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# Effect of midodrine on the prognosis of patients with septic shock: a systematic review and meta-analysis

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**Abstract. – OBJECTIVE: This study aims to assess the efficacy and safety of midodrine on treating patients with septic shock.**

**MATERIALS AND METHODS: Literature search was conducted in PubMed, the Cochrane Library, and Embase. The Mantel-Haenszel method was used to calculate pooled relative risks (RRs) and 95% confidence intervals (95% CI). The mean differences (MD) or standardized mean difference (SMD) were calculated using the inverse variance for continuous variables. Data analysis was performed using Review Manager 5.3.**

**RESULTS: A total of 6 studies were finally included in this meta-analysis. Adding midodrine to patients with septic shock was associated with a reduction in hospital mortality [risk ratio (RR) 0.76; 95% CI, 0.57-1.00; *p*=0.05] and intensive care unit (ICU) mortality (RR 0.59; 95% CI, 0.41-0.87; *p*=0.008). However, there were no significant differences in the duration of intravenous vasopressors [standardized mean difference (SMD) -0.18; 95% CI, -0.47-0.11; *p*=0.23], intravenous vasopressor reinstitution (RR 0.58; 95% CI, 0.19-1.80; *p*=0.35), the length of ICU stay [mean difference (MD) -0.53 days; 95% CI, -2.24-1.17; *p*=0.54], and the length of hospital stay (MD -2.40 days; 95% CI, -5.26-0.46; *p*=0.10) between midodrine group and intravenous vasopressor alone group.**

**CONCLUSIONS: The additional use of midodrine might reduce hospital mortality and ICU mortality in patients with septic shock. More high-quality randomized controlled trials are needed to verify this conclusion.**

*Key Words:*
Midodrine, Septic shock, Intravenous vasopressors, Critical care, Meta-analysis.

## Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset of sepsis with particularly severe circulatory, cellular, and metabolic abnormalities and a higher risk of death. Septic shock is defined as the requirement of vasopressor to maintain a mean arterial pressure of 65 mmHg or higher and serum lactate levels greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia[1]. The incidence of sepsis is reportedly 437 cases per 100,000 person-years, with an in-hospital mortality rate of 17%[2]. Estimated mortality of sepsis patients treated in intensive care unit (ICU) has been found[3] to be up to 41.9%. If sepsis is confirmed or probable, antibiotics should be administered immediately, ideally within one hour of recognition. The Surviving Sepsis Campaign guidelines[4] recommends initial resuscitation with 30 mL/kg of crystalloid within 3 hours. Norepinephrine has been a first-line vasopressor to maintain a target mean arterial pressure of 65 mmHg. Persistent hypotension becomes a barrier to transfer patients out of the ICU, and prolonged ICU stay may increase the risk of infection[5], delirium[6], and may even lead to ICU-acquired weakness[7]. Sepsis imposes a large financial burden on patients. It was reported[8] that the median of the mean hospital-wide cost and ICU cost of sepsis were $32,421 and $27,461, respectively. Reducing the duration of ICU care has the potential to lead to financial savings[9].

Midodrine is an oral α1 receptor agonist with an oral bioavailability of 93%[10]. It can be metabolized by the liver into its active ingredient desglymidodrine, which increases arterial blood pressure due to increased peripheral vasoconstriction[10,11]. Peak plasma concentration is reached approximately 1-2 hours after oral administration with a half-life of 3-4 hours. Midodrine has been used for the treatment of orthostatic hypotension[12]. Studies[13-16] have shown that midodrine also has a role in hepatorenal syndrome, dialysis-induced hypotension, refrac-

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tory hypotension, and hypotension associated with carotid artery stenting. Adverse effects of midodrine reported in previous studies[17] include hypertension, pruritus, paresthesia, and urinary retention. Midodrine may improve clinical outcomes in patients with septic shock and has been reported[18,19] to be a cost-saving treatment. Some studies[20,21] demonstrated that midodrine reduced the duration of intravenous vasopressors and ICU stay. However, there are also studies[22,23] showing little or no effect of midodrine on the duration of intravenous vasopressors or length of ICU stay. Whether midodrine is effective in treating septic shock remains controversial. In this meta-analysis, we systematically assessed the efficacy of midodrine in the treatment of septic shock.

## Materials and Methods

### Search Strategy

We searched electronic databases for relevant articles from inception to January 2022, including Pubmed, Cochrane Library and Embase. We completed this meta-analysis following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) checklist. The study protocol has been registered in PROSPERO (ID: CRD42022308860)[24]. We used the following medical subject headings (MESH) terms and keywords to formulate search strategy: "Sepsis", "Shock, Septic", "Toxic Shock", "Endotoxin Shock", "Shock, Toxic", "Septic Shock", "Bloodstream Infection", "Pyemia", "Septicemia", "Pyohemia", "Blood Poisoning", "Midodrine". Two reviewers independently screened the literature based on prespecified criteria and extracted data. Any conflicts were resolved *via* discussion.

### Inclusion and Exclusion Criteria

We pre-established a search strategy for study selection based on PICOS principles (Participants, Interventions, Comparisons, Outcomes, and Study Design): 1. Participants: patients had a diagnosis of septic shock and required intravenous vasopressor treatment; 2. Intervention group: intravenous vasopressor plus midodrine; 3. Comparison group: intravenous vasopressor alone or plus placebo; 4. Outcomes: hospital mortality, ICU mortality, intravenous vasopressor duration, intravenous vasopressors reinstitution, length of ICU stay, length of hospital stay. Midodrine-related adverse events were also recorded; 5. Study design: Randomized controlled trials (RCT) study and cohort studies, including conference abstracts.

Reviews, case reports, comments, letters, non-human studies were excluded. Studies were excluded if they were written in non-English languages, or if a version in English was unavailable.

### Statistical Analysis

Inverse Variance method for continuous variables and Mantel-Haenszel statistics for dichotomous variables were used. The risk ratio (RR) and mean difference (MD)/standardized mean difference (SMD) were used to express the effect size of dichotomous and continuous outcomes, respectively.

If the study presented the data as median (interquartile range), it was converted to mean±SD according to the methods by McGrath et al[25]. The total confidence interval was 95%. A $p$-value lower than 0.05 was considered to indicate statistically significant. $I^2$ was used for heterogeneity assessment. If $I^2$>50%, the heterogeneity was considered significant, and a random-effects model was applied; otherwise, if $I^2$≤50%, then a fixed-effect model was used. Publication bias was tested by a funnel plot. Statistical analysis was performed using Review Manager 5.3 (Review Manager Web, The Cochrane collaboration, Copenhagen, Denmark).

### Quality Assessment of Included Studies

The Cochrane bias assessment tool was used to evaluate the quality of randomized controlled trials (RCTs). A total of 4 RCTs[19,26-28] were included in this meta-analysis, all studies were of high quality (Figure 1). The quality assessment for cohort studies was carried out using New Castle-Ottawa Scale (NOS) scale. For each item within the selection and outcome categories, a maximum of one star can be given; while for comparability, two stars can be awarded. The maximum score is 9 stars, which indicates the highest quality. A total of 2 cohort studies[21,29] were included in this meta-analysis, with study quality evaluation scores of 8-9 (Table I).

## Results

### Study Selection and Characteristics of Included Studies

A total of 152 articles were obtained by database search, and 18 studies were obtained by reading abstracts and preliminary screening ac-

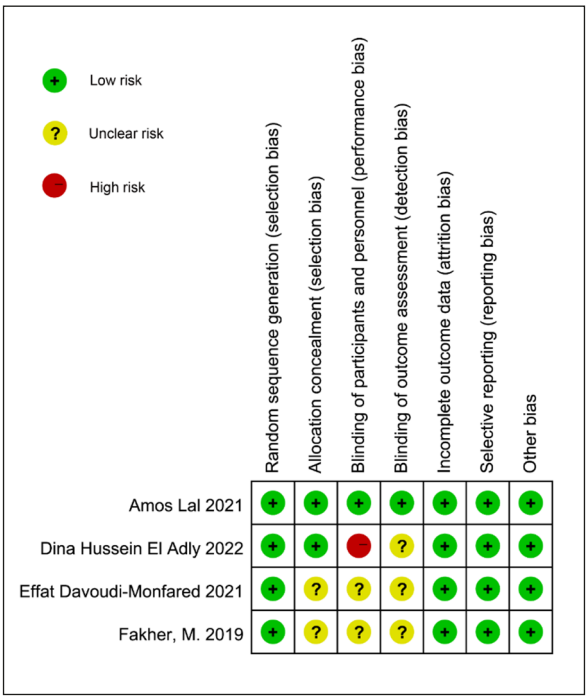


**Figure 1.** Risk of bias summary for RCT studies.

cording to inclusion and exclusion criteria. After full-text review of the remaining 18 studies, 6 studies (4 RCTs[19,26,27,29] and 2 cohort studies[21,28]) were finally included in this meta-analysis. In total, 565 patients were included (287 in the midodrine plus intravenous vasopressor group and 278 in the intravenous vasopressor alone group). The search strategy was shown in Figure 2. The characteristics of included studies were summarized in Table II.

## Main Analysis of the Outcomes of Included Studies

### Hospital mortality

Three studies[21,26,28] reported hospital mortality. We used a fixed-effects model since the heterogeneity was not significant ($I^2$=0%). Figure 2 showed that midodrine decreased hospital mortality in patients with septic shock ($p$=0.05) (Figure 3). There was no evidence of publication bias across the included studies as the funnel plot was symmetric (Figure 4).

### ICU mortality

Two studies[19,21] reported ICU mortality. A fixed effect model was used as the heterogeneity was not significant. Midodrine was associated with reduced ICU mortality compared to intravenous vasopressors alone ($p$=0.008) (Figure 5). There was no evidence of publication bias across the included studies as the funnel plot was symmetric (Figure 6).

### IV vasopressor duration

Four studies[19,26,27,29] reported the duration of intravenous vasopressors. Because unit of time was inconsistent in different studies, we used SMD to describe the effects. As can be seen in Figure 7, the additional use of midodrine did not reduce the duration of intravenous vasopressors ($p$=0.23).

### IV vasopressor reinstitution

As shown in Figure 8[21,26], treatment with midodrine did not significantly reduce the reinstitution of intravenous vasopressors in patients with septic shock ($p$=0.35).

### ICU length of stay

ICU length of hospital stay was reported in four studies[19,21,26,27], and a random-effect model was used for the analysis. The result showed that midodrine did not significantly decrease the length of ICU stay in patients with septic shock ($p$=0.54) (Figure 9).

### Hospital length of stay

Figure 10[21,27] reveals that midodrine tended to reduce the length of hospital stay in patients with septic shock, but the difference was not statistically significant ($p$=0.1). High-quality studies will be necessary to confirm this result.

### Midodrine-related adverse events

Only two studies[21,22] reported adverse effects associated to additional use of midodrine. One study[21] reported a patient with bradycardia and the bradycardia was resolved after withdrawal of midodrine. Another study[22] showed that five cases of bradycardia were observed, and all were from the midodrine group ($p$=0.02).

## Discussion

Sepsis is one of the most common causes of death in the ICU. The primary reason why patients with septic shock are difficult to discharge from the ICU is persistent hypotension. The aim of this study was to investigate the efficacy of midodrine in septic shock. This meta-analysis suggested that midodrine significantly reduced ICU mortality in patients with septic shock.

**Table I.** Quality assessment form for cohort studies.

| Newcastle-Ottawa quality assessment scale | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Selection | | | | Comparability | Outcome | | |
| Reference | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Follow-up was long enough for outcomes to occur | Adequacy of follow up of cohorts |
| Whitson et al[21] 2016 | ★ | ★ | ★ | ★ | ★★ | ★ | ★ | ★ |
| Jung et al[29] 2018 | ★ | ★ | ★ | ★ | ★ | ★ | ★ | ★ |

For each item within the selection and outcome categories, a maximum of one star can be given; while for comparability, two stars can be awarded. The 4 Newcastle–Ottawa Scale(NOS) is available from (https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

**Table II.** Characteristics of included studies.

| Study | Type of study | Time of patient inclusion | Number of patients | Main inclusion criteria | Intervention | Control |
|---|---|---|---|---|---|---|
| Whitson et al[21] 2016 | Cohort study | 2013-2014 | 275 | Patients with septic shock required at least 24 hours of IV adrenergic vasopressors and demonstrated a period of clinical stability associated with stable or decreasing doses of IV vasopressors. | Midodrine starting dose was 10 mg every 8 hours and the dose was incrementally increased until IV vasopressor was not required. | Received IV vasopressors only |
| Adly et al[19] 2022 | RCT | 2017-2019 | 60 | Adult patients with septic shock, require intravenous vasopressin for 24 hours to maintain their target arterial blood pressure. | Received IV vasopressor infusion (norepinephrine)+ oral midodrine 10 mg thrice daily and was discontinued when targeted BP was reached. | Received IV vasopressor infusion (norepinephrine) only |
| Jung et al[29] 2018 | Cohort study | 2013-2017 | 110 | Adult patients with septic shock. vasopressor therapy. | Received midodrine plus vasopressor | Received therapy alone |
| Fakher et al[28] 2019 | RCT | - | 60 | Patients with septic shock required at least 24 hours of IV vasopressors and demonstrated clinical stability with stable or decreasing doses of IV vasopressors. | Received IV vasopressors with adjunctive midodrine 10 mg every eight hours. | Received IV vasopressors only |
| Lal et al[27] 2021 | RCT | 2017-2020 | 32 | Adult patients (≥ 18 years old) were included within 24 hours of meeting the Sepsis-3 definition if the mean arterial pressure remained lower than 70 mmHg despite receiving timely antibiotics and initial IV fluid bolus of 30 cc/kg. | Three doses of 10 mg midodrine *vs.* placebo were administered. | Placebo |
| Davoudi-Monfared et al[26] 2021 | RCT | 2019-2020 | 28 | Adult patients (≥ 18 years old) with septic shock. | Adjunctive midodrine 10 mg three-times a day for 5 days. | Intravenous vasopressors alone |

MAP: mean arterial blood pressure; BP: blood pressure; IV: intravenous; RCT: randomized controlled trial.

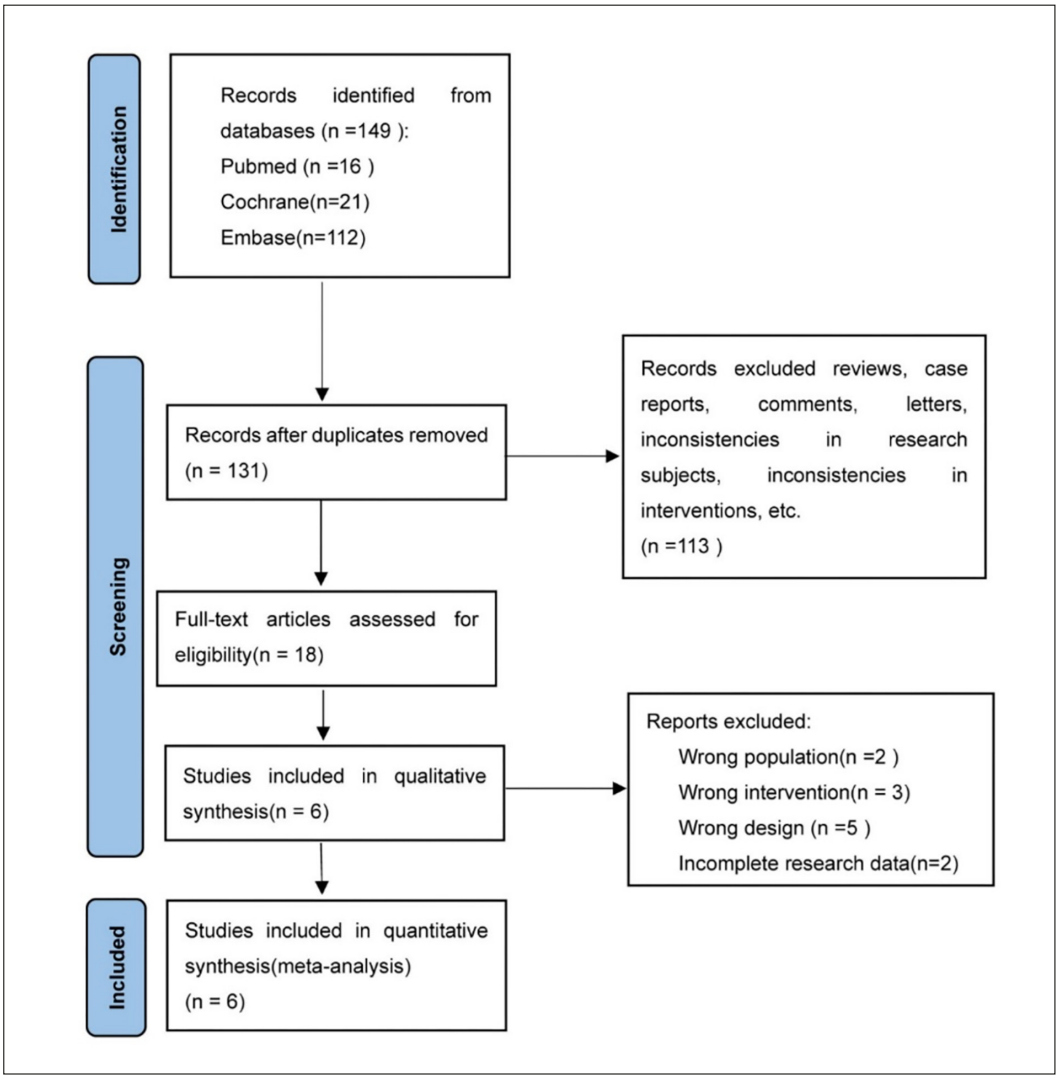


**Figure 2.** PRISMA flow diagram.

This result is similar to the finding in a previous study by Poveromo et al[17], which revealed that in-hospital mortality in the midodrine group was significantly lower than in the vasopressor-only group in adult ICU patients, [8 (8.5%) *vs.* 21 (22.3%), $p$=0.01]. In this meta-analysis, the initial dosage of midodrine ranged from 15 mg per day to 40 mg every 8 hours. Bradycardia was the only midodrine-related adverse event observed, with an estimated incidence of 2.1%.

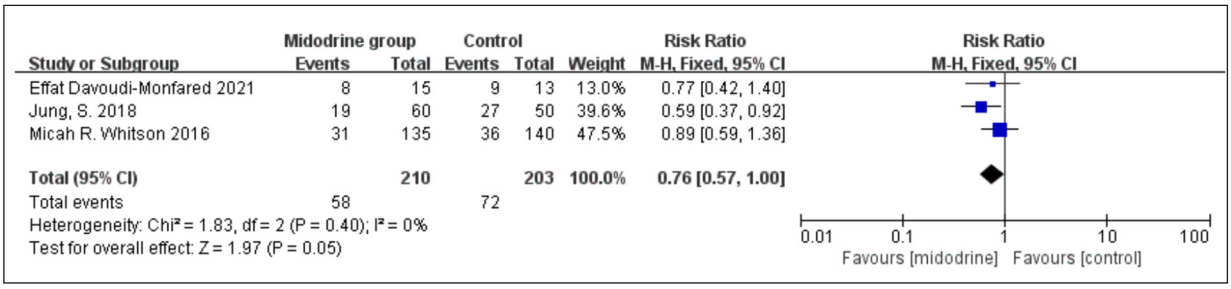


**Figure 3.** The forest plot of hospital mortality.

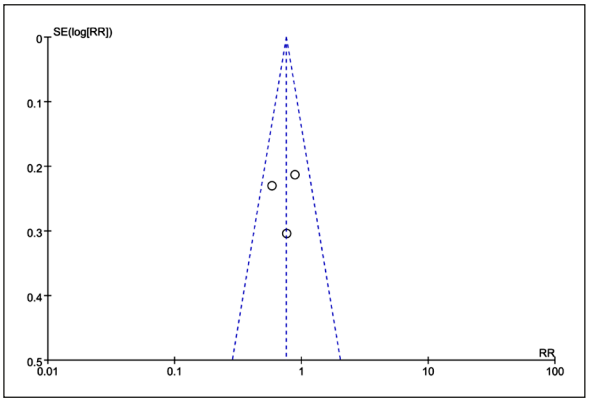


**Figure 4.** The funnel plot of hospital mortality.

This result suggested that midodrine may be safe in this dose range in the treatment of patients with septic shock.

Midodrine is an oral alerfa-1 adrenergic receptor agonist. It increases vessel tone and accelerate weaning of intravenous vasopressors. It has been approved by the Food and Drug Administration (FDA)[30] for the treatment of symptomatic orthostatic hypotension. Whether midodrine is an effective treatment in patients with septic shock is still under debate. To our knowledge, this is the first meta-analysis to examine the efficacy of midodrine in septic shock. Our findings that midodrine reduces ICU and hospital mortality may provide some clues for future treatment of septic shock. However, due to the relatively small number of patients enrolled in the current studies, there may be some confounding factors. Therefore, high-quality studies are needed in the future to further assess whether midodrine can serve as a standard treatment in septic shock.

Midodrine is increasingly being used to increase mean arterial pressure in ICU patients and accelerate the weaning of intravenous vasopressors[31]. Levine et al[20] found that oral midodrine increased the reduction in intravenous vasopressors in surgical ICU patients. They also found that midodrine facilitated the withdrawal of intravenous vasopressors and hastened ICU discharge. ICU stay imposes a large economic burden to septic shock patients. Adly et al[19] performed a cost-effectiveness analysis and found that midodrine plus IV vasopressor was more cost-effective than IV vasopressor only to treat patients with septic shock. The results of this meta-analysis did not show any significant benefit of midodrine in reducing ICU length of stay. A previous meta-analysis[23] reported that midodrine did not reduce ICU length of stay in patients with shock in the intensive care unit, which was in line with our study. The previous study[23] population included cardiogenic, traumatic, and sepsis-induced shock. As we know, midodrine exhibits agonism at the alerfa-1 receptor but no cardiotonic effects; therefore, a more detailed, systematic evaluation is needed when it is used in patients with cardiogenic shock. Septic shock is characterized by decreased vascular tone and peripheral vasodilation; hence, it is suggested that midodrine plays a more important role in septic shock patients than other types of shock. A multicenter, randomized, controlled study[32] assessing the efficacy of midodrine in shock patients is ongoing, giving the potential to perform subgroup analysis on etiology (ClinicalTrials.gov NCT05058612).

### *Limitations*

This meta-analysis also has certain limitations. The included studies[19,21,26-29] differed in midodrine dose, timing of initiation, and timing of withdrawal. The current studies on the efficacy of midodrine in septic shock included a small number of patients; some had large weights, which had a large impact on the pooled effect size. The conclusion may have been greatly

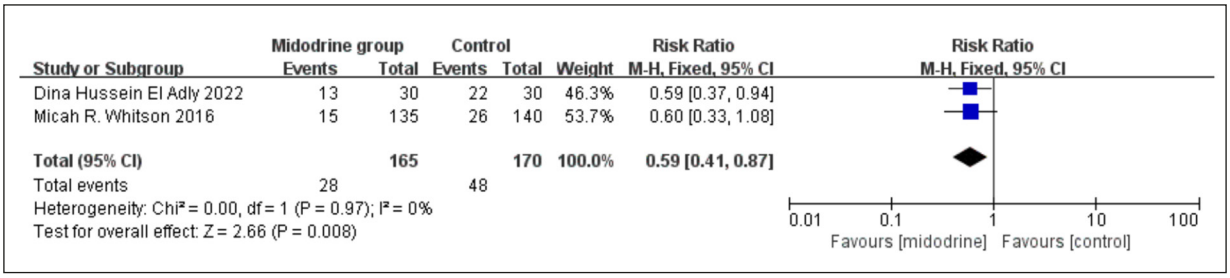


**Figure 5.** The forest plot of ICU mortality.

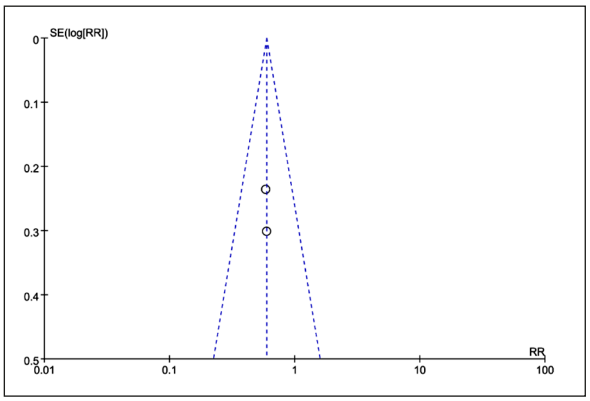


**Figure 6.** The funnel plot of ICU mortality.

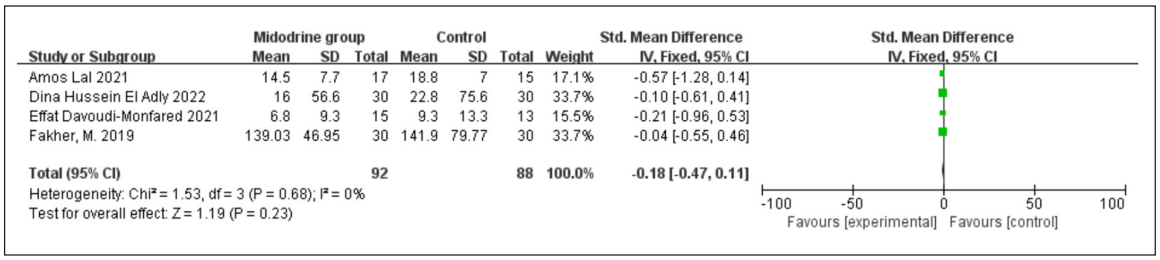


**Figure 7.** The forest plot of IV vasopressor duration.

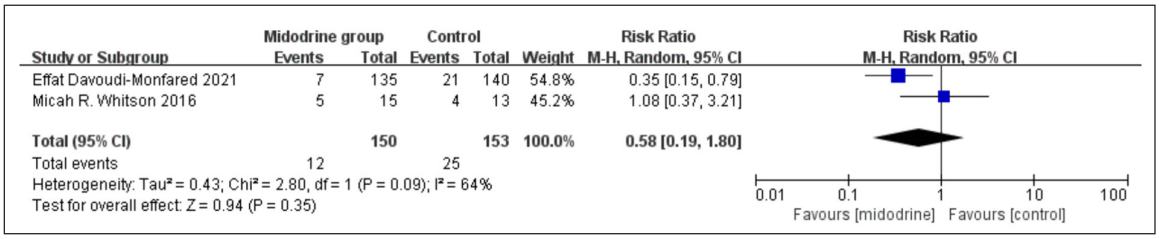


**Figure 8.** The forest plot of IV vasopressor reinstitution.

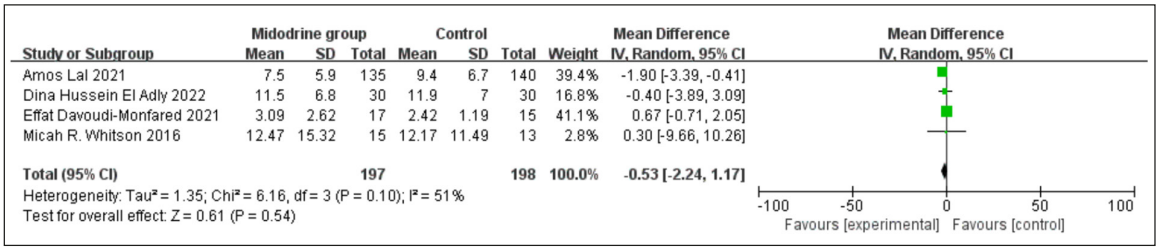


**Figure 9.** The forest plot of ICU length of stay.

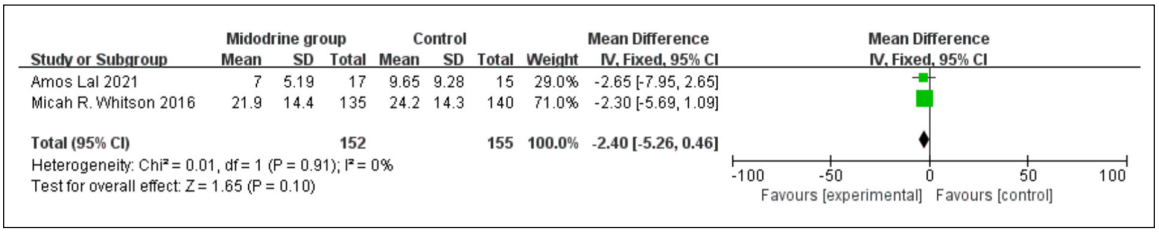


**Figure 10.** The forest plot of hospital length of stay.

influenced by some unmeasured confounding factors; therefore, further rigorously designed studies with large sample sizes are needed to confirm our conclusions. There are currently no RCTs or cohort studies comparing the efficacy between different doses and initiation strategies of midodrine in septic shock; it is unfortunate and may be one of the future research directions. In addition, the current studies only assessed the effect of midodrine on short-term mortality (ICU mortality and in-hospital mortality) in septic shock but did not assess the effect on long-term mortality (half-year or even 1-year mortality). A previous study[33] showed that discharge from ICU on midodrine was associated with a significantly reduced risk of in-hospital mortality [hazard ratio, 0.47 (95% CI, 0.32-0.70); $p<0.001$); however, patients who were discharged from the hospital on midodrine had a higher risk of 1-year mortality [hazard ratio, 1.60 (95% CI, 1.26-2.04); $p<0.001$].

## Conclusions

Additional use of midodrine in septic shock may reduce ICU mortality and hospital mortality. However, this conclusion may have been affected by unmeasured confounders and needs to be further verified by more rigorous studies.

### Conflict of Interest
The Authors declare that they have no conflict of interests.

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### Authors' Contribution
Q.-F. He participated in article drafting, study design, data integration, statistical analysis and writing. X.-K. Xing and T.-Q. Wang participated in literature screening and data extraction, and Z.-X. Jiang participated in verification and review. G. Zhang participated in the study design, revision of article content, data review and article approval.

### Ethics Approval
This article does not include any human or animal research conducted by the authors.

### Informed Consent
This article does not contain any research conducted by the authors on humans and therefore does not require any informed consent.

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### Availability of Data and Materials
All data generated during this study are from previously published studies.We cited all the included studies.

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