The Effect of Pre-admission Metformin Use on Clinical Outcomes in Diabetic Patients with Sepsis: A Post-print of a New Meta-analysis

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Abstract

Background Accumulating evidence indicates that preadmission metformin use may reduce mortality in diabetic patients with sepsis; however, the impact of metformin on clinical outcomes in this population remains controversial. Therefore, a systematic review and meta-analysis of existing studies is warranted to further evaluate whether metformin improves mortality and other clinical outcomes in diabetic patients with sepsis. Objective To systematically evaluate the effects of preadmission metformin use on mortality, initial plasma lactate levels, and organ dysfunction in diabetic patients with sepsis. Methods Computerized searches were conducted for relevant Chinese and English literature on the impact of metformin on clinical outcomes in diabetic patients with sepsis across PubMed, Embase, Cochrane Library, Web of Science, Scopus, SinoMed, Wanfang Data, CNKI, and other databases. The experimental group (MET group) comprised adult diabetic patients with sepsis who used metformin before admission, while the control group (NM group) consisted of adult diabetic patients with sepsis who did not use metformin before admission. The search timeframe spanned from database inception to March 15, 2023. After screening, data extraction, and quality assessment by two researchers, meta-analysis was performed using RevMan 5.3 software. Results This study included 12 articles with a total of 12,320 diabetic patients with sepsis. The Newcastle-Ottawa Scale (NOS) scores of the included studies ranged from 7 to 8. Meta-analysis results demonstrated that mortality (OR=0.61, 95%CI=0.46~0.80, P<0.001) and vasopressor usage (MD=0.83, 95%CI=0.69~0.98, P=0.03) were lower in the MET group than in the NM group. No statistically significant differences were observed between the MET and NM groups in initial plasma lactate levels (MD=0.31, 95%CI=-0.12~0.75, P=0.16), serum creatinine levels (MD=-0.81, 95%CI=-0.48~0.13, P=0.25), initial blood glucose levels (MD=32.94, 95%CI=-10.12~76.01, P=0.13), or mechanical ventilation (MD=0.90, 95%CI=0.77~1.06, P=0.23). Conclusion Preadmission metformin use can reduce mortality and vasopressor usage in diabetic patients with sepsis, providing novel evidence for the beneficial effects of metformin in this population. However, further research is needed to determine whether metformin can reduce sepsis severity scores and decrease maximum norepinephrine dosage in diabetic patients with sepsis.

Full Text

Effects of Pre-hospital Metformin Use on Clinical Outcomes in Patients with Diabetes and Sepsis: An Updated Meta-analysis

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Abstract

Background: Growing evidence suggests that pre-hospital metformin use reduces mortality in patients with diabetes and sepsis. However, the effect of metformin on clinical outcomes in this population remains controversial. Therefore, a systematic review and meta-analysis of existing studies is needed to further evaluate whether metformin can improve mortality and other clinical outcomes in patients with diabetes and sepsis.

Objective: To systematically evaluate the effects of pre-hospital metformin use on mortality, initial plasma lactate level, and organ dysfunction in patients with diabetes and sepsis.

Methods: PubMed, Embase, Cochrane Library, Web of Science, Scopus, China Biomedical Literature Service System, Wanfang, CNKI, and other databases were systematically searched for Chinese and English literature on the effects of pre-hospital metformin use on clinical outcomes in patients with sepsis and diabetes from inception to March 15, 2023. The test group (MET group) comprised adult patients with diabetes and sepsis who received pre-hospital metformin, while the control group (NM group) comprised adult patients with diabetes and sepsis who did not receive pre-hospital metformin. After screening, data extraction, and literature quality evaluation by two researchers, meta-analysis was performed using RevMan 5.3 software.

Results: A total of 12 studies involving 12,320 patients with diabetes and sepsis were included. The Newcastle-Ottawa Scale (NOS) scores of the included studies ranged from 7 to 8. Meta-analysis results showed that the MET group had lower mortality (OR=0.61, 95%CI=0.46-0.80, P<0.001) and vasopressor usage (MD=0.83, 95%CI=0.69-0.98, P=0.03) compared with the NM group. There were no statistically significant differences between the MET and NM groups in initial plasma lactate level (MD=0.31, 95%CI=-0.12-0.75, P=0.16), serum creatinine level (MD=-0.18, 95%CI=-0.48-0.13, P=0.25), initial blood glucose level (MD=32.94, 95%CI=-10.12-76.01, P=0.13), or mechanical ventilation (MD=0.90, 95%CI=0.77-1.06, P=0.23).

Conclusion: Pre-hospital metformin use can reduce mortality and vasopressor usage in patients with diabetes and sepsis, providing updated evidence for metformin' s survival benefit in this population. However, whether metformin can reduce sepsis severity scores or decrease the maximum dose of norepinephrine requires further investigation.

Keywords: Diabetes mellitus; Sepsis; Metformin; Clinical outcomes; Mortality rate; Organ dysfunction; Meta-analysis

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Although its pathophysiological mechanisms remain incompletely elucidated and the specific contributions of potential pathogenic and iatrogenic factors during its onset and progression are still unclear, the major mechanisms involved include immune dysfunction, coagulation disorders, and endothelial cell activation and dysfunction [2-4]. Consequently, sepsis often affects multiple organ systems and can lead to death from organ failure. Increased endothelial permeability mediated by endothelial activation and dysfunction is also considered a key factor in disease progression to septic shock [5-6].

Type 2 diabetes (T2D) and obesity are major global public health problems, with an increasingly severe burden in China. The prevalence of diabetes among adults aged 20-79 years is projected to increase from 8.2% to 9.7% between 2020 and 2030 [7]. Diabetes is associated with increased susceptibility to infection and sepsis, though whether mortality in sepsis patients is affected by diabetes remains controversial, and the benefits of strict glycemic control in sepsis patients require further validation [8-9].

Metformin is the first-line treatment for most T2D patients, reducing glucose absorption, improving insulin sensitivity, and inhibiting hepatic gluconeogenesis [10]. Beyond its glucose-lowering effects, evidence indicates that metformin exerts anti-inflammatory effects by suppressing inflammatory factor expression [11-14]. Studies have shown that metformin reduces interleukin-6 (IL-6) expression and inhibits intestinal inflammatory signaling by suppressing AMP-activated protein kinase (AMPK) and p38 MAP kinase activation [11]. Furthermore, multiple studies have demonstrated that activation of AMPK by certain drugs or small molecules protects against experimental sepsis in animals [15-17], indicating that AMPK plays an indispensable role in sepsis pathogenesis and represents a primary target through which metformin alleviates the inflammatory response in sepsis.

Recent research suggests that metformin may help control the cytokine storm secondary to SARS-CoV-2 infection, offering potential protective effects during infection and associating with better clinical outcomes among current or previous users [18]. YANG et al. [19] reported that pre-admission metformin use was associated with a 39% reduction in 30-day mortality. Additionally, patients not taking metformin had a 2.5-fold higher risk of death within 28 days compared with metformin users [20]. However, some studies have found no association between metformin use and sepsis outcomes or altered host response in patients with diabetes and sepsis [20-22]. Given these controversies, this meta-analysis aims to comprehensively evaluate the effects of metformin on mortality, sepsis severity scores, initial lactate levels, serum creatinine levels, renal replacement therapy, acute kidney injury, mechanical ventilation, vasopressor usage, maximum norepinephrine dose, and initial blood glucose levels to assess whether metformin improves prognosis in patients with diabetes and sepsis.

Methods

1.1 Search Strategy We systematically searched PubMed, Embase, Cochrane Library, Web of Science, Scopus, China Biomedical Literature Service System, Wanfang, CNKI, and other databases for relevant Chinese and English literature published from database inception to March 15, 2023. English search terms included "sepsis," "critically ill patients," and "metformin," while Chinese terms included "脓毒症" (sepsis), "危重症" (critically ill), and "二甲双胍" (metformin). We also manually searched the reference lists of included studies and relevant reviews to identify additional eligible articles. Two researchers independently screened the literature, extracted data, and evaluated study quality before conducting meta-analysis using RevMan 5.3 software.

1.2 Inclusion and Exclusion Criteria **1.2.1 Inclusion Criteria:** (1) Observational studies or eligible clinical trials; (2) Test group (MET group): adult patients with diabetes and sepsis who used metformin before hospital admission; (3) Control group (NM group): adult patients with diabetes and sepsis who did not use metformin before hospital admission; (4) Studies that documented mortality in patients with diabetes and sepsis; (5) Original data such as means, standard deviations, and sample sizes could be directly extracted or obtained after conversion.

1.2.2 Exclusion Criteria: (1) Non-observational studies, ineligible clinical trials, duplicate publications, translations, studies with unextractable data, or animal experiments; (2) Reviews, systematic reviews, and meta-analyses; (3) Studies with unreported or non-convertible data; (4) Conference abstracts, commentaries, or case reports; (5) Articles without relevant clinical outcomes or those involving sepsis patients with comorbidities; (6) Irrelevant studies or those with low-quality scores.

1.3 Quality Assessment Two investigators independently screened the literature, extracted data, and assessed quality according to the inclusion and exclusion criteria. Extracted data included first author, publication year, study type, country, sample size, study period, primary outcome measures, and NOS score. Disagreements were resolved by consulting the original literature, contacting authors, or seeking input from other researchers. We used the Newcastle-Ottawa Scale (NOS) to assess the risk of bias in included studies [23], which evaluates study population selection, intergroup comparability, and outcome measurement (score range: 0-9). Two researchers conducted independent assessments, with a third researcher consulted in case of disagreement. Scores of 7-9 were considered high-quality studies with low risk of bias.

1.4 Statistical Methods We performed meta-analysis using RevMan 5.3 software to systematically evaluate the effects of pre-hospital metformin use on mortality, hyperlactatemia, and organ dysfunction in patients with diabetes and sepsis. Mean difference (MD) was used as the effect measure for continuous variables, while odds ratio (OR) was used for dichotomous variables, both expressed with 95% confidence intervals (CI). Heterogeneity was assessed using the ^{2} test and I^2 statistic. When I^2>50% and P\$ \$0.10, indicating substantial heterogeneity, we used a random-effects model to calculate pooled statistics and explored sources of heterogeneity; otherwise, a fixed-effects model was employed. Statistical significance was defined as $P<0.05$. Funnel plots were used to assess publication bias when more than 10 studies were included.

Results

2.1 Literature Search Results The database search yielded 1,014 relevant articles: PubMed (n=171), Embase (n=774), Cochrane Library (n=42), Web of Science (n=15), Scopus (n=12), China Biomedical Literature Service System (n=0), Wanfang (n=0), and CNKI (n=0). After removing duplicates (n=327) and screening titles and abstracts, 687 articles remained. We then excluded 632 articles, leaving 55 full-text articles for review. After reading the full texts, we excluded 43 articles (17 irrelevant studies, 9 reviews, 2 with unextractable data, 1 animal study, and 14 conference abstracts). Ultimately, 12 studies were included: 11 retrospective cohort studies [19-20,22,24-31] and 1 prospective observational study [21]. The literature screening process is shown in Figure 1 [Figure 1: see original paper].

2.2 Study Characteristics The 12 included studies were published between 2011 and 2022 and comprised 12,320 patients with diabetes and sepsis (MET group: 2,880; NM group: 9,440). Eight studies [20,22,24-25,27-30] were single-center, while four [19,21,26,31] were multicenter. Study durations ranged from 20 to 132 months, and NOS scores ranged from 7 to 8. The primary outcome was mortality in patients with diabetes and sepsis, while secondary outcomes included sepsis severity scores, initial lactate levels, serum creatinine levels, renal replacement therapy, acute kidney injury, mechanical ventilation, vasopressor usage, maximum norepinephrine dose, and initial blood glucose levels. Basic characteristics of the included studies are presented in Table 1 , and the risk of bias assessment is shown in Figures 2 [Figure 2: see original paper] and 3 [Figure 3: see original paper].

2.3 Meta-Analysis Results **2.3.1 Effect of Metformin on Mortality in Patients with Diabetes and Sepsis:** Twelve studies [19-22,24-31] reported the effect of metformin on mortality. Significant statistical heterogeneity was observed ($P<0.001$, $I^2=75\%$). Using a random-effects model, meta-analysis showed that mortality was significantly lower in the MET group than in the NM group (OR=0.61, 95%CI=0.46-0.80, $P<0.001$) (Figure 4 [Figure 4: see original paper]).

2.3.2 Effect of Metformin on Initial Plasma Lactate Levels: Eight studies [19-22,24-25,29] reported the effect of metformin on initial plasma lactate levels. Significant heterogeneity was present ($P<0.001$, $I^2=69\%$). Random-effects meta-analysis revealed no statistically significant difference between the MET and NM groups (MD=0.31, 95%CI=-0.12-0.75, P=0.16) (Figure 5 [Figure 5: see original paper]).

2.3.3 Effect of Metformin on Serum Creatinine Levels: Five studies [20,22,27-29] reported the effect of metformin on serum creatinine levels. Significant heterogeneity was observed ($P=0.002$, $I^2=76\%$). Random-effects meta-analysis showed no statistically significant difference between groups (MD=-0.18, 95%CI=-0.48-0.13, P=0.25) (Figure 6 [Figure 6: see original paper]).

2.3.4 Effect of Metformin on Initial Blood Glucose Levels: Four studies [19-21,28] reported the effect of metformin on initial blood glucose levels. Significant heterogeneity was present ($P<0.001$, $I^2=96\%$). Random-effects meta-analysis revealed no statistically significant difference between groups (MD=32.94, 95%CI=-10.12-76.01, P=0.13) (Figure 7 [Figure 7: see original paper]).

2.3.5 Effect of Metformin on Mechanical Ventilation: Four studies [19,21,28-29] reported the effect of metformin on mechanical ventilation. No significant heterogeneity was observed ($P=0.58$, $I^2=0$). Random-effects meta-analysis showed no statistically significant difference between groups (MD=0.90, 95%CI=0.77-1.06, P=0.23) (Figure 8 [Figure 8: see original paper]).

2.3.6 Effect of Metformin on Sepsis Severity Scores: Six studies [19-21,27-29] reported sepsis severity scores, but each used different scoring systems, including Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE IV, Sequential Organ Failure Assessment (SOFA), and PIRO (predisposition, infection, response, and organ dysfunction) scores. Therefore, pooled comparison was not feasible.

2.3.7 Effect of Metformin on Vasopressor Usage: Four studies [19,21,28-29] reported vasopressor usage. Only one study [29] reported the maximum dose of norepinephrine, precluding data analysis. Three studies [19,21,28] reported vasopressor usage rates, with significant heterogeneity among them (P=0.004, I^2=82%). Random-effects meta-analysis showed that vasopressor usage was significantly lower in the MET group than in the NM group (MD=0.83, 95%CI=0.69-0.98, P=0.03) (Figure 9 [Figure 9: see original paper]).

2.4 Bias Analysis Funnel plot analysis was performed for studies reporting mortality in patients with diabetes and sepsis. The funnel plot (Figure 10 [Figure 10: see original paper]) showed relatively symmetrical distribution of included studies around the axis, indicating low publication bias.

Discussion

Metformin, a commonly prescribed diabetes medication, may have therapeutic potential in patients with diabetes and sepsis. It reduces glucose absorption, improves insulin sensitivity, inhibits hepatic gluconeogenesis [10], and exerts anti-inflammatory effects by suppressing inflammatory cytokines such as IL-6 [11-14]. It also shows promise in controlling the cytokine storm secondary to SARS-CoV-2 infection, demonstrating potential protective effects during infection and associating with better clinical outcomes [18]. However, some studies have found no statistically significant differences in mortality or other clinical outcomes between metformin users and non-users among patients with diabetes and sepsis, and no association with altered host response [20-22,30]. Given these controversies, our meta-analysis examined the effects of metformin on sepsis severity scores, initial lactate concentration, serum creatinine concentration, renal replacement therapy, acute kidney injury, mechanical ventilation, vasopressor usage, maximum norepinephrine dose, and initial blood glucose to further clarify whether metformin improves prognosis in this population.

Our meta-analysis included 12 studies comprising 12,320 patients with diabetes and sepsis, comprehensively evaluating the relationship between pre-hospital metformin use and clinical outcomes including mortality, sepsis severity scores, initial lactate levels, serum creatinine levels, renal replacement therapy, acute kidney injury, mechanical ventilation, vasopressor usage, maximum norepinephrine dose, and initial blood glucose levels. The results showed that the MET group had significantly lower mortality and vasopressor usage compared with the NM group ($P<0.05$), while no significant differences were observed in initial plasma lactate, serum creatinine, initial blood glucose levels, or mechanical ventilation rates ($P>0.05$). Previous studies have reported no significant difference in mortality between metformin users and non-users [21-22,25,28-30], while others have demonstrated that pre-hospital metformin use significantly reduces 30-day mortality [19-20,26]. Thus, the relationship between pre-hospital metformin use and mortality in patients with diabetes and sepsis remains controversial. One large clinical study reported no significant association between metformin and 30-day mortality [30], while newer research suggests metformin is significantly associated with reduced 90-day mortality [31]. Subsequently, a meta-analysis including 8,195 patients indicated that pre-hospital metformin use could reduce mortality in diabetic sepsis patients. Therefore, despite ongoing controversies in the literature, our meta-analysis provides updated evidence that pre-hospital metformin use reduces mortality and vasopressor usage in patients with diabetes and sepsis. However, we could not confirm whether metformin reduces initial plasma lactate, serum creatinine, or initial blood glucose levels, or decreases the need for renal replacement therapy, acute kidney injury, or mechanical ventilation. Furthermore, whether metformin can reduce sepsis severity scores or decrease maximum norepinephrine dose requires further investigation.

The mechanisms underlying the association between pre-hospital metformin use and reduced mortality in patients with diabetes and sepsis remain unclear. Accumulating evidence suggests that metformin can improve T lymphocyte autophagy and mitochondrial function, ameliorate hyperglycemia, and reduce chronic inflammation [14,32]. It may also attenuate inflammatory responses by reducing serum levels of pro-inflammatory cytokines IL-6 and tumor necrosis factor-α (TNF-α) [14,33]. Additionally, metformin may activate AMPK by inhibiting complex I of the electron transport chain, increasing the AMP:ATP/ADP:ATP ratio, thereby reducing inflammation and modulating other molecular processes [11,15-17,34]. Metformin may also have potential therapeutic roles in various infectious diseases. Laboratory studies have demonstrated efficacy against multiple pathogens, including *Trichinella spiralis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, hepatitis B virus, hepatitis C virus, and human immunodeficiency virus [35]. Thus, the antimicrobial effects of metformin may benefit patients with diabetes and sepsis and improve clinical outcomes.

Meta-analysis is a method for comprehensive statistical analysis of multiple studies on a specific topic. When between-study variation exceeds expectation, statistical heterogeneity exists in the pooled results. The heterogeneity in our study may derive from differences in sample size, initial lactate levels, and concomitant use of other anti-diabetic medications. The risk of bias assessment showed low risk across included studies, and publication bias was low.

This study conducted a comprehensive literature search, included 12 studies with 12,320 sepsis patients, and had a large sample size, enhancing the persuasiveness of our findings. However, several limitations exist. First, the validity of the meta-analysis may be limited, requiring more high-quality, large-sample studies for further verification. Second, most original studies did not report metformin dosage or concomitant anti-diabetic medications, leaving unclear whether different metformin doses and other glucose-lowering drugs affect outcomes in patients with diabetes and sepsis. Finally, our literature search was restricted to Chinese and English publications, potentially introducing publication bias.

In conclusion, this meta-analysis suggests that metformin has therapeutic potential in patients with diabetes and sepsis, and pre-hospital metformin use may be associated with reduced mortality and decreased vasopressor usage. However, we could not confirm whether metformin reduces initial plasma lactate, serum creatinine, or initial blood glucose levels, or decreases the need for renal replacement therapy, acute kidney injury, or mechanical ventilation. Furthermore, high-quality studies are needed to clarify the relationship between metformin and organ dysfunction-related outcomes such as sepsis severity scores and maximum norepinephrine dose, and to explore the specific mechanisms by which metformin reduces mortality in patients with diabetes and sepsis. Future clinical studies should also investigate the optimal dosing range and timing of metformin administration in this population.

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Note: Figure translations are in progress. See original paper for figures.