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Review Article

The therapeutic effect of norepinephrine alone or in combination with vasopressin on septic shock patients: a meta-analysis

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Abstract: Objective: To evaluate the effects of norepinephrine alone versus norepinephrine in combination with vasopressin on clinical outcomes in patients with septic shock using a Meta-analysis. Methods: Randomized controlled trials (RCTs) comparing norepinephrine monotherapy and combination therapy with vasopressin in septic shock patients were identified through searches of China Knowledge, Wanfang, VIP, and Pubmed databases for studies published between January 1, 2010 and December 31, 2024. Eligible studies were screened based on predefined inclusion and exclusion criteria. Methodological quality was assessed, and data were analyzed using RevMan 5.4 software. Results: Fifteen RCTs involving 1,481 patients were included. Meta-analysis demonstrated that the combination therapy (norepinephrine + vasopressin) significantly improved mean arterial pressure, lactate clearance, heart rate, central venous oxygen saturation, oxygen delivery, and urine output, while reducing blood ammonia and intestinal-type fatty acid-binding protein levels (all $P<0.00001$). However, mortality did not differ significantly between the groups ($OR=1.13$, 95% CI: 0.94, 1.35; $P=0.19$). The results of the subgroup variable analysis demonstrated that lactate and heart rate were homogeneous across different age groups, and mean arterial pressure was homogeneous across different sample size groups ($P>0.05$). Conclusion: The addition of vasopressin to norepinephrine significantly improves hemodynamic parameters in septic shock patients but does not obviously reduce mortality. Further high-quality RCTs are warranted to validate these findings.

Keywords: Septic shock, norepinephrine, vasopressin, hemodynamics, clinical prognosis

Introduction

Septic shock is a state of circulatory failure characterized by sustained hypotension due to uncontrolled systemic inflammatory response triggered by infection [1]. Statistics have shown that infectious shock accounts for 10% of intensive care unit (ICU) patients, with a 28-day mortality rate reaching up to 60%, and both morbidity and mortality have shown an upward trend in recent years [2]. Recent studies suggest that patient prognosis is closely related to hemodynamic stability, underscoring the importance of timely hemodynamic support [3]. According to the 2021 Surviving Sepsis Campaign Guidelines, norepinephrine is the preferred vasopressor recommended for septic shock management [4]. Norepinephrine stimulates α_1-adrenergic receptors to trigger peripheral vasoconstriction, resulting in rapid increase in mean arterial pressure (MAP), while β1 receptor activation moderately enhances cardiac output and improves perfusion to vital organs such as the kidneys and brain [5]. However, monotherapy with norepinephrine may induce excessive vasoconstriction of visceral vessels, exacerbating intestinal ischemia and hypoxia. Moreover, patients with septic shock often exhibit relative vasopressin (AVP) deficiency; exogenous VAP supplementation can compensate for this deficiency and enhance vascular responsiveness to other vasoactive drugs [6]. Studies have shown that vasopressin acts on V1 receptors in vascular smooth muscle to induce vasoconstriction independent of adrenergic pathways [7].

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Although numerous studies have examined the effect of norepinephrine alone or in combination with vasopressin in septic shock patients, discrepancies in sample sizes, study designs, patient inclusion criteria, and outcome measures limit the generalizability of their findings. The existing studies are often small-scale, report inconsistent endpoints, and lack high-level evidence-based support [8, 9]. On this basis, the current study adopted a meta-analysis approach to systematically synthesize clinical evidence published in the past decade. For the first time, it incorporated microcirculatory perfusion parameters and intestinal function indicators into the efficacy evaluation system and conducted subgroup analysis based on disease severity. This study aims to clarify whether norepinephrine combined with terlipressin is superior to monotherapy in improving microcirculation perfusion in patients with septic shock, whether the protective effects on intestinal mucosal barrier function are dose-dependent, and how treatment timing influences efficacy. These findings may provide a reference for clinical selection of vasoactive drug combination regimens, particularly for optimizing organ protection strategies and reducing microcirculation-related complications in patients with septic shock.

Data and methods

Data collection

Inclusion criteria: (1) Study type: randomized controlled trials (RCT); (2) Studies on septic shock as defined by the 2016 International Sepsis Guidelines [10]; (3) Interventions included norepinephrine or in combination with other vasopressors; (4) Reported outcome measures included hemodynamic parameters and clinical prognostic indexes.

Exclusion criteria: (1) Studies lacking clear diagnostic criteria; (2) Non-RCTs, such as animal experiments, reviews, and case reports; (3) Studies involving pediatric patients or non-septic shock patients; (4) Studies with incomplete or ambiguous data.

Literature screening and data extraction

Literature selection followed the PRISMA flowchart. Two reviewers independently screened the literature, extracted data, and assessed study quality using NoteExpress 3.3.0.8102. Excel 2019 was used to organize relevant information, including basic study details (title, authors, publication year, country, sample size), patient characteristics (age, sex), and intervention specifics (primary drugs used, treatment protocols for intervention and control groups). Search terms included “norepinephrine”, “vasopressin”, “septic shock”, “hemodynamics”, “clinical prognosis” and related keywords.

Quality evaluation: The quality of the included studies was assessed using the Cochrane Collaboration’s Risk of Bias tool, which evaluates the following domains: random sequence generation, allocation concealment, blinding, completeness of outcome data, selective reporting, and other potential sources of bias. In addition, the Jadad scale (maximum score: 5) was used to further assess the quality of RCTs, with 3-5 indicating high-quality studies and 0-2 indicating low-quality studies. Two reviewers independently evaluated the risk of bias for each study and assigned judgments for each domain. Any discrepancies were resolved through discussion or consultation with a third reviewer.

Publication bias was assessed using funnel plots and Egger’s regression test (when ≥10 studies were included) and cross-validated by Begg’s rank correlation test. The overall quality of evidence was evaluated using the GRADE system, which rated the primary outcomes in five dimensions: study design, risk of bias, inconsistency, indirectness, and imprecision. Based on these criteria, the evidence was categorized into four grades: high, moderate, low, and very low.

Statistical analyses

Statistical analysis was conducted using RevMan 5.4 software. For dichotomous outcomes, odds ratio (OR) with 95% confidence intervals (CI) were calculated for dichotomous variables. Heterogeneity was assessed using the Chi-square test (Q statistic, $P<0.10$ indicating heterogeneity) and I^2 statistic. If $I^2 \leq 50\%$ and $P>0.10$, a fixed-effects model (Mantel-Haenszel method) was applied. If $I^2>50\%$ or $P \leq 0.10$, indicating moderate to high heterogeneity, a random-effects model was used, and the source of heterogeneity was further explored via subgroup analysis and Meta-regression. A sensitiv-

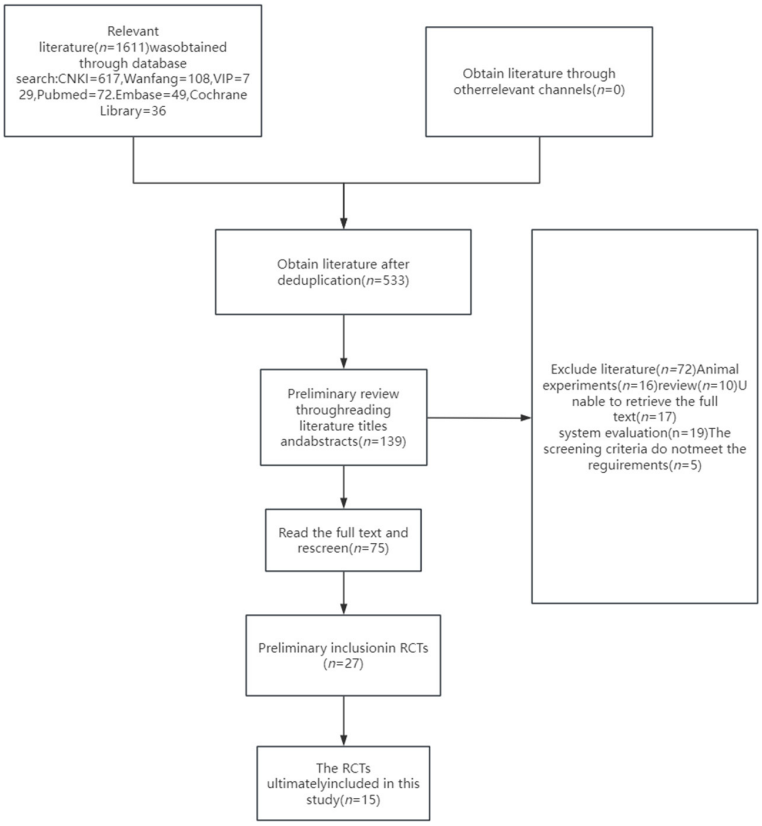

Figure 1. Literature screening flowchart.

ity analysis was performed by sequentially excluding each indicator involved in the study in order to assess the sensitivity of the results. A forest plot of the sensitivity analysis was created using the CNSknowall website. Publication bias was assessed using a funnel plot.

Results

Literature search

The databases searched included CNKI, Wanfang, VIP, Pubmed, Embase, and the Cochrane Library. The search period was from January 1, 2010 to December 31, 2024. Search terms included "norepinephrine", "vasopressin", "septic shock", "hemodynamics", "clinical prognosis" and other related terms. A total of 1,611 articles were initially identified: 617 from CNKI, 108 from Wanfang, 729 from VIP, 72 from Pubmed, 49 from Embase, and 36 from the Cochrane Library. After screening, 10 articles [11-25] met the inclusion criteria and were included in the final analysis. The literature screening process is shown in **Figure 1**.

Basic characteristics of the included studies

All RCTs included a total of 1,481 participants, with 751 in the treatment group and 730 in the control group. The sample size ranged from 15 to 203, and no dropouts were reported (**Table 1**).

Quality assessment of study methodology

All 15 included studies had a Jadad score of 2, indicating low methodological quality. Although randomization was reported in all studies, none provided details on allocation concealment, and none described participant withdrawals or dropouts. Quality assessment results are presented in **Table 2** and **Figure 2**.

Results of meta-analysis

Effect of vasopressin in combination with norepinephrine on mean arterial pressure: Seven studies [11, 12, 14, 15, 18, 23, 24] reported MAP as a hemodynamic outcome, involving 540 subjects (244 in the treatment group, 246 in the control group). Heterogeneity was identified among included studies (χ^2=18.22, I^2=67%, P=0.01), and a random-effects model was applied. The results showed that vasopressin significantly improved mean arterial pressure in patients with septic shock compared with norepinephrine (*OR*=-6.78, *95% CI* (-9.34, -4.23), Z=5.21, P<0.00001) (**Figure 3A**).

Sensitivity analysis of the seven studies showed that, except for reference [15], the results remained consistent after excluding individual studies (**Figure 3B**). A funnel plot analysis of publication bias indicated minimal publication bias among the articles (**Figure 3C**).

Effect of vasopressin in combination with norepinephrine on serum lactic acid: Nine studies [11-13, 16, 18, 19, 21-23] assessed lactate levels, with a total of 773 subjects included (389 in the treatment group and 384 in the

Table 1. Basic characteristics of the included studies

Author's year	Sample size		Average age		Baseline level	Intervention		outcome indicator
	Treatment group (m/f)	Control group (m/f)	Treatment group	Control group		Treatment group	Control group	
Li2018 [11]	15 (16/14)	15 (17/13)	60.33±10.14	59.73±10.49	comparable	Norepinephrine + pressin	Norepinephrine	Mean arterial pressure, lactate, mortality, heart rate, Urine output
Yu2023 [12]	51 (28/23)	51 (29/22)	45.04±3.78	44.96±3.88	comparable	Norepinephrine + pressin	Norepinephrine	Mean arterial pressure, lactate, heart rate, aerobic delivery, central venous oxygen saturation, Diaminase, Intestinal fatty acid binding protein
Huang2022 [13]	40 (26/14)	40 (23/17)	45.18±3.82	45.86±4.11	comparable	Norepinephrine + pressin	Norepinephrine	Lactate, aerobic delivery, central venous oxygen saturation, Diaminase, Intestinal fatty acid binding protein
Jiang2015 [14]	40 (27/13)	40 (23/17)	59.20±2.30	58.70±2.40	comparable	Norepinephrine + pressin	Norepinephrine	Mean arterial pressure, heart rate, Urine output
Wu2014 [15]	20 (12/8)	20 (13/7)	54.95±7.50	55.16±7.62	comparable	Norepinephrine + pressin	Norepinephrine	Mean arterial pressure, heart rate
Liu2024 [16]	44 (28/16)	43 (26/17)	47.23±5.36	46.72±5.31	comparable	Norepinephrine + pressin	Norepinephrine	Lactate, aerobic delivery, central venous oxygen saturation
Menich2019 [17]	48 (26/22)	48 (24/24)	61.80±17.80	61.30±13.70	comparable	Norepinephrine + pressin	Norepinephrine	mortality rate
Li2018 [18]	50 (24/26)	50 (27/23)	63.85±16.14	64.12±15.41	comparable	Norepinephrine + pressin	Norepinephrine	Mean arterial pressure, lactate, heart rate, death rate, Urine output
Liao2023 [19]	40 (20/20)	40 (21/19)	62.24±2.35	62.13±2.31	comparable	Norepinephrine + pressin	Norepinephrine	Lactate, aerobic delivery, central venous oxygen saturation, Diaminase, Intestinal fatty acid binding protein
Sahoo2022[20]	25 (8/17)	25 (5/20)	48.88±17.98	48.84±19.08	comparable	Norepinephrine + pressin	Norepinephrine	mortality rate
Shen2024 [21]	58 (35/23)	58 (33/25)	49.73±5.44	48.88±17.98	comparable	Norepinephrine + pressin	Norepinephrine	lactate
Qin2019 [22]	43 (26/17)	39 (28/11)	67.24±16.20	68.17±17.94	comparable	Norepinephrine + pressin	Norepinephrine	lactate
Hammond2019 [23]	48 (23/25)	48 (24/24)	58.60±14.60	56.90±15.40	comparable	Norepinephrine + pressin	Norepinephrine	Mean arterial pressure, lactate
Luo2013 [24]	26 (21/5)	22 (19/3)	84.50±10.10	83.90±11.20	comparable	Norepinephrine + pressin	Norepinephrine	Mean arterial pressure
Russell2013 [25]	203 (112/91)	191 (121/70)	60.00±45.78	60.70±16.70	comparable	Norepinephrine + pressin	Norepinephrine	mortality rate

Table 2. Evaluation of the quality of the included literature

Author's year	sample size	stochastic approach	Assignment hiding	Withdrawal and exit	Jadad Rating
Li2018 [11]	30	References to stochastic	unintroduced	undescribed	2
Yu2023 [12]	102	References to stochastic	unintroduced	undescribed	2
Huang2022 [13]	80	References to stochastic	unintroduced	undescribed	2
Jiang2015 [14]	80	References to stochastic	unintroduced	undescribed	2
Wu2014 [15]	40	References to stochastic	unintroduced	undescribed	2
Liu2024 [16]	87	References to stochastic	unintroduced	undescribed	2
Menich2019 [17]	96	References to stochastic	unintroduced	undescribed	2
Li2018 [18]	100	References to stochastic	unintroduced	undescribed	2
Liao2023 [19]	80	References to stochastic	unintroduced	undescribed	2
Sahoo2022 [20]	50	References to stochastic	unintroduced	undescribed	2
Shen2024 [21]	116	References to stochastic	unintroduced	undescribed	2
Qin2019 [22]	82	References to stochastic	unintroduced	undescribed	2
Hammond2019 [23]	96	References to stochastic	unintroduced	undescribed	2
Luo2013 [24]	48	References to stochastic	unintroduced	undescribed	2
Russell2013 [25]	394	References to stochastic	unintroduced	undescribed	2

control group). Heterogeneity was observed among the included studies (χ^2=58.42, I^2=86%, P<0.00001), and a random-effects model was applied to pool the effect sizes. The results showed that vasopressin significantly improved lactate levels in patients with septic shock compared with non-adrenergic agents (*OR*= 0.68, *95% CI:* (0.52, 0.83), Z=8.54, P<0.00001) (**Figure 4A**).

Sensitivity analysis of the nine studies showed that the results remained consistent even when individual studies were excluded (**Figure 4B**). A funnel plot analysis was conducted to assess publication bias, indicating the presence of publication bias among the articles (**Figure 4C**).

Effect of vasopressin in combination with norepinephrine on heart rate (HR): Six studies [11, 12, 14, 15, 17, 18] reported heart rate, involving a total of 518 participants (260 in the treatment group and 258 in the control group). Significant heterogeneity was observed among the studies (χ^2=280.50, I^2=98%, P<0.00001), and a random-effects model was applied. The results indicated that vasopressin significantly improved heart rate in septic shock patients compared to norepinephrine (*OR*=13.42, *95% CI:* (1.97, 24.88), Z=2.30, P=0.02) (**Figure 5A**).

Sensitivity analysis of the six studies showed consistent results when individual studies were sequentially excluded (**Figure 5B**). A funnel plot was used to assess publication bias, and the result suggested potential bias among the included articles (**Figure 5C**).

Effect of vasopressin in combination with norepinephrine on central venous oxygen saturation ($ScvO_2$): Four studies [12, 13, 16, 19] reported $ScvO_2$, involving a total of 349 participants (175 in the treatment group and 174 in the control group). Homogeneity was identified among the studies (χ^2=0.38, I^2=0%, P=0.94), thus a fixed effects model was used to pool the effect sizes. The results showed that vasopressin significantly improved $ScvO_2$ in septic shock patients compared to norepinephrine (*OR*=-7.09, *95% CI:* (-8.65, -5.53), Z=8.90, P<0.00001) (**Figure 6A**).

Sensitivity analysis of the four studies demonstrated consistent results when individual studies were sequentially excluded (**Figure 6B**). A funnel plot was used to assess publication bias, and the result suggested potential bias among the included articles (**Figure 6C**).

Effect of vasopressin in combination with norepinephrine on oxygen delivery: Four literatures [12, 13, 16, 19] assessed aerobic delivery volume, and a total of 349 research subjects were included, including 175 in the treatment group and 174 in the control group. Homogeneity was observed among the included studies (χ^2=0.02, I^2=0%, P=1.00), and a fixed effects model was

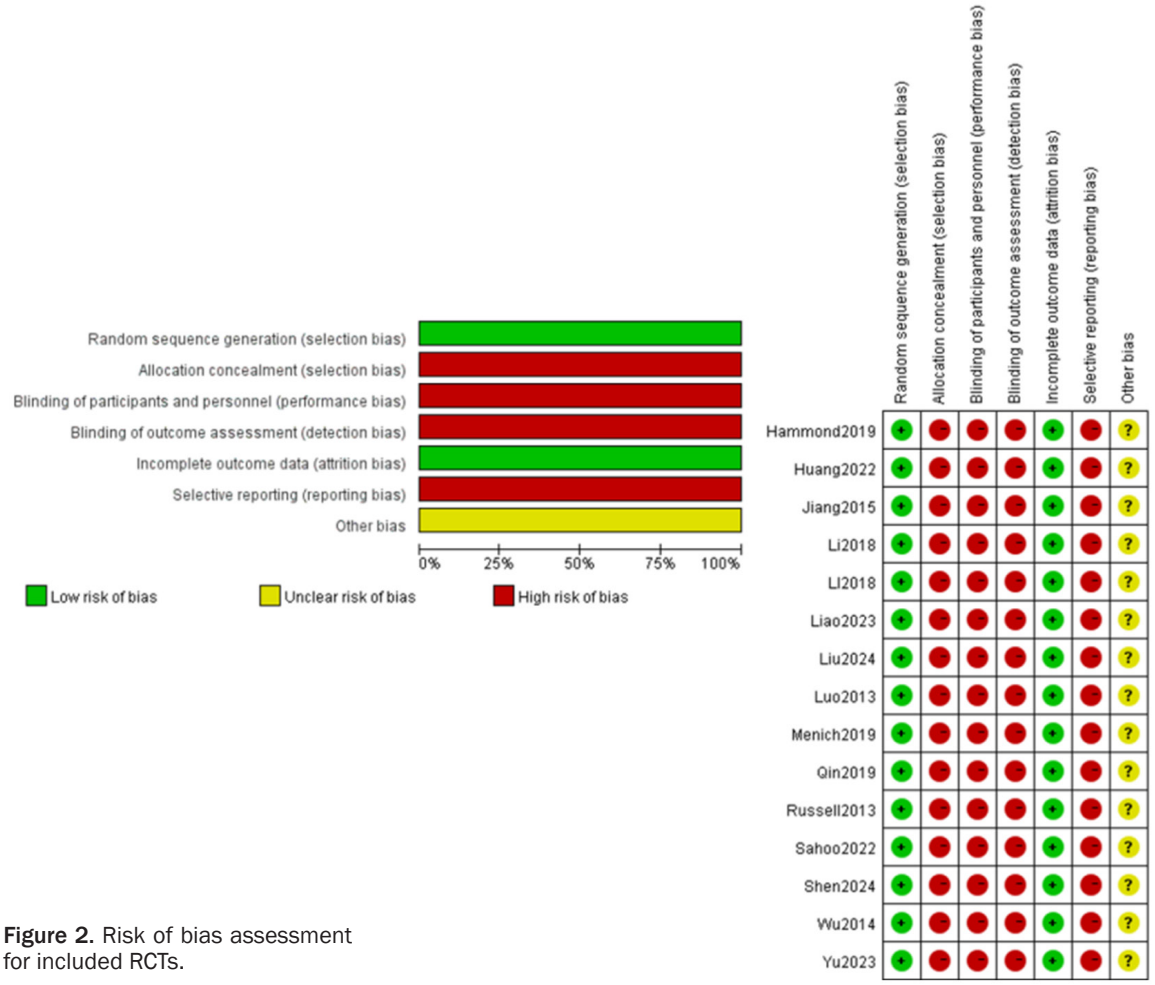

Figure 2. Risk of bias assessment for included RCTs.

used to explore the relevant effect sizes. The results showed that vasopsin significantly improved the aerobic delivery volume in patients with septic shock compared to norepinephrine (*OR*=-83.36, *95% CI:* (-95.13, -71.58), *Z*=13.87, *P*<0.00001) (**Figure 7A**).

Sensitivity analysis of the four studies showed after excluding each study, the combined effect sized remained stable (**Figure 7B**). A funnel plot was drawn to analyze publication bias, indicating that there is a certain degree of publication bias among the articles (**Figure 7C**).

Effect of vasopressin in combination with norepinephrine on urine output: Three literatures [11, 14, 18] analyzed urine volume and included a total of 210 research subjects, including 105 cases in the treatment group and 105 cases in the control group. Homogeneity was observed among the included studies (χ^2=0.21, I^2=0%, *P*=0.90), supporting the use of a fixed effects model. The results showed that vasopressin significantly improved urine output in patients with septic shock compared to norepinephrine (*OR*=-7.98, *95% CI*: (-9.48, -6.47), *Z*=10.38, *P*<0.00001 (**Figure 8A**).

Sensitivity analysis of the three studies showed that after excluding each study, the combined effect size remained consistent (**Figure 8B**). A funnel plot was drawn to analyze publication bias, and the result indicated that the publication bias among the articles was relatively small (**Figure 8C**).

Effect of vasopressin in combination with norepinephrine on Diamine Oxidase (DAO): Three literatures [12, 13, 19] reported diaminase and included a total of 261 research subjects, including 131 cases in the treatment group and 131 cases in the control group. Homogeneity was observed among the included studies (χ^2=0.11, I^2=0%, *P*=0.95), and a fixed effects

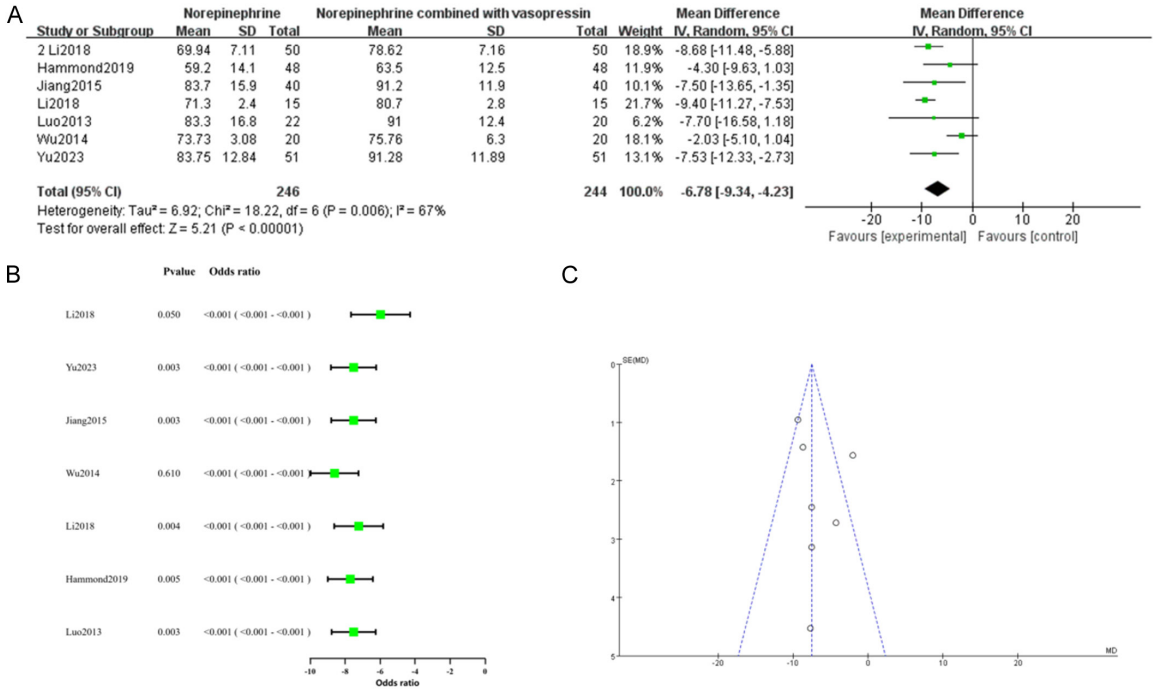

Figure 3. Meta-analysis of the effect of vasopressin in combination with norepinephrine on mean arterial pressure. Note: (A) Forest plot of the effect of vasopressin on mean pulsating pressure; (B) Sensitivity analysis of the effect of vasopressin on mean pulsating pressure; (C) Funnel plot of the effect of vasopressin on mean pulsating pressure.

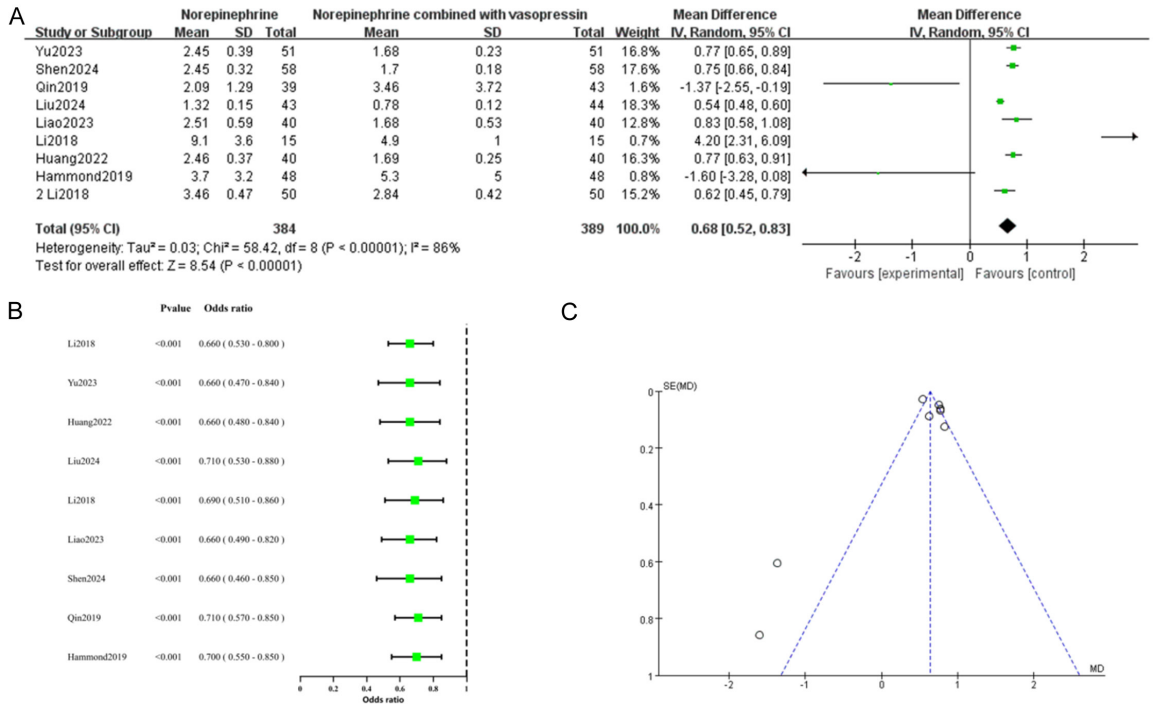

Figure 4. Meta-analysis of the effect of vasopressin in combination with norepinephrine on lactate acid content. Note: (A) Forest map of the effect of vasopressin on lactic acid; (B) Sensitivity analysis of vasopressin on lactic acid; (C) Funnel plot of the effect of vasopressin on lactic acid.

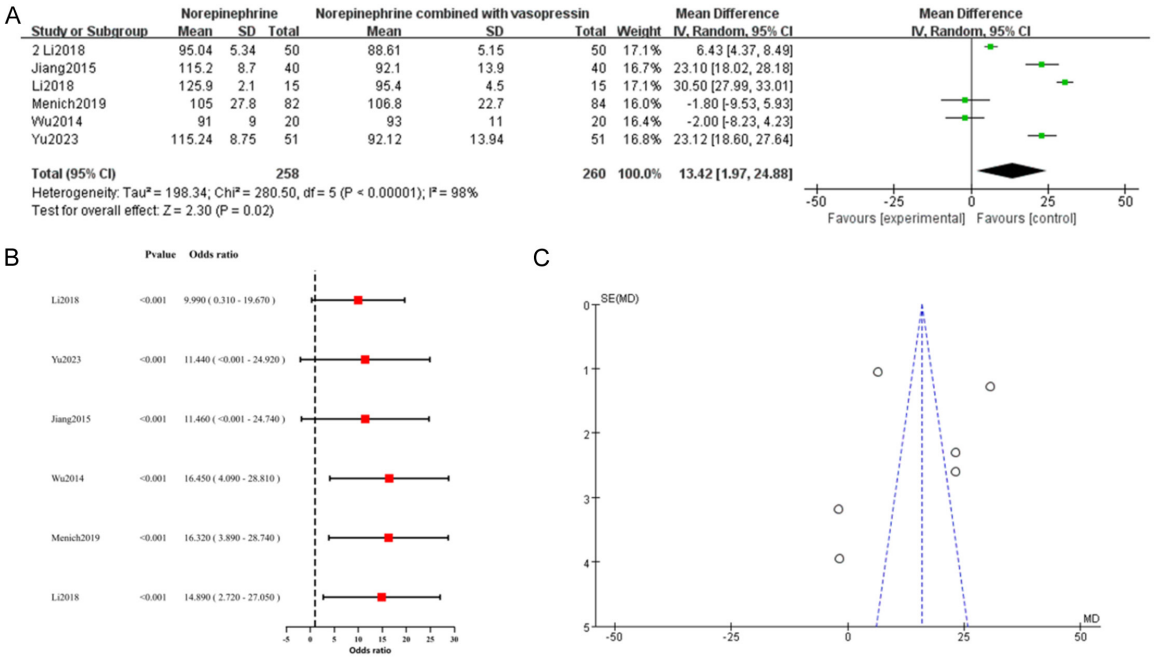

Figure 5. Meta-analysis of the effect of vasopressin in combination with norepinephrine on heart rate. Note: (A) Forest map of the effect of vasopressin on heart rate; (B) Sensitivity analysis of the effect of vasopressin on heart rate; (C) Funnel plot of the effect of vasopressin on heart rate.

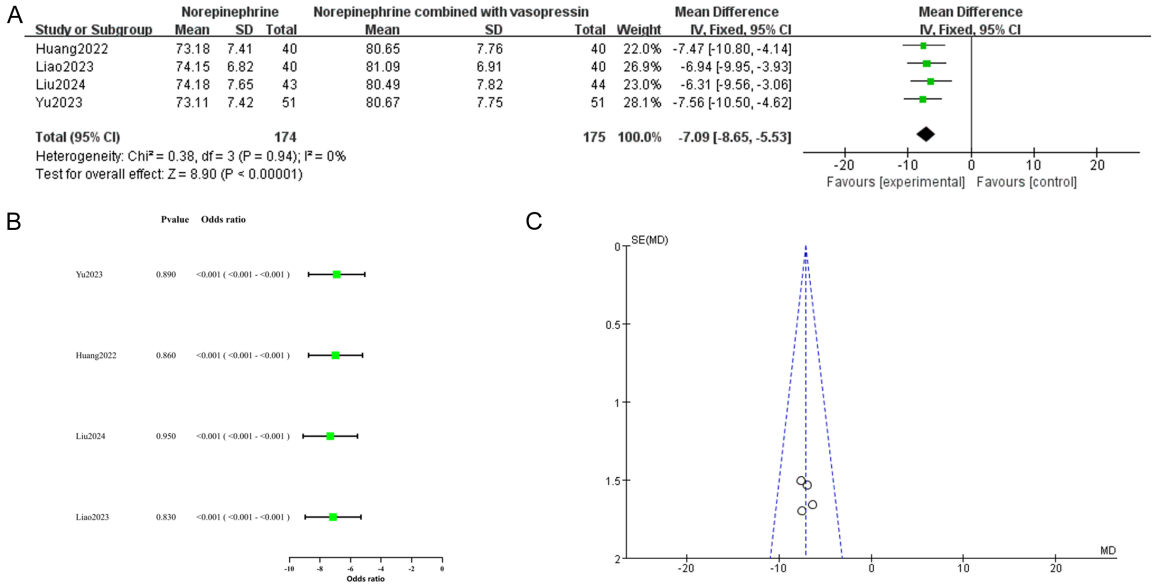

Figure 6. Meta-analysis of the effect of vasopressin in combination with norepinephrine on central venous oxygen saturation ($ScvO_2$). Note: (A) Forest map of the effect of vasopressin on central venous oxygen saturation; (B) Sensitivity analysis of the effect of vasopressin on central venous oxygen saturation; (C) Funnel plot of the effect of vasopressin on central venous oxygen saturation.

model was conducted to detect the combined effect sizes. The results showed that vasopressin significantly improved the diaminase level in patients with septic shock compared to norepinephrine (*OR*=0.79, *95% CI:* (0.65, 0.92), *Z*=11.02, *P*<0.00001) (**Figure 9A**).

Sensitivity analysis of the three studies showed that the combined effect size remained consistent after excluding each study sequentially (**Figure 9B**). A funnel plot was drawn to analyze publication bias, and the result indicated that the stability among the articles was good and

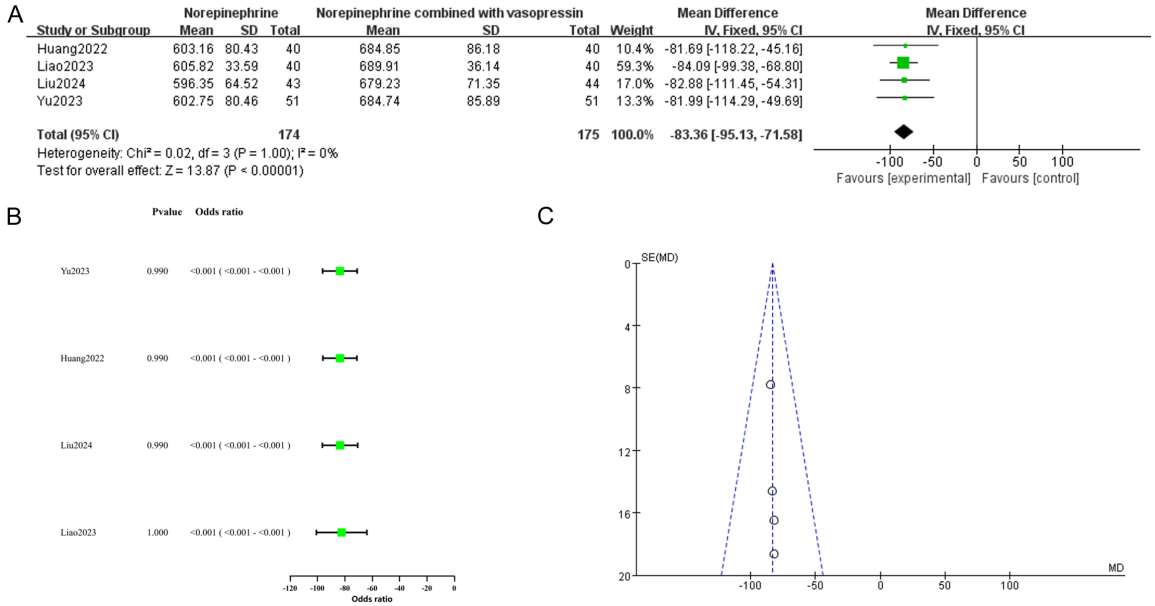

Figure 7. Meta-analysis of the effect of vasopressin in combination with norepinephrine on oxygen delivery. Note: (A) Forest plot of the effect of vasopressin on aerobic transport volume; (B) Sensitivity analysis of the effect of vasopressin on aerobic transport volume; (C) Funnel plot of the effect of vasopressin on aerobic transport volume.

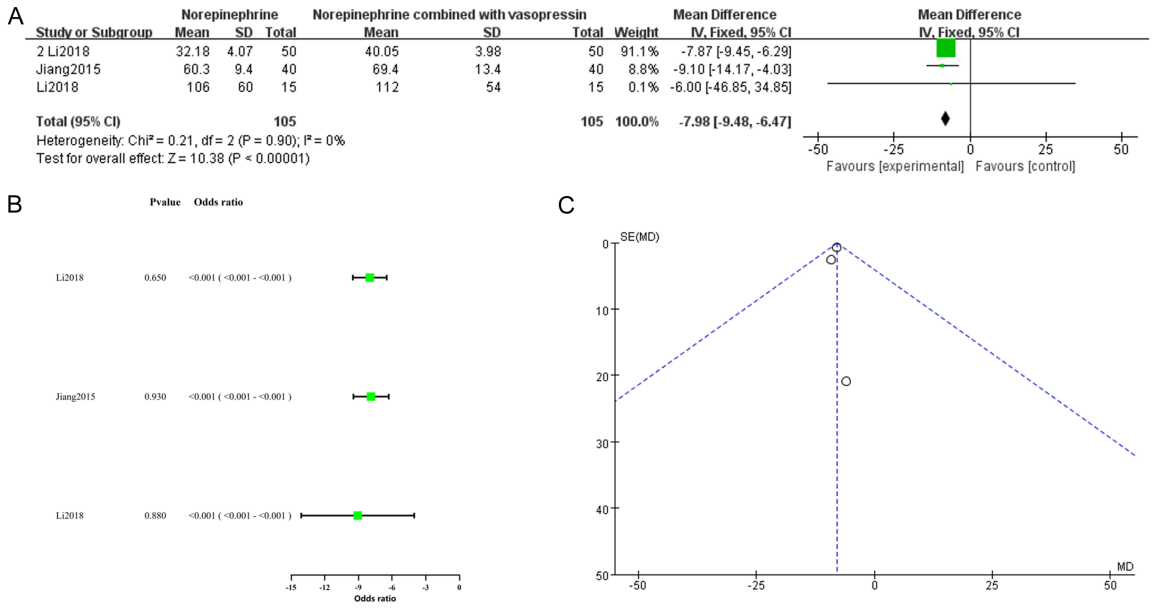

Figure 8. Meta-analysis of the effect of vasopressin in combination with norepinephrine on urine output. Note: (A) Forest map of the effect of vasopressin on urine output; (B) Sensitivity analysis of the effect of vasopressin on urine volume; (C) Funnel plot of the effect of vasopressin on urine output.

there was no obvious publication bias (**Figure 9C**).

Effect of vasopressin in combination with norepinephrine on intestinal-type fatty acid binding proteins (I-FABP): Three literatures [12, 13, 19] reported intestinal fatty acid binding protein, involving a total of 261 research subjects, including 131 cases in the treatment group and 131 cases in the control group. Homogeneity was revealed among the included studies (χ^2=0.05, I^2=0%, P=0.97), supporting the adoption of a fixed effects model. The results showed that vasopressin significantly improved

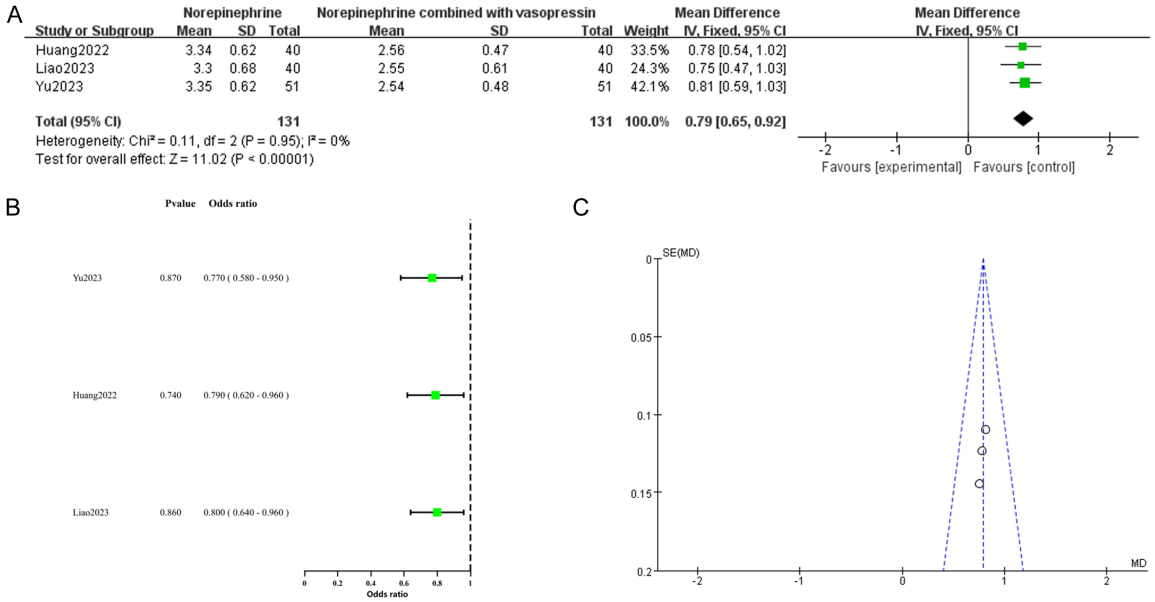

Figure 9. Meta-analysis of the effect of vasopressin in combination with norepinephrine on diamine oxidase. Note: (A) Forest map of the effect of vasopressin on diaminase; (B) Sensitivity analysis of vasopressin on diaminase; (C) Funnel plot of the effect of vasopressin on diaminase.

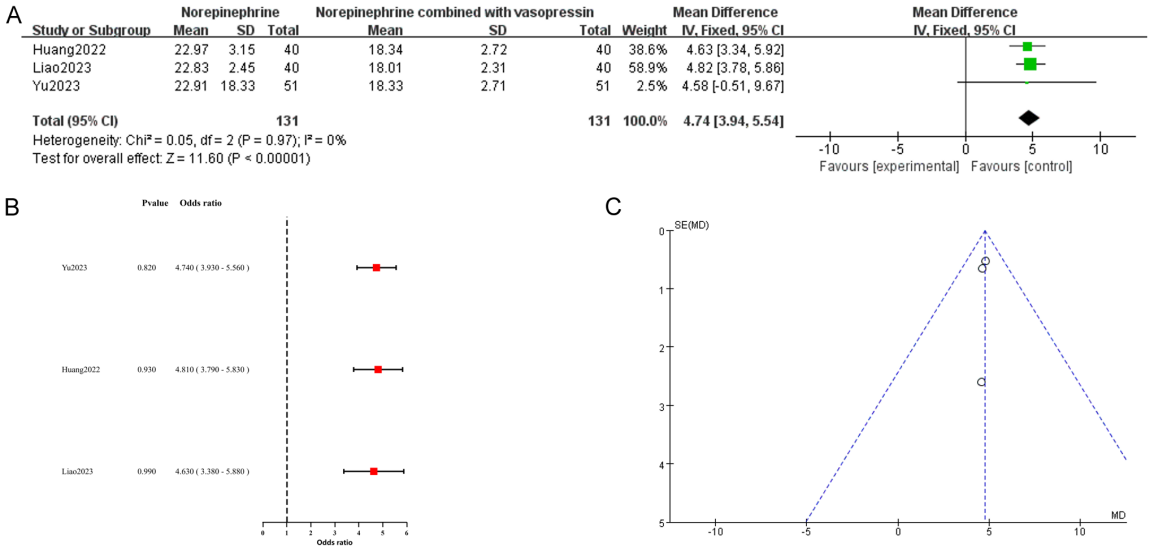

Figure 10. Meta-analysis of the effect of vasopressin in combination with norepinephrine on intestinal-type fatty acid binding proteins (I-FABP). Note: (A) Forest plot of the effect of vasopressin on intestinal fatty acid binding proteins; (B) Sensitivity analysis of the effect of vasopressin on intestinal fatty acid binding proteins; (C) Funnel plot of the effect of vasopressin on intestinal fatty acid binding proteins.

the intestinal fatty acid binding protein level in patients with septic shock compared to norepinephrine (*OR*=4.74, *95% CI*: (3.94, 5.54), *Z*=11.60, *P*<0.00001) (**Figure 10A**).

Sensitivity analysis of the three studies showed that the combined effect size remained consistent after excluding each study sequentially (**Figure 10B**). A funnel plot was drawn to analyze publication bias, and the result indicated that the stability among the articles was good and there was no obvious publication bias (**Figure 10C**).

Effect of vasopressin in combination with norepinephrine on mortality: Five literatures [11,

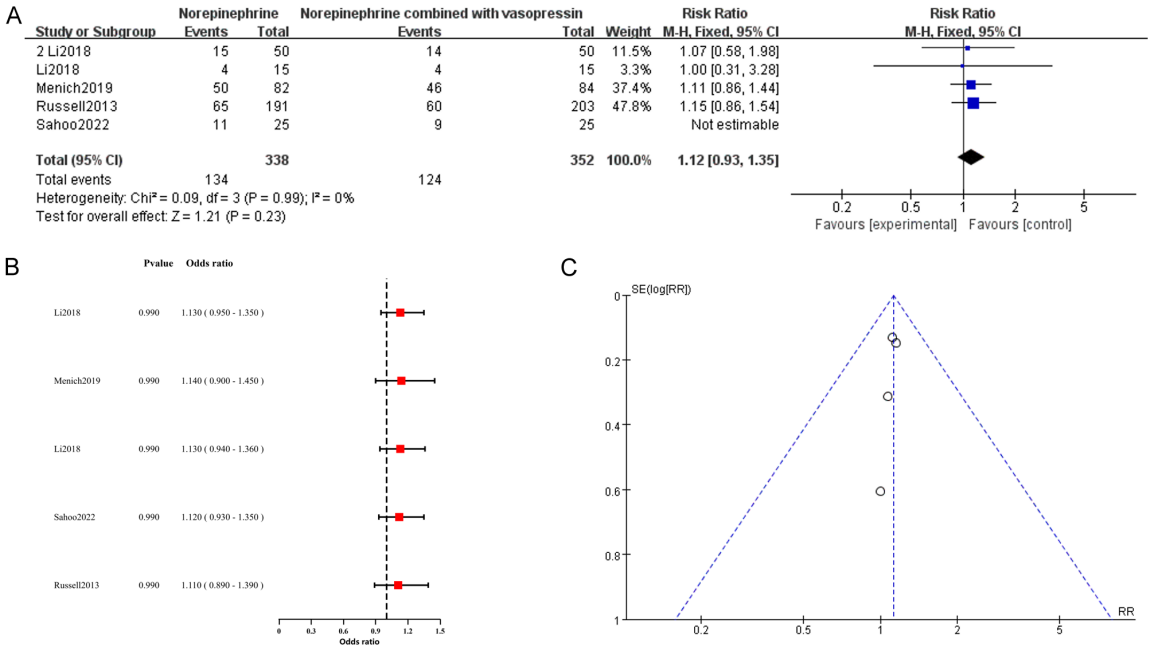

Figure 11. Meta-analysis of the impact of vasopressin on mortality. Note: (A) Forest map of the impact of vasopressin on mortality rate; (B) Sensitivity analysis of the impact of vasopressin on mortality; (C) Funnel plot of the impact of vasopressin on mortality.

17, 18, 20, 25] reported mortality, involving a total of 740 research subjects (377 cases in the treatment group and 363 cases in the control group). Homogeneity was observed among the included studies (χ^2=0.15, I^2=0%, *P*=1.00), thus supporting the adoption of a fixed effect model. The results showed that vasopressin had a smaller impact on mortality compared with norepinephrine combined with vasopressin (*OR*=1.13, *95% CI:* (0.94, 1.35), *Z*=1.32, *P*=0.19) (**Figure 11A**).

Sensitivity analysis of the five studies showed that after excluding each study sequentially, the combined effect size remained consistent (**Figure 11B**). A funnel plot was drawn to analyze publication bias, and the result indicated that the stability among the articles was good and there was no obvious publication bias (**Figure 11C**).

Meta-analysis results of the effects of different subgroup variables on the treatment outcomes of patients with septic shock

Meta-analysis results: effects of subgroup variables on mean arterial pressure in patients with septic shock: When grouped by age, three studies [12, 15, 23] had an average age of 18-59 years, while four studies [11, 14, 18, 24] had an average age of ≥60 years. Subgroup analysis revealed significant heterogeneity among studies (χ^2=14.06, I^2=92.9%, *P*=0.0002). There was a significant difference in mean arterial pressure among sepsis shock patients in studies with an average age of 18-59 years (*OR*=-3.76, *95% CI* (-6.08, -1.43), *Z*=3.16, *P*=0.002), a significant difference in mean arterial pressure among patients with septic shock aged ≥60 years across studies (*OR*=-9.04, *95% CI* (-10.52, -7.56), *Z*=11.94, *P*<0.00001), and the combined difference across all studies was significant (*OR*=-7.51, *95% CI* (-8.76, -6.26), *Z*=11.77, *P*<0.00001) (**Figure 12**). Grouped by sample size, three literatures [11, 15, 24] had a total sample size of no more than 50 cases, and four literatures [12, 14, 18, 23] had a total sample size of more than 50 cases. Subgroup analysis showed homogeneity among the studies (χ^2=0.03, I^2=0%, *P*=0.85), and a significant difference in mean arterial pressure among septic shock patients with a sample size of ≤50 cases (*OR*=-7.42, *95% CI* (-8.99, -5.85), *Z*=2.47, *P*=0.01). There was a significant difference in mean arterial pressure among patients with septic shock among studies with a sample size of more than 50 cases (*OR*=-7.67, *95% CI* (-9.74, -5.60), *Z*=7.52, *P*<0.00001), and a significant difference after the combination of all studies (*OR*=-7.51, *95% CI* (-8.76, -6.26), *Z*=11.77, *P*<0.00001) (**Figure 13**).

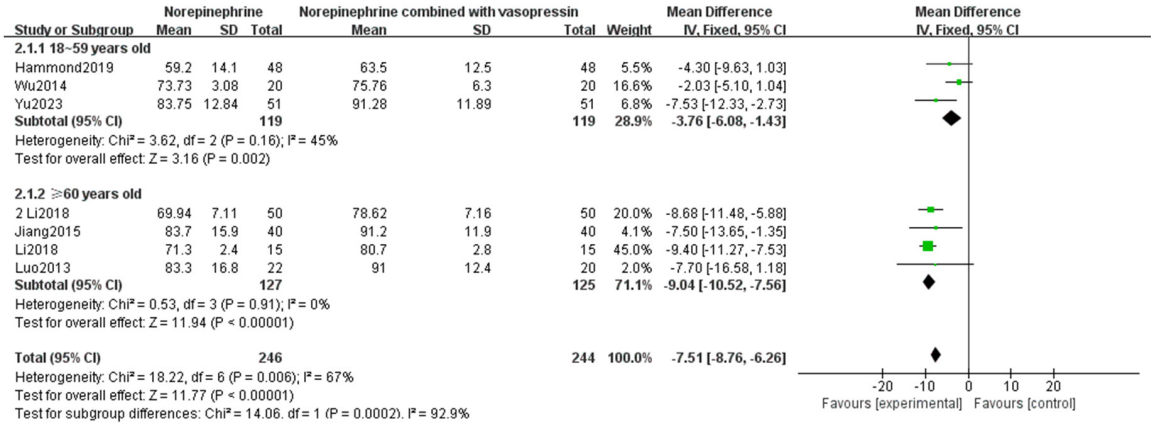

Figure 12. Meta-analysis of the effect of age on mean arterial pressure in patients with septic shock.

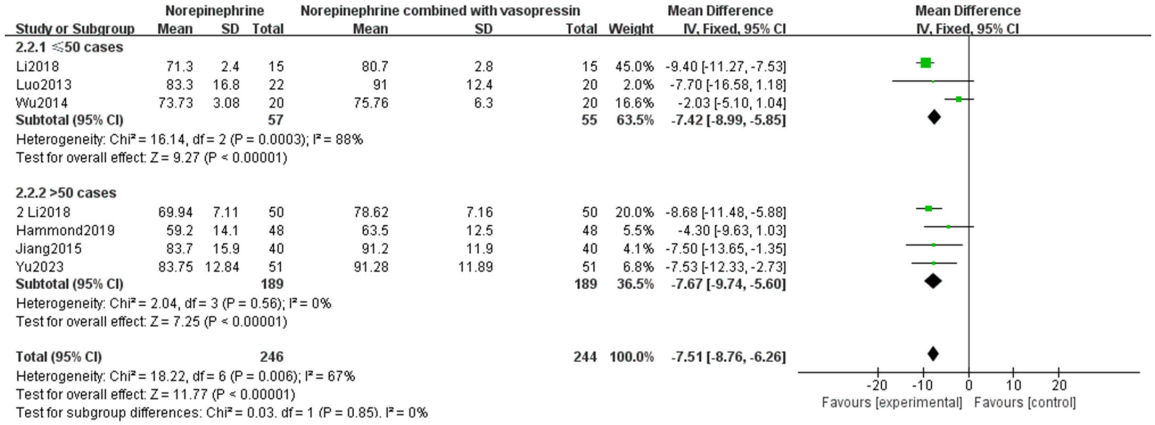

Figure 13. Meta-analysis of the effect of sample size on the mean pulsating pressure in patients with septic shock.

Meta-analysis results: effects of subgroup variables on lactate in patients with septic shock: Grouped by age, five studies [12, 13, 16, 21, 23] included participants aged 18 to 59 years, and four studies [11, 18, 19, 22] involved individuals aged ≥60 years old. Subgroup analysis showed significant homogeneity among the studies (χ^2=0.41, I^2=0%, *P*=0.52), and a significant difference in lactate among septic shock patients with an average age of 18-59 years (*OR*=0.63, *95% CI* (0.59, 0.68), *Z*=28.70, *P*<0.00001). There was a significant difference in lactate among septic shock patients with an average age of ≥60 years *(OR*=0.68, *95% CI* (0.54, 0.82), *Z*=9.46, *P*<0.00001), and a significant difference after the combination of all studies (*OR*=0.64, *95% CI* (0.60, 0.68), *Z*=9.46, *P*<0.00001) (χ^2=0.41, I^2=0%, *P*=0.52) (**Figure 14**). Grouped by sample size, four studies [11, 13, 19, 22] had a total sample size of ≤85 cases, and four studies [12, 16, 18, 21, 23] had a total sample size of more than 85 cases. Subgroup analysis showed heterogeneity among studies (χ^2=5.89, I^2=83%, *P*=0.02), and a significant difference in lactate among septic shock patients with a sample size of ≤50 cases (*OR*=0.78, *95% CI* (0.66, 0.90), *Z*=12.71, *P*<0.00001). There was a significant difference in lactate among septic shock patients with a sample size of more than 50 cases *(OR*=0.62, *95% CI* (0.57, 0.66), *Z*=27.52, *P*<0.00001), and a significant difference when all studies were combined (*OR*=0.64, *95% CI* (0.60, 0.68), *Z*=30.21, *P*<0.00001) (**Figure 15**).

Meta-analysis results: effects of subgroup variables on heart rate in patients with septic shock: Grouped by age, three studies [12, 14, 15] involved participants aged 18 to 59 years, while three studies [11, 17, 18] focused on patients aged ≥60 years. Subgroup analysis showed significant homogeneity among the

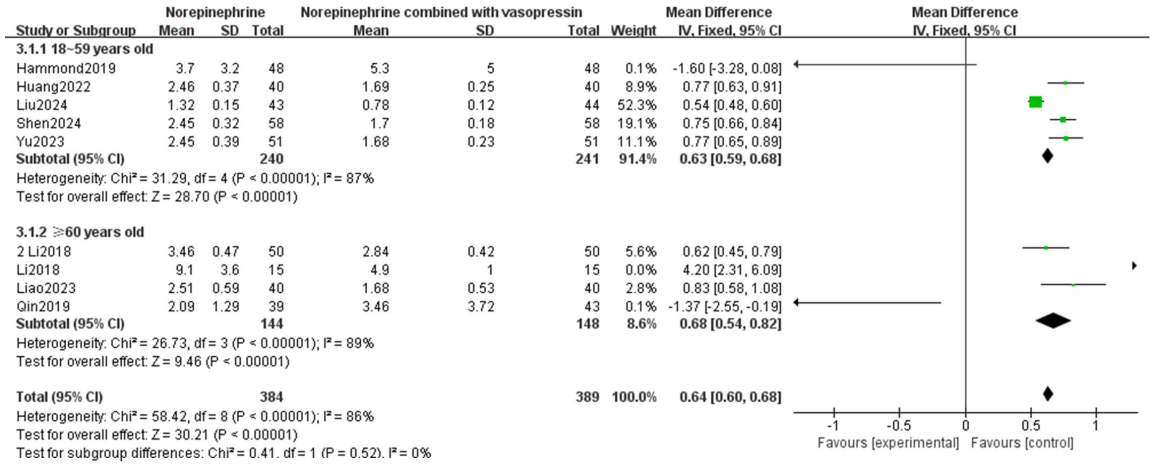

Figure 14. Meta-analysis of the effect of age on lactate in patients with septic shock.

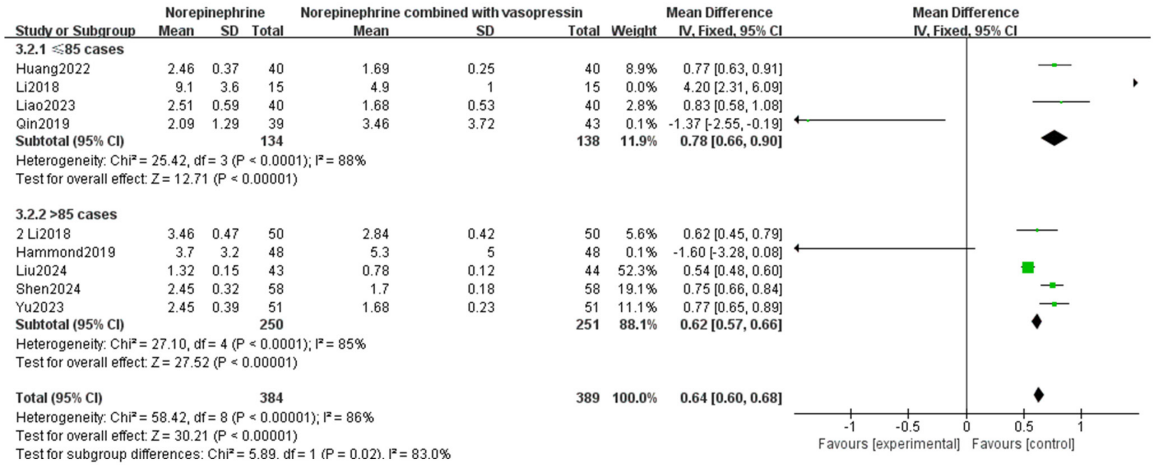

Figure 15. Meta-analysis of the effect of sample size on lactic acid in patients with septic shock.

studies (χ^2=1.44, I^2=30.6%, *P*=0.23), and a significant difference in heart rate among septic shock patients with an average age of 18-59 years (*OR*=17.41, *95% CI* (14.44, 20.38), *Z*=11.50, *P*<0.00001). There was a significant difference in heart rate among septic shock patients with an average age of ≥60 years (*OR*=15.36, *95% CI* (13.80, 16.91), *Z*=19.21, *P*<0.00001), and a significant difference after the combination of all studies (*OR*=15.80, *95% CI* (14.42, 17.18), *Z*=22.44, *P*<0.00001) (**Figure 16**). Grouped by sample size, three studies [11, 14, 15] included less than 90 cases, while three studies [12, 17, 18] had a total sample size of >90 cases. Subgroup analysis showed heterogeneity among studies (χ^2=138.64, I^2=99.3%, *P*<0.00001), and a significant difference in heart rate among septic shock patients with a sample size of ≤50 cases (*OR*=25.46, *95% CI* (23.34, 27.57), *Z*=23.55, *P*<0.00001). There was a significant difference in heart rate among patients with septic shock among studies with a sample size of more than 50 cases (*OR*=8.68, *95% CI* (6.86, 10.50), *Z*=9.35, *P*<0.00001), and a significant difference after the combination of all studies (*OR*=15.80, *95% CI* (14.42, 17.18), *Z*=22.44, *P*<0.00001) (**Figure 17**).

Discussion

The pathogenesis of septic shock is complex, and microcirculation disturbance plays a key role in the progression of tissue and organ failure [26]. Inflammatory response and immune dysfunction impair the vasodilatory function of

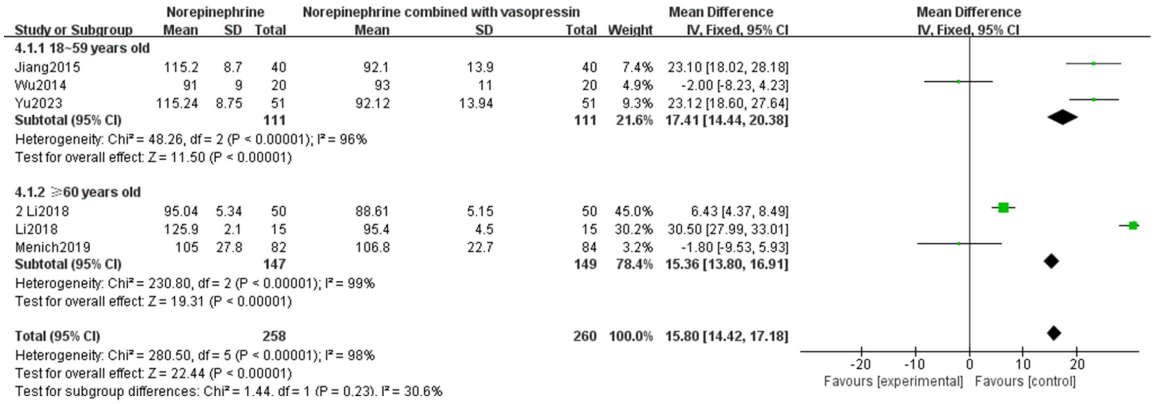

Figure 16. Meta-analysis of the effect of age on heart rate in patients with septic shock.

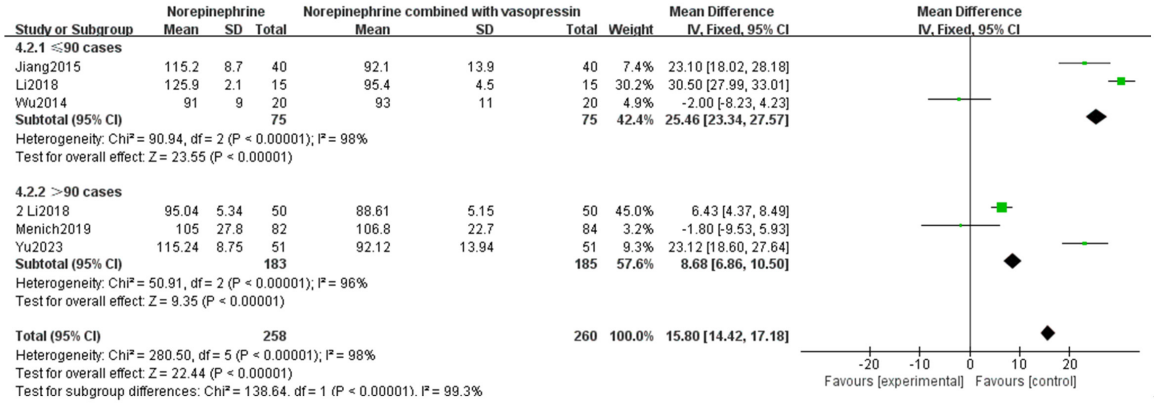

Figure 17. Meta-analysis of the effect of sample size on heart rate in patients with septic shock.

microvessels, increase vascular resistance, and reduce blood flow, ultimately leading to inadequate tissue and organ perfusion [27]. Concurrently, increased vascular permeability, which leads to plasma extravasation and hemoconcentration, further aggravates microcirculatory disorder. Due to hypoxia, cells shift from aerobic to anaerobic metabolism, producing excess lactic acid and leading to tissue acidosis [28]. Persistent hypoxia and acidosis can induce cell dysfunction and apoptosis, eventually causing organ failure and death [29]. Therefore, timely and effective intervention is critical. Early active treatment can interrupt the vicious cycle of inflammatory response, inhibit the excessive cytokine release, protect vascular endothelial integrity, and thereby restore microcirculatory perfusion.

The rational application of vasoactive drugs is essential in improving hemodynamic status, maintaining perfusion of vital organs, and improving microcirculation [30]. In septic shock, inflammatory mediators suppress the synthesis and release of vasopressin, leading to vasopressin deficiency that often requires exogenous supplementation [31]. Norepinephrine and vasopressin are widely used in clinical practice for septic shock management, yet the conclusions of individual studies are not persuasive enough due to the limitations of small sample size and inconsistent designs. This study addressed those limitations through a systematic meta-analysis, pooling data from multiple RCTs to evaluate the effects of norepinephrine alone or in combination with vasopressin on the hemodynamics and clinical prognosis of patients with septic shock.

Among the included studies, seven reported mean arterial pressure as a hemodynamic outcome. Meta-analysis revealed low heterogeneity, and fixed-effects modeling demonstrated that the combination treatment significantly

improved MAP compared to norepinephrine monotherapy. These results suggest that vasopressin has a clear advantage in enhancing hemodynamic stability in patients with septic shock.

Unlike norepinephrine, which acts on the adrenergic receptors, vasopressin increases peripheral vascular resistance by inducing vasoconstriction via activation of V1 receptors on vascular smooth muscle cells, especially in small arteries and microarterioles [32]. In septic shock, vasodilatation leads to a significant decrease in peripheral vascular resistance, and vasopressin acts to counteract this pathological vasodilation, thereby increasing vascular tone and MAP.

Lactate is an important biomarker reflecting tissue perfusion and oxygen metabolism. In septic shock, inadequate tissue perfusion and hypoxia lead to increased lactate production [33]. Persistently high lactate levels are indicative of unresolved tissue hypoxia. Nine studies assessed serum lactate levels, and the pooled results revealed significantly reduced lactate levels in the combination group compared to the monotherapy group. The mechanism by which vasopressin reduces lactate may be attributed to its vasoconstrictive effect, which enhances effective tissue perfusion and oxygen supply, facilitating a shift back to aerobic metabolism and reducing lactate production [34]. Moreover, vasopressin inhibits inflammatory response. In septic shock, excessive inflammatory response disrupts normal cellular metabolism and impairs lactate clearance. By attenuating the release of pro-inflammatory mediators, vasopressin alleviates inflammation-induced metabolic suppression and restores normal cellular metabolic function, enhancing the clearance of lactate.

Six studies included heart rate as a hemodynamic outcome, and the pooled analysis showed significantly lower heart rates in the combination treatment group, indicating that vasopressin can help patients restore normal heart rate compared with norepinephrine. Four studies assessed $ScvO_2$ and aerobic delivery, and the pooled results demonstrated higher $ScvO_2$ and aerobic delivery in the combination group, indicating that vasopressin helps improve nutrient metabolism and optimize the oxygen delivery. The potential mechanisms underlying these effects include vasopressin's ability to regulate endothelial cell function, reduce the inflammatory mediator, and lower capillary permeability, thereby mitigating tissue edema and optimizing oxygen diffusion at the microvascular level. In addition, vasopressin enhances myocardial contractility and supports cardiac output, collectively improves oxygen delivery and tissue oxygenation [35].

Three studies included urine volume, DAO, and I-FABP as outcome measures, and the pooled analysis showed that the treatment group had significantly higher urine output and lower levels of DAO and I-FABP, indicating that vasopressin exerts positive effect on septic shock by improving renal function, alleviating intestinal injury, and lowering the level of inflammation-related substances. Vasopressin enhances vascular smooth muscle contraction, thereby improving hemodynamic status and increasing renal perfusion, which contributes to greater urine output. Septic shock is often accompanied by impaired intestinal barrier function, resulting in elevated release of I-FABP. Vasopressin appears to mitigate this injury by maintaining intestinal mucosal integrity and reducing the translocation of I-FABP into the bloodstream. Additionally, its anti-inflammatory properties may inhibit the release of inflammatory mediators, thereby attenuating tissue damage and organ damage [36].

Sensitivity analysis further supported the stability of the research results. After excluding each study in sequence, the consistency slightly decreased. Except for the change in the heterogeneity of mean arterial pressure after excluding a reference [15], the heterogeneity of other indicators slightly decreased, but overall, it still had statistical significance. The subgroup analysis results of this study show that age may be the cause of the heterogeneity in lactate and heart rate levels among different studies, and sample size may be the cause of the heterogeneity in mean arterial pressure levels among different studies. There are differences in physiological metabolism and cardiovascular regulation among individuals of different age groups, which may lead to heterogeneity in lactic acid production and heart rate response. Different sample sizes can lead to variations in data representativeness, random errors, etc., affecting the consistency of mean arterial pressure results.

The study found that patients aged 18-50 experienced significantly better treatment outcomes than those over 50 years. As age increases, the cardiovascular system gradually undergoes degenerative changes, with a decrease in the number of myocardial cells and worsening of myocardial fibrosis leading to a decrease in cardiac systolic and diastolic function. Additionally, decreased vascular elasticity and stiffness result in elevated peripheral vascular resistance. These age-related alterations may reduce the cardiovascular responsiveness to vasopressin. Although vasopressin increases vascular tone, the aging heart may be unable to tolerate the resulting afterload, thereby limiting treatment effectiveness in older patients [37].

Moreover, studies with a sample size ≥50 exhibited significantly more robust effect sizes than those with <50. A larger sample size helps to reflect the actual effectiveness of intervention measures, enhance the statistical power of research, reduce random errors, and improve the accuracy of results. Future study designs should account for the sample size effect to improve methodological quality and outcome validity.

In conclusion, the combined use of vasopressin can significantly improve hemodynamic parameters in patients with septic shock. However, no significant reduction in mortality was observed, and more high-quality studies are still needed for further validation. The interpretation of these results must be considered in light of several limitations. The overall methodological quality of included studies was moderate. Some studies lack adequate descriptions of random sequence generation, allocation concealment, and blinding implementation, potentially introducing bias. In addition, the relatively small sample sizes in some trials may have limited the ability to detect rare adverse events and reduced the power of subgroup analyses. Therefore, high-quality, large-scale RCTs are still needed to further validate the clinical utility and long-term efficacy of combined use of vasopressin in the treatment of septic shock, thereby providing more reliable basis for clinical treatment.

Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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