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# Vasopressin vs noradrenaline: Have we found the perfect recipe to improve outcome in septic shock?

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ABSTRACT

*Purpose:* The metabolic and circulatory disturbances in patients with septic shock results in a high mortality rate. There is a lack of high-level evidence on the optimal approach. We present a meta-analysis elucidating the outcomes of regimes with only noradrenaline versus a combination of noradrenaline and vasopressin in managing septic shock.

*Methods:* A literature search of studies comparing the use of noradrenaline and vasopressin in septic shock was conducted, using MEDLINE and EMBASE databases. The primary outcome evaluated was mortality rate. Subgroup analysis of secondary measures was also conducted using Review Manager 5.3 software.

*Results:* Four RCTs of 1039 patients were included. There is good evidence supporting a comparable mortality rate (RR: 0.92, 95% CI: 0.78, 1.08, $p = .32$, $I^2 = 0\%$), and moderate evidence supporting an equivalent length of ICU stay (MD: 0.14, 95% CI: -1.37, 1.65, $p = .86$, $I^2 = 46\%$) and occurrence of adverse events (RR: 1.19, 95% CI: 0.83, 1.70, $p = .35$, $I^2 = 13\%$) between the two cohorts.

*Conclusion:* The two regimes have equivalent outcomes, but vasopressin has a role in selected patients experiencing less severe septic shock beyond a 36-h period. Further work will make definitive clinical recommendations for optimal strategy of vasopressin or noradrenaline usage.



## 1. Introduction

Septic shock, identified as a clinical subset of sepsis, is characterized by persistent hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) higher than 65 mm Hg and a serum lactate level > 2 mmol/L despite adequate volume resuscitation [1]. The ensuing circulatory and metabolic derangements lead to a high mortality rate reported in 55% of cases [2]. Conventionally, noradrenaline is used as the first-line agent but there is no specific vasopressor that is superior in optimizing clinical outcomes [3,4]. Noradrenaline increases MAP due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared [5]. However, after several studies attributed the vasodilation in septic shock to a deficiency of vasopressin, the modulation of vasopressin receptors has become a therapeutic target in the management of septic shock [6,7].

The use of vasopressors has been addressed by previous work. In the treatment of circulatory failure, a Cochrane systemic review did not show significant difference in mortality between the various vasopressors, but the authors did not pool results for patients in septic shock [7,8]. Other work has reported the superiority of noradrenaline over dopamine in patients with septic shock with regards to immediate and all-cause mortality [9,10]. In the Vasopressin and Septic Shock Trial (VASST), the authors reported no difference in overall mortality between noradrenaline compared with a combination of vasopressin and noradrenaline, although vasopressin did improve survival in patients with less severe shock and prevented renal failure [11]. However, subsequent trials, including the Vasopressin vs Noradrenaline as Initial Therapy in Septic Shock (VANISH) trial did not observe any significant difference in survival or renal failure between the different cohorts, although this may be limited by the confounding effect of concurrent steroid with noradrenaline [12,13]. Current strategy advocates initial noradrenaline usage and subsequent addition and escalation to usage of vasopressin. There are some who suggest initial empirical low dose vasopressin to increase vasomotor tone and subsequent initiation and titration of noradrenaline. Hence, there is a lack of evidence-based consensus regarding the first-line vasopressor to manage critically ill patients. Thus, the present meta-analysis aims to compare the outcomes of noradrenaline against vasopressin in managing patients with septic shock. Our hypothesis is that the addition of vasopressin will improve outcomes, since it directly alleviates the physiological damage that underlies septic shock, as suggested by existing literature.

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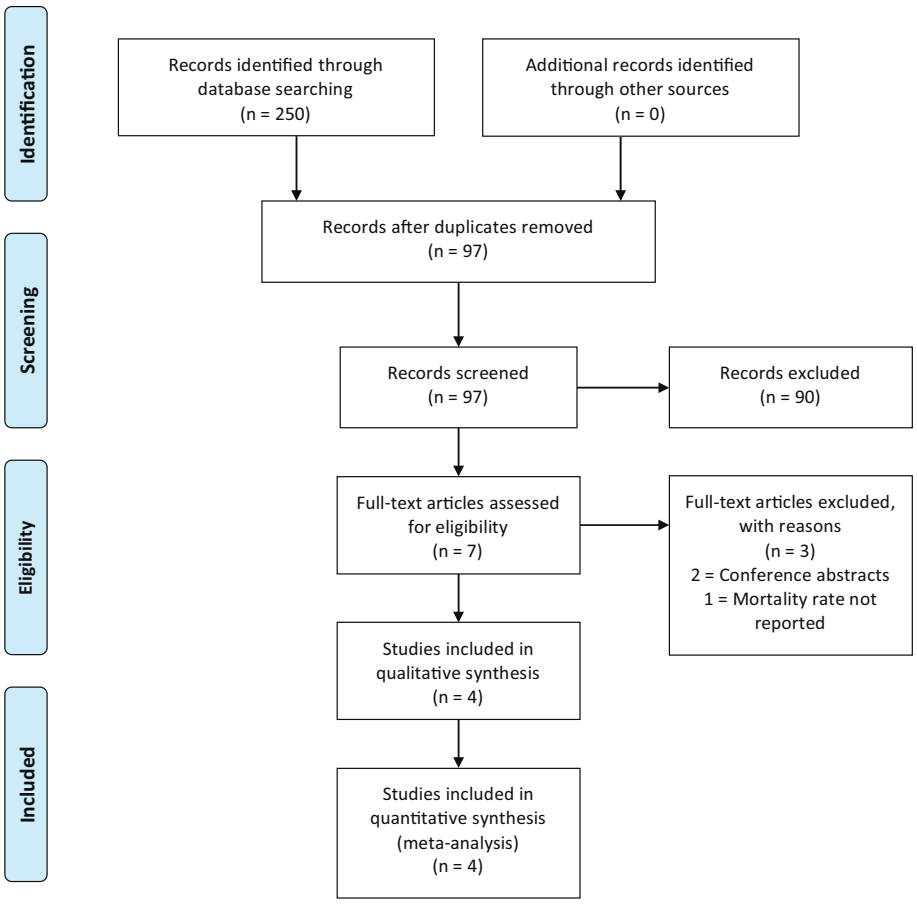


**Fig. 1.** PRISMA flow chart.

## 2. Methods

Literature search methods, inclusion and exclusion criteria, outcome measures and statistical analysis were defined according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14]. Patients were not involved in the conception, design, analysis, drafting, interpretation or revision of this research. Thus, ethics approval was not required.

### 2.1. Electronic search

The following databases were searched: a) MEDLINE (1946 till April week 1 2018) via OvidSP, last search on 4th April 2018; b) MEDLINE in-process and other non-indexed citations (latest issue) via OvidSP, last search on 4th April 2018; c) Ovid EMBASE (1974 to latest issue), last search 4th April 2018; d) Scopus (1996 till present), last search on 4th April 2018. Search terms used three strings, which were then linked by an AND modifier. The first string included: vasopressin OR arginine-vasopressin; the second string: noradrenaline OR noradrenaline; the third string: sepsis OR septic shock OR. Truncated search terms utilizing the wildcard character and the "related articles" function were used to broaden the search. Additionally, the references of included articles were hand-searched to identify any additional studies.

### 2.2. Study selection

All randomized controlled trials (RCTs) in which early vasopressin use was compared with noradrenaline were selected. In addition, all studies included in the meta-analysis met the following criteria: a) adult patients (≥16 years) with sepsis (at least two of the systemic inflammatory response criteria due to known or suspected infection), b) vasopressor requirement despite adequate intravenous fluid resuscitation as assessed by clinical examination, central venous pressure, oxygen saturation, or other physiological parameters using repeated fluid challenges, c) no previous continuous infusion of vasopressors during current admission, d) no known end-stage renal disease, mesenteric ischemia, Raynaud's phenomenon, systemic sclerosis or other vasospastic disease, e) non-pregnant. No restrictions were made on language. Non-human studies, experimental trials, case-control studies,

**Table 1**
Study characteristics.

| Study | Number of patients (*n*) | | Age | | M:F ratio | | Severity score system | Baseline severity score | | Duration of therapy |
|---|---|---|---|---|---|---|---|---|---|---|
| | VP | NE | VP | NE | VP | NE | | VP | NE | |
| Lauzier 2006 | 13 | 10 | 51.2 (17.2) | 58.1 (17.5) | 6:7 | 8:2 | APACHE II | 22.8 (3.4) | 23.5 (4.2) | Up to 48 h |
| Russell 2008 | 397 | 382 | 59.3 (16.4) | 61.8 (16.0) | 246:151 | 229:153 | APACHE II | 27.0 (7.7) | 27.1 (6.9) | As required |
| Morelli 2009 | 15 | 15 | 67.3 (6.5) | 65.5 (6.5) | 10:5 | 12:3 | SAPS II | 58.2 (13.9) | 59.5 (13.1) | Up to 48 h |
| Gordon 2016 | 104 | 103 | 68.2 (7.5) | 66.0 (7.5) | 52:52 | 65:37 | APACHE II | 24.0 (7.5) | 23.7 (9.0) | As required |

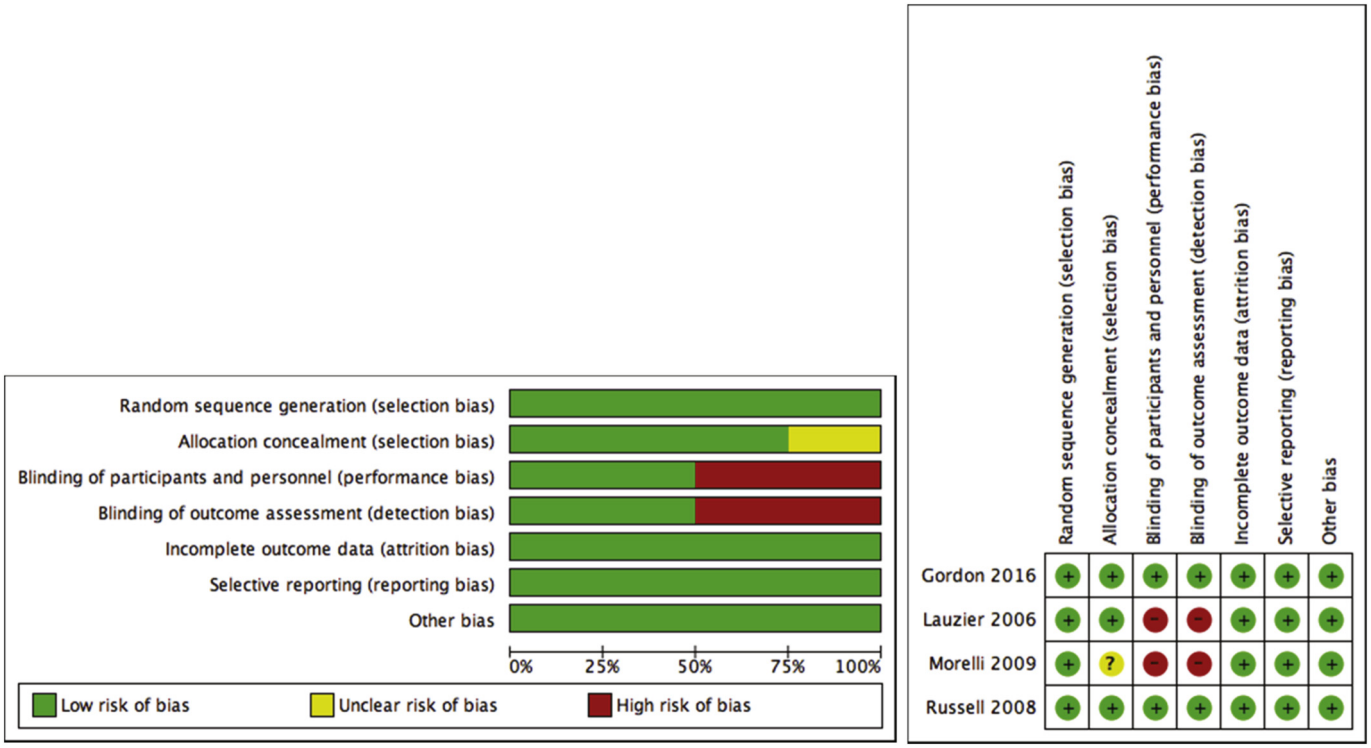


**Fig. 2.** Risk of bias tables.

cohort studies, review articles, editorials, case reports, letters, conference abstracts and unpublished studies were excluded.

### 2.3. Outcome measures

The primary outcome assessed was the mortality rate in both cohorts. Other secondary outcomes included: days alive, rate of organ dysfunction, length of stay in the intensive care unit (ICU) and rate of adverse events.

### 2.4. Data extraction

Two independent reviewers (E.L.G. and S.C.) screened all the titles and abstracts for inclusion, both of whom were blinded to authors, journals, institutional affiliations and dates of publication. Both reviewers evaluated each selected reference independently and summarized relevant study characteristics. In case of disagreement, a consensual decision between the two reviewers under involvement of a third independent reviewer (M.K.) was reached. The following data items were extracted: the year of publication, study design, sample size, country of study, type of patients, patient characteristics, outcome measures, and conclusions. Authors of the original publications were contacted in the event of insufficient data, but this was not the case in this analysis. Data were entered into Review Manager 5.3 (Cochrane Collaboration, Oxford, United Kingdom).

### 2.5. Quality assessment and risk of bias

The quality and risk of bias of the RCTs was assessed using the Cochrane Collaboration Tool. All risk of bias domains were given equal consideration. For sensitivity analysis, trials were defined as having an overall high risk of bias if they were assessed to be of high risk in any of the following domains: random sequence generation, allocation concealment, blinding of participants, blinding of assessors, outcome data incomplete or selective reporting. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence.

### 2.6. Statistical analysis

Risk ratio (RR) and mean difference (MD) are presented with 95% confidence interval (CI). Review Manager 5.3 (Cochrane Collaboration, Oxford, United Kingdom) was used for data analysis. Medians were converted to means using the formula described by Hozo et al. [15]. The fixed-effects model was used to pool the results. The standard heterogeneity test, the $I^2$ statistic, was used to assess the consistency of the effect sizes, which indicates the percentage of the variability in effect estimates because of true between-study variance rather than within-study variance. Statistical heterogeneity was defined as low, moderate and high with an $I^2$ of above 25%, 50% and 75%, respectively [16]. Results above 60% were considered as substantial heterogeneity. The risk of publication bias was assessed using a funnel plot.

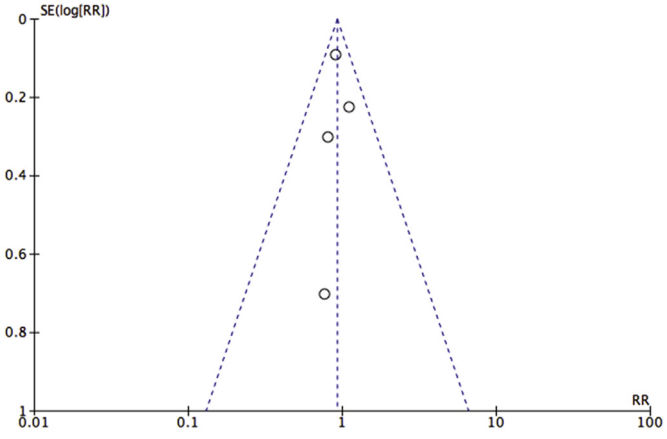


**Fig. 3.** Funnel plot assessing publication bias.

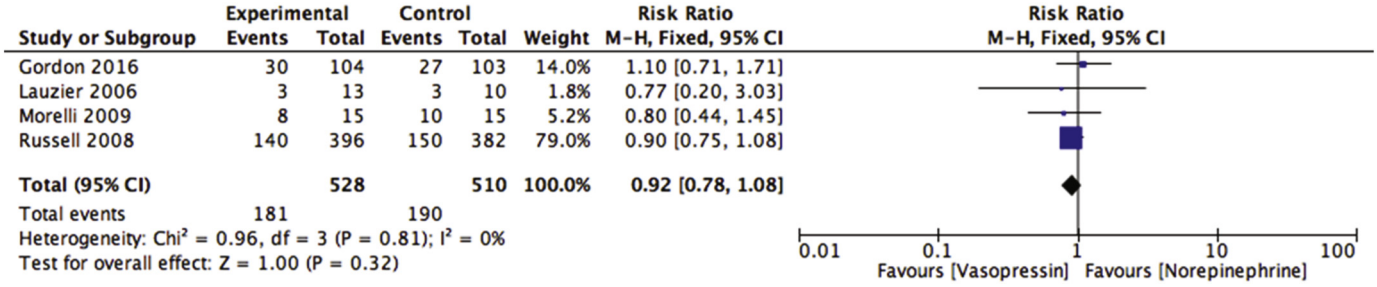


**Fig. 4.** 28-day mortality rate.

## 3. Results

### 3.1. Study characteristics

Four RCTs comprising of 1039 patients were included in this meta-analysis (Fig. 1, Table 1) [17-19]. There were 529 patients in the vasopressin group and 510 patients in the noradrenaline group. The total number of patients in each study ranged from 23 to 779. The studies were conducted in four countries including the United Kingdom, Canada, France and Italy. The mean age across the studies was 62.16 ± 5.76 years. Males comprised 60.4% of the total study population.

### 3.2. Quality assessment and risk of bias of included studies

Most studies were found to exhibit a low risk of bias (Fig. 2). Overall, all studies exhibited a low risk of bias in terms of random sequence generation, incomplete outcome data and selective reporting. Two studies failed to provide information regarding allocation of participants. Additionally, one study was not double-blinded. The risk of publication bias was examined using a funnel plot (Fig. 3). No asymmetry was detected.

### 3.3. Mortality rate

Four studies evaluated the mortality rate at different time-points throughout the study. Overall, vasopressin treatment was associated with a marginally lower 28-day mortality rate compared to noradrenaline treatment, with a RR of 0.92 (95% CI: 0.78, 1.08, $p = .32$, $I^2 = 0\%$). No evidence of heterogeneity was present and the quality of evidence was deemed high.

### 3.4. ICU length of stay

The duration of stay in the ICU was reported by three studies. There was a slightly increased ICU length of stay in the vasopressin group compared to the noradrenaline group, with a MD of 0.14 (95% CI: -1.37, 1.65, $p = .86$, $I^2 = 46\%$). Moderate heterogeneity was present and the quality of evidence was deemed moderate.

### 3.5. Adverse events

Three studies documented the incidence of adverse events following treatment with vasopressin and noradrenaline. Patients treated with vasopressin had a marginally increased risk of adverse events compared to those treated with noradrenaline, with a RR of 1.19 (95% CI: 0.83, 1.70, $p = .35$, $I^2 = 13\%$). There was low heterogeneity present and the quality of evidence was deemed to be moderate.

### 3.6. Additional outcome measures

Additional outcome measures reported included regional hemodynamics, sequential organ failure assessment (SOFA) score, organ dysfunction/failure and use of inotropes. Due to significant heterogeneity in the data, a pooled meta-analysis could not be performed. A qualitative assessment demonstrated comparable outcomes between both groups.

## 4. Discussion

With the available evidence, the paper suggests no statistically significant difference in the mortality, length of ICU stay and adverse event rate in using noradrenaline compared with a combination of noradrenaline and vasopressin in managing patients with septic shock (Figs. 4–6), using fixed-effects analysis. This is in discord with most of the previous work, both primary studies and reviews, and supports the role of either approaches in the acute setting [20]. Further analyses could not be performed on the additional outcomes due to significant heterogeneity. These findings illustrate that both noradrenaline and vasopressin are equally effective in managing hemodynamic parameters in septic shock. (See Fig. 6.)

The results can be explained by the role of noradrenaline and vasopressin in critically ill patients. The characteristic hemodynamic disturbance caused by septic shock is generalized vasodilation and myocardial depression, and vasopressors can restore acceptable mean arterial pressures. In the critical care setting, noradrenaline increases MAP due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with vasopressin [4]. Vasopressin increases mean arterial pressure [21]; maintains cardiac output [22]; improves renal function [23]; and reduces the dependence on catecholamines like noradrenaline [24]. The basis of using vasopressin stems from studies reporting a deficiency of baroreceptor-mediated release of vasopressin in septic shock [5], possibly due to primary autonomic failure, sympathetic dysfunction and depletion of neurohypophysial stores [25-27]. In patients with suppressed response to catecholamines, infusions of vasopressin enhanced the response to vasopressin. Hence, titrating vasopressin at a controlled rate alongside noradrenaline should theoretically improve outcomes of survival.

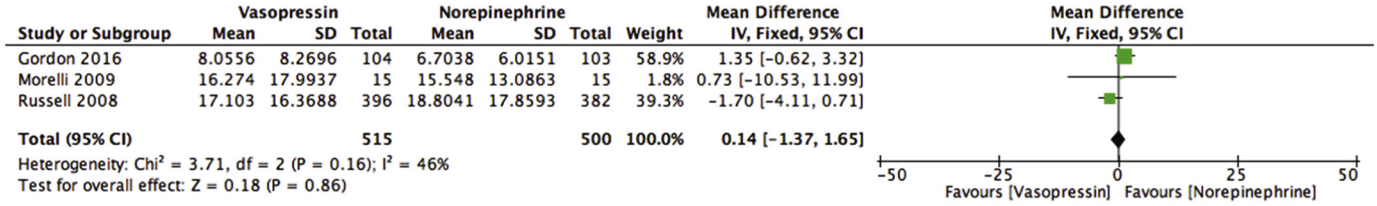


**Fig. 5.** ICU length of stay.

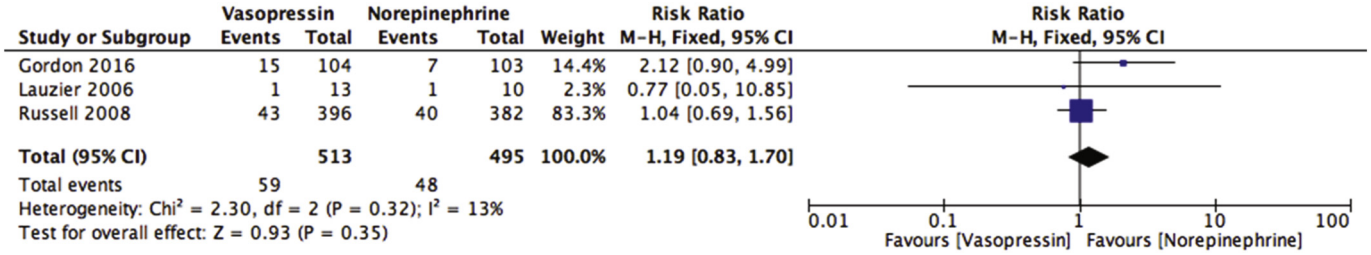


**Fig. 6.** Adverse events.

However, the decrease in vasopressin levels depends on time of onset and the specific patient. Vasopressin levels have been shown to decrease after 36 h and not in the initial phases of septic shock [6]. Furthermore, a vasopressin-deficient state is not observed in all patients, since the baroreceptor-mediated reflex is not always appropriately mounted and can be either impaired or delayed in some patients [29]. There is also a contributory effect from other comorbidities which could interfere with the vasopressin response other than those accounted for in the primary studies. Translational studies have also postulated that different endotoxins cause different extents of septic shock and so act as stimulus for vasopressin release to different extents. Although the included RCTs did not stratify patients based on the causative organism, this may explain the benefits of vasopressin in patients with less severe septic shock, defined as a dose of noradrenaline <15 μg/min, in the VASST trial. Thus, tailoring the use of vasopressin in specific patient groups with less severe septic shock at a later stage beyond 36 h may be beneficial, and can be the focus of future work in this area.

In our analysis, we could not evaluate the impact of adverse events such as complications of vasopressors used, or those of septic shock. Both noradrenaline and vasopressin have a variable effect in different organs, and this can be evaluated using the SOFA score. Improvement in SOFA score has been associated with lower mortality rates [30]. Specifically, vasopressin has selective vasoconstrictive and vasodilatory effects on the renal efferent and afferent arterioles due to nitric oxide production, respectively [31,32]. This directly translates to an improvement in the 28-day mortality in patients at risk of renal failure. Another direct cause of sepsis-related mortality is myocardial depression, and vasopressin analogues improve this by lowering heart rate and hence cardiac strain [33]. Hence, vasopressin can play a role in preventing organ-related deterioration in at-risk patients.

Vasopressor therapy is largely aimed at optimizing cardiovascular function, and traditionally, this has been guided by blood pressure parameters. However, it is increasingly becoming evident that this may not be the best method. For example, a recent analysis showed that aiming for higher blood pressure targets might increase mortality in patients who have been treated with vasopressors for more than 6 h, while patients managed with lower blood pressures experienced less adverse events [34]. Consistent with this, the latest updates have shifted away from using the mean arterial pressure towards end-organ function in measuring the body's response to vasopressors [35]. Additionally, cardiovascular parameters are determined not only by vasopressors but also by fluid support. Conventional practice has been early goal-directed therapy (EGDT) with intravenous fluids, as this had reduced mortality [36]. But, recent trials have demonstrated the contrary that EGDT can have deleterious impact on survival, too. This sheds doubt on what the optimal fluid therapy is and how this will impact the vasopressor regime [37].

The authors acknowledge that this analysis has several limitations. Firstly, the analysis only includes four studies, and one study accounts for a major proportion of the sample size. However, this is the first meta-analysis to compare the effects of noradrenaline and vasopressin using evidence from only adequately powered level I randomized controlled trials. So, while results may be skewed towards the study with the biggest sample size, we were able to minimize any inherent bias due to the lack of controls and randomization, as evident from the low heterogeneity scores in the analysis. Although studies had used matched cohorts with no significant differences between baseline characteristics, there is a possibility of confounding due to variables that were not accounted for such as the causative organism, microbial load or impaired vasopressin release system. Additionally, the primary studies did not measure vasopressin levels and the dose and regime of vasopressors used were not standardized across studies, adding a confounding effect that cannot be evaluated given the complexity between circulating vasopressor hormone concentrations and their pharmacological effects in vivo. Lastly, analysis of delayed effects of the various regimes plotting mortality and morbidity beyond 28 days can be evaluated as future work.

## 5. Conclusion

In conclusion, it can be suggested that there is no significant difference in 28-day survival or length of ICU stay between a regime of only noradrenaline compared to a combination of noradrenaline and vasopressin. However, there is a role for vasopressin in selected patients experiencing less severe septic shock beyond a 36-h period. Further work is necessary to characterize an optimal regime, and to determine whether initial vasopressin usage as well as additional patient factors that have a similar predictive role on whether vasopressin will play a role.

## Author contributions

SC and ELG performed the systematic review and meta-analysis, including the literature search, data extraction and analysis. MAK and VGR were involved in the conception of the study as well as in drafting the article and revising it for submission to the journal.

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