratio—based on their sequential enrollment number—to receive either terlipressin plus catecholamine vasopressors or a placebo plus catecholamine vasopressors. Randomization was performed using a computer-generated table from www.randomization.com. Predefined lists were kept in sealed envelopes opened only after participants signed informed consent. This procedure was conducted by an investigator (S.T.) who had no other role in patient enrollment or clinical management. All other investigators, attending physicians, nurses, patients, and patients' relatives were blinded to the treatment assignment.

A pharmacist, who had no other role in the trial, prepared the study drug. Containers were identical in appearance and labeled only with sequential numbers following the randomization order. For the active study drug, terlipressin acetate 1 mg was diluted in 50 ml of 0.9% sodium chloride solution to yield a concentration of 0.02 mg/ml. The placebo group received only 0.9% sodium chloride solution. Study drug infusions—active or placebo—were administered via a peripheral line or central venous catheter when available, beginning at 1 ml/h. For a 70 kg patient, this corresponds to approximately 0.005 mcg/kg/min of terlipressin. The infusion rate could be increased by 1 ml/h every 30 min to achieve a MAP above 65 mmHg, up to a maximum of 5 ml/h. In a 70 kg patient, this maximum corresponds to roughly 100 mcg/h (0.025 mcg/kg/min of terlipressin). During study drug titration, attending physician was permitted to titrate open-label norepinephrine and/or epinephrine in addition to the study drug (terlipressin or placebo) to achieve the target MAP.

Once participants maintained a MAP of at least 75 mmHg for more than 30 min, the catecholamine vasopressors (epinephrine and norepinephrine) were tapered to 0.15 mcg/kg/h. This safety margin was employed to minimize the risk of subsequent hypotension, which might occur if catecholamines were reduced immediately upon reaching the lower MAP threshold of 65 mmHg. Maintaining a higher MAP threshold prior to tapering vasopressors could prevent rebound hypotension and the need for vasopressor dose escalation. After

the catecholamine dose had been decreased to 0.15 mcg/kg/h or lower, while maintaining a MAP above 65 mmHg for 30 min, the study drug was tapered by 1 ml/h every 30 min until discontinued. Attending physicians could adjust other septic shock treatments according to the 2021 Surviving Sepsis Campaign guidelines [3], which include fluid resuscitation with crystalloids, appropriate antibiotic therapy, source control, and organ support.

Study outcomes

The primary outcome was successful septic shock hemodynamic stabilization within 6 h. This outcome was defined as maintaining a MAP of at least 65 mmHg with a total catecholamine requirement below 0.2 mcg/kg/min. The total catecholamine dose was calculated by summing the norepinephrine, epinephrine, dopamine and dobutamine doses (mcg/kg/min), with the dopamine and dobutamine doses each divided by 100. The formula was as follows [18]:

$$\begin{aligned}\text{Catecholamine dose} &= \text{norepinephrine dose} \\ &+ \text{epinephrine dose} + [\text{dopamine}/100] + \\ &[\text{dobutamine }/100]\end{aligned}$$

The secondary outcomes were 28-day mortality, ICU mortality, and hospital mortality. Additional endpoints included MAP monitoring for up to 72 h, the proportion of patients requiring mechanical ventilation, the proportion requiring renal replacement therapy, and the number of organ support – free days through day 28. Organ support—free days were calculated based on the method described by Russell and colleagues [19].

For safety outcomes, we recorded the new onset of cardiac arrhythmias and organ ischemia events, including intestinal ischemia, digital ischemia, digital gangrene, and acute myocardial infarction. Digital ischemia was defined as reduced blood flow to the fingers or toes, characterized by pallor, coolness, or cyanosis. Digital gangrene was defined as irreversible tissue necrosis of the fingers or toes, presenting with dark discoloration, dry or mummified tissue, and loss of sensation. We also recorded the rate of recurrent shock, defined as a mean arterial pressure (MAP) below 65 mmHg lasting longer than 30 min within 48 h after discontinuation of the study drug and open-label vasopressors. These events were adjudicated by the attending physician according to prespecified definitions, with day-by-day assessments. No changes were made to trial outcomes once the trial began.

Statistical analysis

Because no prior data existed regarding the effect of adjunct terlipressin on MAP in septic shock, we hypothesized that adding terlipressin would increase the primary outcome (successful septic shock hemodynamic stabilization within 6 h) by 25 percentage points over the control group. We based this assumption on data from the ATHOS-3 study, in which patients in the placebo group had a 25% rate of MAP improvement [20]. To detect an approximate 25% difference in successful septic shock stabilization at 80% power ($\alpha = 0.05$), we calculated that each study arm required at least 57 participants. Accounting for a 15% dropout rate, we aimed to recruit 65 participants per group, for a total of 130.

We assessed the normality of continuous variables using the Kolmogorov – Smirnov test. Normally distributed variables are presented as means with standard deviations, and they were analyzed using the *t*-test. Non-normally distributed variables are given as medians and interquartile ranges (IQRs) and were analyzed by the Wilcoxon rank-sum test. Categorical variables are shown as frequencies and percentages, and they were evaluated with the chi-square test or Fisher's exact test, as appropriate. We compared the primary and secondary outcomes using chi-square analysis and expressed results as relative risks (RRs) with 95% confidence intervals. For mortality outcomes, 28-day mortality was measured from the date of septic shock diagnosis. All primary and secondary outcome analyses followed the intention-to-treat principle, and $P < 0.05$ was considered statistically significant.

To identify a subphenotype of patients who may benefit from terlipressin, we compared baseline characteristics, including age, gender, severity scores, underlying diseases, infection sites, vital signs, hemodynamic parameters, baseline organ function, and treatments received before study drug initiation, between responders and non-responders at 6 h. For continuous variables, receiver operating characteristic (ROC) curve analysis was used to determine optimal cut-off values based on Youden's index. Variables were dichotomized using these cut-offs and included in univariate analyses. Variables with $P < 0.05$ in univariate analysis were entered into a multivariate binary logistic regression model. Results are presented as adjusted odds ratios (aORs) with 95% confidence intervals. Factors with $P < 0.05$ in multivariate analysis were considered independent predictors of response to terlipressin. Data were analyzed using IBM SPSS Statistics, version 29 (IBM Corp, Armonk, NY, USA).

Results

Patients

Participants were enrolled between April 9, 2020, and January 31, 2024. During this period, 315 septic shock patients with persistent hypotension requiring a high dose of norepinephrine—alone or combined with epinephrine—to maintain a MAP of 65 mmHg or higher were screened. Of these, 130 patients met the inclusion criteria. Sixty-six of these patients were randomized to the terlipressin group, and 64 patients were assigned to

the placebo group. No participants withdrew consent, so all 130 patients were included in the final analysis (Fig. 1).

Baseline characteristics—including age, sex, site of infection, and comorbidities—were similar in both groups (Table 1). The median baseline measures were also comparable. In the terlipressin group, the APACHE II score was 26 (IQR = 21 – 31), the SOFA score was 14 (IQR = 11 – 16), the MAP was 62 mmHg (IQR = 56 – 68), and serum lactate was 5.5 mmol/L (IQR = 3.0 – 11.9). In the placebo group, the APACHE II score was 27 (IQR = 22 – 31), the SOFA score was 13 (IQR = 10 – 15), the MAP was 61 mmHg (IQR = 57 – 64), and serum lactate was 8.0 mmol/L (IQR = 3.2 – 12.0). All patients received norepinephrine, and epinephrine was given to 5 of 66 patients (15.6%) in the terlipressin group and to 3 of 64 (9.4%) in the placebo group. The median total catecholamine dose was 0.39 mcg/kg/min (IQR = 0.29 – 0.73) in the terlipressin group, compared with 0.39 mcg/kg/min (IQR = 0.27 – 0.62) in the placebo group. The median time from septic shock diagnosis to initiation of the study drug was also similar, at 14 h (IQR = 9 – 25) in both groups.

Outcomes

The primary outcome—achieving a target MAP above 65 mmHg with a norepinephrine and/or epinephrine dose below 0.2 mcg/kg/min by the sixth hour—occurred more frequently in the terlipressin group than in the control group (22.7% vs 9.4%; RR = 1.53, 95% CI = 1.09–2.14, *P* = 0.039; Table 2). Figure 2A shows the MAP values (median [IQR]) over 72 h in both groups. The median of MAP measurements increased from 65 mmHg at baseline to above 85 mmHg within 6 h after enrollment, then remained stable from 6 to 72 h in both groups. There were no statistically significant differences in MAP between groups at any time (Fig. 2A). Patients in the terlipressin group required significantly lower catecholamine doses by 24 h (Fig. 2B). However, at 24 h, the median vasopressor dose (including terlipressin) was 0.16 mcg/kg/min (IQR 0.04–0.42) in the terlipressin group and 0.26 mcg/kg/min (IQR 0.09–0.43) in the placebo group, *P* = 0.084. By 24 h and 72 h, a higher proportion of patients in the terlipressin group achieved a MAP above 65 mmHg with a total catecholamine dose below 0.2 mcg/kg/min, although the difference was not statistically significant. The duration of catecholamine administration did not differ between groups (median = 61 h [IQR = 37 – 88] vs 67 h [IQR = 38 – 111], *P* = 0.463; Table 2).

Figure 2C illustrates serum lactate levels over time in the terlipressin and control groups. Both groups showed a gradual decrease in serum lactate following enrollment. By 6 h, the median reduction in serum lactate did not differ significantly between the terlipressin and control groups (11% [IQR = – 35% to 16%] vs 5% [IQR = – 35% to 18%]; *P* = 0.762). At 24 h, the median cardiac index was also similar between the 2 groups (3.4 L/min/m^2 [IQR = 2.7 – 4.5] vs 2.8 L/min/m^2 [IQR = 2.0 – 3.8]; *P* = 0.886).

At day 28, mortality was 60.6% in the terlipressin group and 64.1% in the control group (RR = 0.93, 95% CI = 0.66 – 1.31, *P* = 0.684; Table 2). The Kaplan – Meier 28-day mortality curves are shown in Fig. 3. The hazard ratio for 28-day mortality in the terlipressin group versus the placebo group was 0.96 (95% CI = 0.62 – 1.48, *P* = 0.838). ICU mortality and hospital mortality did not differ between groups. There were no statistically significant differences in days alive and free of vasopressors, mechanical ventilation, or renal replacement therapy up to day 28. The same applied to organ support – free days to day 28, both in the overall population and among patients who survived to day 28 (Table 2). ICU length of stay and hospital length of stay were also similar across groups.

For adverse events, new-onset atrial fibrillation was observed in 13.6% of terlipressin group patients and 12.5% of control group patients (RR = 1.05, 95% CI = 0.61 – 1.80, *P* = 0.848; Table 2). Fatal arrhythmias, defined as ventricular fibrillation or ventricular tachycardia, occurred in 4.5% of terlipressin group patients and 4.7% of controls (RR = 0.98, 95% CI = 0.43 – 2.23, *P* = 1.000). Digital ischemia and bowel ischemia were not significantly different between groups. After discontinuing catecholamine vasopressors, 34.8% of patients in the terlipressin group and 32.8% in the control group experienced recurrent shock (RR = 1.05, 95% CI = 0.72 – 1.52, *P* = 0.806).

For identifying a subphenotype of patients who may benefit from terlipressin, the results of univariate and multivariate analyses are presented in Table 3. Patients with a SOFA score below 12 (adjusted odds ratio [aOR] = 33.33, 95% CI = 3.45–100.0, *P* = 0.003) and an initial serum lactate level below 4 mmol/L (aOR = 33.33, 95% CI = 3.12–100.0, *P* = 0.004) were independently associated with responsiveness to terlipressin.

Discussion

In this double-blind randomized controlled trial, we examined patients with refractory septic shock who needed norepinephrine above 0.2 mcg/kg/min, or norepinephrine combined with epinephrine, to maintain a MAP of at least 65 mmHg. We found that terlipressin administration was associated with a higher rate of septic shock hemodynamic stabilization by 6 h, compared with standard treatment. No significant differences were noted in adverse events, including cardiac arrhythmias, digital ischemia, bowel ischemia, or recurrent shock. The 28-day and in-hospital mortality rates were also similar between the 2 groups.

Table 1 Baseline demographic, clinical, hemodynamic, and treatment characteristics at enrollment

Clinical parameters	Terlipressin (*n* = 66)	Placebo (*n* = 64)	*P*
Age, median (IQR), y	65 (50–77)	64 (54–76)	0.983
Gender, *n* (% male)	42 (63.6)	43 (67.2)	0.670
Body mass index, median (IQR), kg/m^2	21 (19–24)	23 (19–26)	0.422
APACHE II score, median (IQR)	26 (21–31)	27 (22–31)	0.496
SOFA score, median (IQR)	14 (11–16)	13 (10–15)	0.655
Underlying diseases, *n* (%)			
Hypertension	40 (60.6)	33 (51.6)	0.299
Diabetes mellitus	35 (53.0)	23 (35.9)	0.074
Chronic kidney disease	20 (30.3)	20 (31.3)	0.907
Coronary artery disease	10 (15.2)	6 (9.4)	0.425
Cerebrovascular disease	9 (13.6)	7 (10.9)	0.791
Cirrhosis	8 (12.1)	3 (4.7)	0.207
Site of infection, *n* (%)			
Respiratory tract infection	38 (57.6)	31 (48.4)	0.297
Intra-abdominal infection	14 (21.2)	15 (23.4)	0.761
Septicemia	8 (12.1)	13 (20.3)	0.205
Urinary tract infection	5 (7.6)	7 (10.9)	0.558
Skin and soft tissue infection	6 (9.1)	6 (9.4)	0.955
Other	3 (4.5)	5 (7.8)	0.935
Vital signs, hemodynamic parameters and baseline organ function, median (IQR)			
Temperature, ℃	36.9 (36.0–37.9)	37.1 (36.0–37.9)	0.758
Mean arterial blood pressure, mmHg	62 (56–68)	61 (57–64)	0.309
Heart rate, beats per min	114 (100–130)	111 (89–128)	0.398
Respiratory rate, breaths per min	28 (24–32)	27 (24–30)	0.497
Central venous pressure, mmHg	12 (9–17)	14 (11–17)	0.244
Serum lactate, mmol/L	5.5 (3.0–11.9)	8.0 (3.2–12.0)	0.458
Serum creatinine, mg/dL	2.2 (1.1–4.0)	2.5 (1.5–4.5)	0.861
PaO_2:FiO_2 ratio	253 (123–360)	261 (164–365)	0.728
Left ventricular ejection fraction, %	55 (44–63)	57 (47–68)	0.372
Cardiac index, L/min/m^2	3.6 (2.6–4.6)	3.2 (2.3–5.6)	0.305
Treatment received			
Fluid responsive test, *n (%)*			
- Central venous pressure guiding	62 (93.9)	61 (95.3)	0.729
- Inferior vena cava diameter variation	28 (42.4)	25 (39.1)	0.697
- Pulse pressure variation	9 (13.6)	9 (14.1)	0.944
Fluid resuscitation volume, median (IQR), mL	4,752 (2,777–7,591)	4,420 (2,732–6,095)	0.373
Vasoactive drugs, *n* (%)			
- Norepinephrine	66 (100)	64 (100)	1.000
- Epinephrine	5 (15.6)	3 (9.4)	0.708
- Dopamine	0 (0.0)	1 (3.1)	1.000
- Dobutamine	5 (15.6)	1 (3.1)	0.196
Vasoactive dose, median (IQR), mcg/kg/min[a]	0.39 (0.29–0.73)	0.39 (0.27–0.62)	0.656
Hydrocortisone, *n* (%)	66 (100)	63 (98.4)	0.492
Time from septic shock diagnosis to study drug initiation, median (IQR), hrs	14 (9–25)	14 (9–25)	1.000

Abbreviations: °C degrees Celsius, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *IQR* interquartile range, *kg/m^2* kilogram per square meter, *L/min* liters per minute, *L/min/m^2* liters per minute per square meter, *mcg/kg/min* micrograms per kilogram per minute, *min* minute; *mL/kg* milliliters per kilogram, *mmHg* millimeters of mercury, *mmol/L* millimole per liter, *mg/dL* milligram per deciliter, *PaO_2* partial pressure of oxygen in arterial blood, *FiO_2* fraction of inspired oxygen, *SOFA* sequential organ failure assessment, *y* years, *hrs* hours

[a]Vasoactive dose or norepinephrine dose equivalents were calculated with the following equation:

Norepinephrine dose equivalent (micrograms per kilogram per minute [mcg/kg/min]) = (norepinephrine [mcg/kg/min] + epinephrine [mcg/kg/min] + dopamine [mcg/kg/min])/100 [18]

Table 2 Primary and secondary outcomes

Outcomes	Terlipressin (*n* = 66)	Placebo (*n* = 64)	Relative risk (95%CI)	*P*
Primary outcomes				
Achieve target MAP ≥ 65 mmHg with norepinephrine and/or epinephrine dose ≤ 0.2 mcg/kg/min at 6th h, *n* (%)	15 (22.7)	6 (9.4)	1.53 (1.09–2.14)	0.039
Secondary outcomes				
Hospital mortality, *n* (%)	45 (68.2)	48 (75.0)	0.85 (0.60–1.21)	0.389
28-d mortality, *n* (%)	40 (60.6)	41 (64.1)	0.93 (0.66–1.31)	0.684
ICU mortality, *n* (%)	39 (59.1)	37 (57.8)	1.03 (0.73–1.45)	0.882
Achieve target MAP ≥ 65 mmHg with norepinephrine and/or epinephrine dose ≤ 0.2 mcg/kg/min at 24th h, *n* (%)	27 (40.9)	19 (29.7)	1.26 (0.91–1.77)	0.181
Achieve target MAP ≥ 65 mmHg with no vasopressor at 72nd h, *n* (%)	32 (48.9)	26 (40.6)	1.17 (0.83–1.64)	0.306
Time to achieve MAP ≥ 65 mmHg, median (IQR), h:min	1 (0:00–1:30)	1 (0:15–2:00)		0.437
Serum lactate decrease at 6 h, %[a]	−11 (−35 to 16)	−5 (−35 to 18)		0.762
Catecholamine duration, median (IQR), h	61 (37–88)	67 (38–111)		0.463
Study drug duration, median (IQR), h	24 (13–46)	28 (9–48)		0.903
Vasoactive dose (include terlipressin) at 24 h, median (IQR), mcg/kg/min[b]	0.16 (0.04–0.42)	0.26 (0.09–0.43)		0.084
Catecholamine dose (did not include terlipressin) at 24 h, median (IQR), mcg/kg/min[c]	0.15 (0.04–0.41)	0.26 (0.09–0.43)		0.037
Maximum terlipressin dose, median (IQR), mcg/kg/min[d]	0.007 (0.005–0.019)	0.008 (0.005–0.026)		0.684
Days alive and free of vasopressors to Day 28, median (IQR), d				
-Overall patients	1 (0–20)	5 (0–22)		0.667
-Survival patients[e]	22 (16–24)	22 (8–25)		0.976
Mechanical ventilation, *n (%)*	59 (89.4)	60 (93.8)	0.72 (0.32–1.61)	0.372
Days alive and free of mechanical ventilator to Day 28, median (IQR), d				
-Overall patients	0 (0–6)	0 (0–11)		0.453
-Survival patients[e]	9 (1–22)	12 (8–24)		0.129
Renal replacement therapy, *n (%)*	42 (63.6)	44 (68.8)	0.89 (0.61–1.30)	0.410
Days alive and free of renal replacement therapy to Day 28, median (IQR), d				
-Overall patients	1 (0–21)	3 (0–24)		0.385
-Survival patients[e]	24 (12–28)	21 (12–28)		0.992
Days alive and free of organ support to Day 28, median (IQR), d				
-Overall patients	0 (0–6)	0 (0–8)		0.191
-Survival patients[e]	8 (0–21)	12 (4–24)		0.173
LVEF at 24th h, median (IQR), (%)	50 (44–63)	50 (40–66)		0.459
Cardiac index at 24th h, median (IQR), L/min/m^2	3.4 (2.7–4.5)	2.8 (2.0–3.8)		0.886

Table 2 (continued)

Outcomes	Terlipressin (*n* = 66)	Placebo (*n* = 64)	Relative risk (95%CI)	*P*
ICU length of stay, median (IQR), d	8 (4–15)	7 (4–18)		0.777
Hospital length of stay, median (IQR), d	15 (5–30)	20 (6–31)		0.526
Adverse events, *n* (%)				
Arrhythmia				
- Atrial fibrillation	9 (13.6)	8 (12.5)	1.05 (0.61–1.80)	0.848
- Supraventricular tachycardia	4 (6.1)	3 (4.7)	1.16 (0.48–2.77)	1.000
-Ventricular fibrillation/tachycardia	3 (4.5)	3 (4.7)	0.98 (0.43–2.23)	1.000
Digital ischemia	19 (28.8)	17 (27.4)	1.04 (0.69–1.55)	0.863
Digital gangrene	2 (3.0)	1 (1.6)	1.48 (0.29–7.44)	1.000
Bowel ischemia	0 (0)	2 (3.1)	0.48 (0.41–0.58)	0.240
Recurrent shock	23 (34.8)	21 (32.8)	1.05 (0.72–1.52)	0.806

Abbreviations: MAP mean arterial pressure, *LVEF* left ventricular ejection fraction, *mcg/kg/min* micrograms per kilogram per minute, *d* days, *h* hours, *ICU* intensive care unit, *IQR* interquartile range, *L/min* liters per minute, *L/min/m*^{2} liters per minute per square meter, *mmol/L* millimoles per liter

[a]The decrease in the serum lactate concentration (%) was calculated with the following equation:

([serum lactate at baseline – serum lactate at 6 h after start study drug]/serum lactate at baseline) × 100. The negative value indicated decreasing of lactate from baseline, while positive value indicated increasing of lactate from baseline

[b]Vasoactive dose or norepinephrine dose equivalents (included terlipressin dose) were calculated with the following equation:

Norepinephrine dose equivalent (micrograms per kilogram per minute [mcg/kg/min]) = (norepinephrine [mcg/kg/min] + epinephrine [mcg/kg/min] + dopamine [mcg/kg/min]/100 + 10 × terlipressin dose [mcg/kg/min]) [25].

[c]Catecholamine dose (did not include terlipressin dose) were calculated with the following equation:

Norepinephrine dose equivalent (micrograms per kilogram per minute [mcg/kg/min]) = (norepinephrine [mcg/kg/min] + epinephrine [mcg/kg/min] + dopamine [mcg/kg/min]/100) [18].

[d]For the placebo group, the actual terlipressin dose was zero. The illustrated dose represents an estimated value, calculated based on the placebo infusion rate and the patient's body weight

[e]Data analyzed from 26 patients in terlipressin group and 23 patients in placebo group who survived to day 28

Patients with refractory septic shock who require high catecholamine doses have a high mortality rate. This outcome may reflect disease severity alone, or a combination of disease severity and treatment-related complications. Several studies have reported that increasing doses of catecholaminergic agents correlate with higher mortality in septic shock [7–10]. The threshold for "high-dose" catecholamines associated with poorer outcomes ranges between 0.2 and 0.5 mcg/kg/min. Excessive vasoconstriction of the splanchnic circulation can occur at these doses, leading to severe lactic acidosis and peripheral ischemia. High catecholamine doses can also exacerbate tachycardia and precipitate life-threatening arrhythmias such as ventricular fibrillation or tachycardia [21]. Current guidelines suggest adding vasopressin rather than further escalating norepinephrine beyond 0.25 – 0.5 mcg/kg/min [3]. However, information on the use of terlipressin as a second-line vasopressor is limited.

Our findings align with previous studies reporting that terlipressin reduces norepinephrine requirements in patients with septic shock. In a pilot study conducted by Morelli et al., continuous low-dose terlipressin infusion reduced catecholamine requirements and was associated with less rebound hypotension compared to norepinephrine alone [22]. More recently, Liu et al. and Sahoo et al. demonstrated significant norepinephrine-sparing effects with adjunctive terlipressin, although without a consistent mortality benefit [23, 24]. However, unlike these trials, our study incorporated a standardized primary outcome combining MAP target and total catecholamine dose. We also calculated norepinephrine equivalence which integrating terlipressin dose, as proposed in recent literature to assess the true vasopressor burden [25]. We observed a nonsignificant trend toward lower overall vasopressor exposure in the terlipressin group compared to placebo. Unlike norepinephrine, which has beta-agonist properties and an inotropic effect, terlipressin lacks inotropic activity. Although vasoconstriction alone could potentially increase afterload and impair cardiac contractility, our study included follow-up echocardiograms showing no significant difference in left ventricular ejection fraction between the terlipressin and placebo

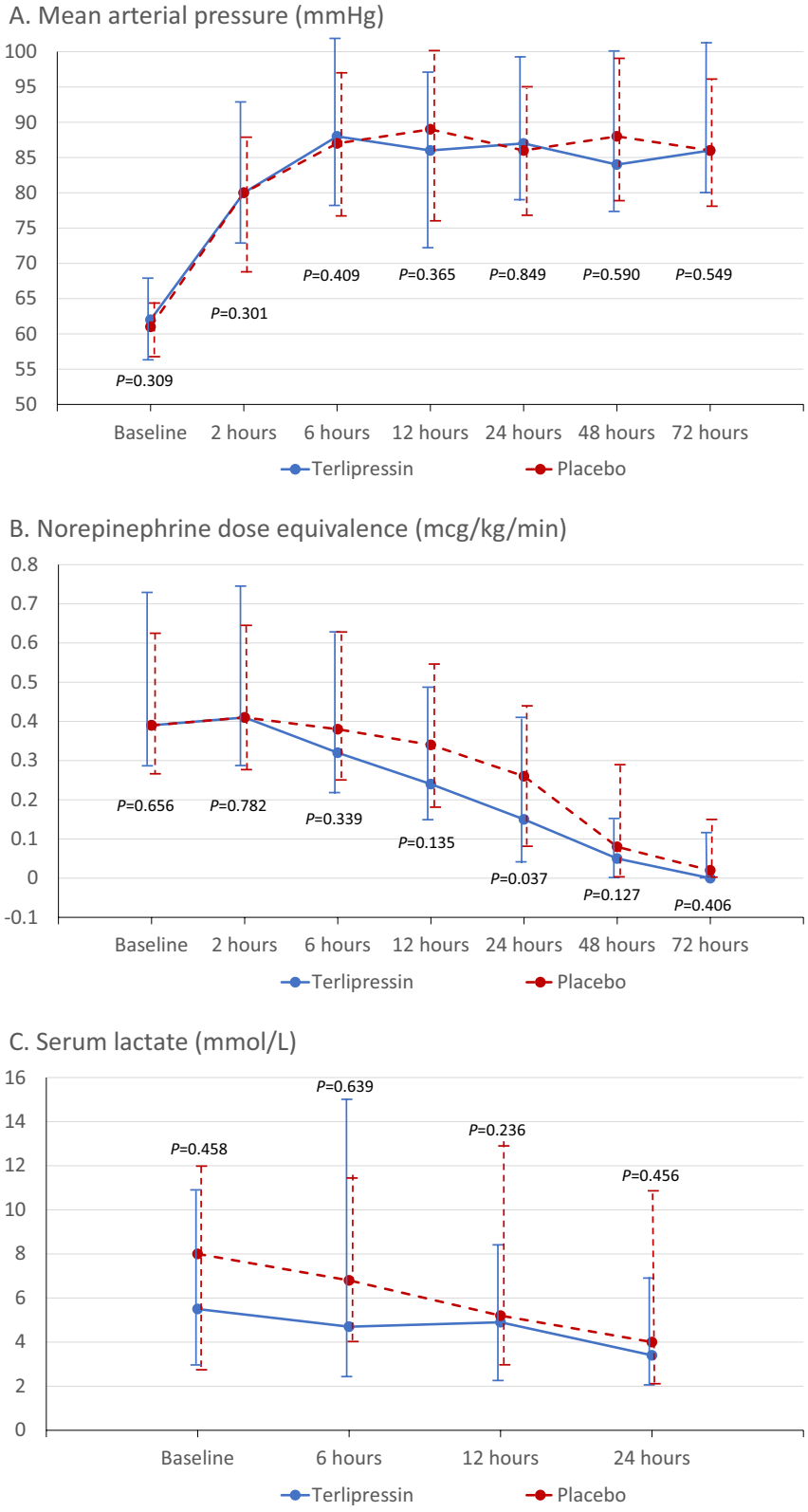
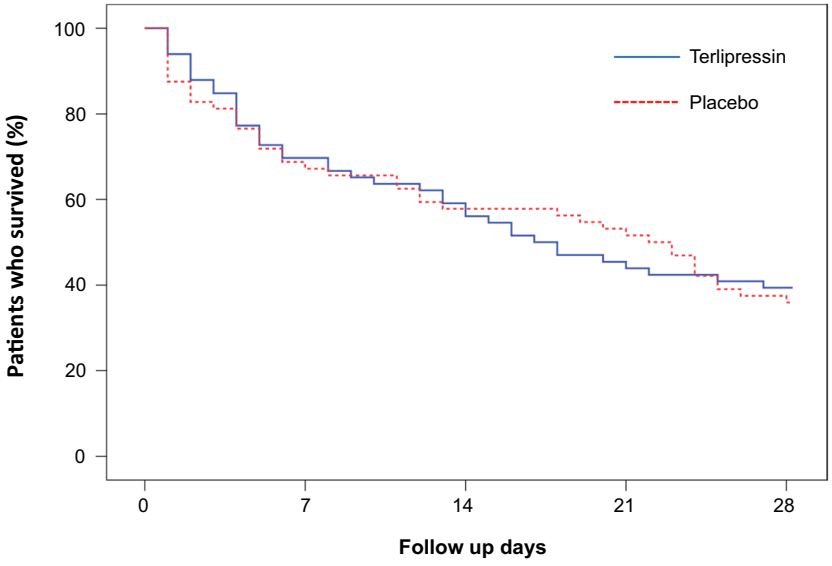


Fig. 2 Temporal trends in hemodynamic and metabolic variables after randomization **a** Mean arterial pressure, **b** cumulative catecholamine dose (expressed as norepinephrine equivalents), and **c** serum lactate concentrationData are median (IQR) over the first 72 h after enrollment. The horizontal dashed line in Panel A marks the target mean arterial pressure of 65 mmHg.



Number at Risk					
Terlipressin	66	46	37	29	26
Placebo	64	44	36	33	23

Fig. 3 Kaplan—Meier survival curves through day 28Twenty-eight–day survival did not differ significantly between groups (hazard ratio = 0.956, 95% CI = 0.618–1.478, *P* = 0.838).

Table 3 Univariate and multivariate analysis for independent predictors of terlipressin responders

Clinical parameters	Univariate		Multivariate	
	Odd ratio (95%CI)	P-value	Adjusted Odd ratio (95%CI)	P-value
APACHE II > 25	0.69 (0.51–0.91)	0.008	N/A	
SOFA < 12	2.13 (1.39–3.23)	< 0.001	33.33 (3.45–100.0)	0.003
Coronary artery disease	1.64 (0.87–3.09)	0.040	N/A	
Pneumonia	1.31 (1.02–1.68)	0.046	N/A	
Initial serum lactate < 4 mmol/L	2.17 (1.37–3.45)	< 0.001	33.33 (3.12–100.0)	0.004
Total dose of catecholamine > 0.25 mcg/kg/min before study drug[a]	0.28 (0.11–0.75)		N/A	
Adrenaline	0.68 (0.49–0.96)	< 0.001	N/A	
pH > 7.3	1.55 (1.20–2.02)	0.015	N/A	
HCO_3 > 18 mmol/L	1.36 (0.95–1.95)	0.001	N/A	
Mechanical ventilator	0.53 (0.22–1.25)	0.042	N/A	

Abbreviations: *APACHE II* Acute Physiology and Chronic Health Evaluation II, *SOFA* sequential organ failure assessment, *°C* degrees Celsius; *mmol/L* millimole per liter, *mcg/kg/min* micrograms per kilogram per minute, *N/A* not remained in the final multivariate analysis model

[a] Vasoactive dose or norepinephrine dose equivalents were calculated with the following equation:

Norepinephrine dose equivalent (micrograms per kilogram per minute [mcg/kg/min]) = (norepinephrine [mcg/kg/min] + epinephrine [mcg/kg/min] + dopamine [mcg/kg/min])/100 [18].

groups. Therefore, terlipressin does not appear to impair cardiac contractility based on these findings.Additionally, its use has not been associated with significant changes in indicators of tissue perfusion such as lactate clearance or cardiac index.

Regarding adverse events, our study observed no significant differences between the terlipressin and control groups in terms of cardiac arrhythmias, bowel ischemia, digital ischemia, or recurrent shock. This finding contrasts with results from a large randomized trial by Liu et al., which reported a significantly higher incidence of adverse events—especially digital ischemia—in patients receiving terlipressin compared with controls [23]. Although our study population had a lower baseline norepinephrine requirement (0.39 mcg/kg/min) than the Liu et al. study (0.48 mcg/kg/min), our patient populations exhibited more extensive multi-organ dysfunction beyond circulatory failure. Extensive multiorgan dysfunction, together with high vasopressor burden could resulted in high incidence of digital ischemia reported in our study. These differences highlight the clinical heterogeneity of septic shock and underscore the importance of assessing organ dysfunction such as renal and respiratory impairment when evaluating the effects of vasopressor strategies. To explore potential subphenotypes more likely to respond to terlipressin, patient characteristics were compared between responders and non-responders. Lower baseline SOFA scores and serum lactate levels appeared to be associated with early hemodynamic

response, although small sample size limits definitive conclusions. No new-onset acute myocardial infarction occurred in our population.

Several randomized controlled trials have examined the efficacy of terlipressin in treating septic shock, yet their findings remain inconclusive with respect to mortality benefits and potential ischemic complications [22–24, 26]. These discrepancies may be explained by variations in patient characteristics and terlipressin dosing regimens. However, a recent meta-analysis indicates that adding terlipressin to norepinephrine may reduce norepinephrine requirements, improve renal perfusion, and enhance the microcirculation in septic shock [27–29]. In addition, a meta-analysis of 51 randomized trials comparing non-catecholamine plus catecholamine vasopressors to catecholamine vasopressors alone in critically ill or perioperative patients found that using non-catecholamine vasopressors was associated with reduced mortality in septic shock [30].

This study has several limitations. First, we enrolled patients with refractory septic shock who were receiving very high doses of norepinephrine (median = 0.39 mcg/kg/min). The median time from septic shock diagnosis to terlipressin initiation was 14 h (IQR = 9 – 25). This delay was primarily due to the time required to obtain informed consent before starting the study drug. During this waiting period, norepinephrine doses were often adjusted to maintain adequate blood pressure. Delaying terlipressin introduction until after patients had received substantial catecholamines may have diminished any positive effect of a second vasopressor on septic shock outcomes. Second, the sample size was powered to detect differences in hemodynamic stabilization, rather than mortality or complications. Thus, the study may have been underpowered to assess mortality benefits or the risk of adverse events associated with terlipressin. Finally, this single-center trial was conducted at a tertiary university-affiliated hospital, which could limit the generalizability of the findings. Clinicians who consider using terlipressin should carefully compare this study's context with their own clinical setting. Additional multicenter trials with larger sample sizes and earlier enrollment—at lower norepinephrine doses—are needed to determine whether adding terlipressin as a second vasopressor improves survival in septic shock.

Conclusions

This study underscores the efficacy of terlipressin as a second vasopressor in patients with septic shock refractory to high-dose catecholamines. Adding terlipressin was associated with a reduction in catecholamine requirement, yet this benefit did not extend to overall mortality. Potential adverse events, including cardiac arrhythmias and organ ischemia, did not differ significantly between terlipressin and placebo. Larger, multicenter trials with earlier terlipressin initiation at lower norepinephrine doses are needed to confirm its role in septic shock management.

Abbreviations

ICU	Intensive care unit
IQR	Interquartile range
MAP	Mean arterial blood pressure
RR	Relative risk

Acknowledgements

The authors gratefully acknowledge Mr. David Park, Research Department, Faculty of Medicine, Siriraj Hospital, Mahidol University, for editing this manuscript.

Author contributions

ST and CC designed the study, performed the statistical analysis, and interpreted the data. TA and TT performed patient acquisition, data collection and the statistical analysis. ST and TT created the figures and tables. All the authors contributed to the drafting and writing of the manuscript, had full access to all the data, and approved the final version for publication.

Funding

Open access funding provided by Mahidol University. This research was supported by the Siriraj Research Fund, Faculty of Medicine Siriraj Hospital, Mahidol University (grant number: R016433013). Written informed consent was obtained from each patient or from next of kin or legal guardians when the patient was unable to consent.

Data availability

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

Declarations

Ethics approval and consent to participate

The Siriraj Institutional Review Board approved the study protocol (reference: Si 049/2020). Written informed consent was obtained from each patient or from next of kin or legal guardians when the patient was unable to consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 12 June 2025 / Accepted: 14 September 2025
Published online: 21 October 2025

References

1. Meyer NJ, Prescott HC. Sepsis and septic shock. N Engl J Med. 2024;391(22):2133–46. https://doi.org/10.1056/NEJMra2403213.
2. Geri G, Vignon P, Aubry A, Fedou AL, Charron C, Silva S, et al. Cardiovascular clusters in septic shock combining clinical and echocardiographic parameters: a post hoc analysis. Intensive Care Med. 2019;45(5):657–67. https://doi.org/10.1007/s00134-019-05596-z.
3. 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. Crit Care Med. 2021;49(11):e1063–143. https://doi.org/10.1097/CCM.0000000000005337.
4. Egi M, Ogura H, Yatabe T, Atagi K, Inoue S, Iba T, et al. The Japanese clinical practice guidelines for management of sepsis and septic shock 2020 (J-SSCG 2020). J Intensive Care. 2021;9(1):53. https://doi.org/10.1186/s40560-021-00555-7.

5. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle update. Crit Care Med. 2018;46(6):997–1000. https://doi.org/10.1097/CCM.0000000000003119. PMID: 29767636.
6. 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. https://doi.org/10.1164/rccm.201806-1034OC.
7. Domizi R, Calcinaro S, Harris S, Beilstein C, Boerma C, Chiche JD, et al. Relationship between norepinephrine dose, tachycardia and outcome in septic shock: a multicenter evaluation. J Crit Care. 2020;57:185–90.
8. Auchet T, Regnier MA, Girerd N, Levy B. Outcome of patients with septic shock and high-dose vasopressor therapy. Ann Intensive Care. 2017;7:43.
9. Yamamura H, Kawazoe Y, Miyamoto K, Yamamoto T, Ohta Y, Morimoto T. Effect of norepinephrine dosage on mortality in patients with septic shock. J Intensive Care. 2018;6:12.
10. Tongyoo S, Tanyalakmara T, Naorungroj T, Promsin P, Permpikul C. The association of high dose vasopressor and delayed vasopressor titration with 28-day mortality in adult patients with septic shock. J Health Sci Med Res. 2022;41(1):e2022886. https://doi.org/10.31584/jhsmr.2022886.
11. Belletti A, Musu M, Silvetti S, Saleh O, Pasin L, Monaco F, et al. Non-adrenergic vasopressors in patients with or at risk for vasodilatory shock. A systematic review and meta-analysis of randomized trials. PLoS ONE. 2015;10(11):e0142605. https://doi.org/10.1371/journal.pone.0142605.
12. Russell JA, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med. 2008;358(9):877–87. https://doi.org/10.1056/NEJMoa067373.
13. Pesaturo AB, Jennings HR, Voils SA. Terlipressin: vasopressin analog and novel drug for septic shock. Ann Pharmacother. 2006;40(12):2170–7. https://doi.org/10.1345/aph.1H373.
14. Aritajati T, Chayakul C, Tongyoo S. Terlipressin 2022 for refractory septic shock: a study protocol of a single center, placebo-controlled double-blind phase III RCT (The TERESEP study). Clin Crit Care [internet]. [cited 2025 May 6];30:2022:e0003. available from: https://he02.tci-thaijo.org/index.php/ccc/article/view/254966.
15. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726–32. https://doi.org/10.7326/0003-4819-152-11-201006010-00232.
16. 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;315:801–10.
17. Alvarado Sánchez JI, Caicedo Ruiz JD, Diaztagle Fernández JJ, Amaya Zuñiga WF, Ospina-Tascón GA, Cruz Martínez LE. Predictors of fluid responsiveness in critically ill patients mechanically ventilated at low tidal volumes: systematic review and meta-analysis. Ann Intensive Care. 2021;11(1):28. https://doi.org/10.1186/s13613-021-00817-5.
18. Goradia S, Sardaneh AA, Narayan SW, et al. Vasopressor dose equivalence: a scoping review and suggested formula. J Crit Care. 2021;61:233–40. https://doi.org/10.1016/j.jcrc.2020.11.002.
19. Russell JA, Lee T, Singer J, De Backer D, Annane D. Days alive and free as an alternative to a mortality outcome in pivotal vasopressor and septic shock trials. J Crit Care. 2018;47:333–7. https://doi.org/10.1016/j.jcrc.2018.05.003.
20. Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, et al. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med. 2017;377:419–30.
21. Tongyoo S, Permpikul C, Haemin R, Epichath N. Predicting factors, incidence and prognosis of cardiac arrhythmia in medical, non-acute coronary syndrome, critically ill patients. J Med Assoc Thai. 2013;96(Suppl 2):S238-45.
22. Morelli A, Ertmer C, Rehberg S, Lange M, Orecchioni A, Cecchini V, et al. Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. Crit Care. 2009;13:R130.
23. Liu ZM, Chen J, Kou Q, Lin Q, Huang X, Tang Z, et al. Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial. Intensive Care Med. 2018;44:1816–25.
24. Sahoo P, Kothari N, Goyal S, Sharma A, Bhatia PK. Comparison of norepinephrine and terlipressin vs norepinephrine alone for management of septic shock: a randomized control study. Indian J Crit Care Med. 2022;26(6):669–75. https://doi.org/10.5005/jp-journals-10071-24231.
25. Kotani Y, Di Gioia A, Landoni G, et al. An updated "norepinephrine equivalent" score in intensive care as a marker of shock severity. Crit Care. 2023;27:29. https://doi.org/10.1186/s13054-023-04322-y.
26. Li W, Deng J. Effect of continuous infusion therapy with low-dose terlipressin combined with norepinephrine on hemodynamics, inflammatory markers, and prognosis in patients with severe septic shock. Mil Med. 2025;190(1–2):116–23. https://doi.org/10.1093/milmed/usae369.
27. Mao F, Liang D, Tang Z, Xu Y, Lin L. Terlipressin combined with norepinephrine in the treatment of septic shock: a systematic review. Shock. 2023;60(4):479–86. https://doi.org/10.1097/SHK.0000000000002204.
28. Huang L, Zhang S, Chang W, Xia F, Liu S, Yang Y, et al. Terlipressin for the treatment of septic shock in adults: a systematic review and meta-analysis. BMC Anesthesiol. 2020;20(1):58. https://doi.org/10.1186/s12871-020-00965-4.
29. Zhu Y, Huang H, Xi X, Du B. Terlipressin for septic shock patients: a meta-analysis of randomized controlled study. J Intensive Care. 2019;7:16.
30. Kotani Y, Belletti A, D'Amico F, Bonaccorso A, Wieruszewski PM, Fujii T, et al. Non-adrenergic vasopressors for vasodilatory shock or perioperative vasoplegia: a meta-analysis of randomized controlled trials. Crit Care. 2024;28(1):439. https://doi.org/10.1186/s13054-024-05212-7.

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