

The association between hypoglycemia and mortality in sepsis and septic shock: A systematic review and meta-analysis

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Abstract

Over 48 million cases of sepsis and 11 million sepsis-related deaths were reported in 2017, making it one of the leading causes of mortality. This meta-analysis compared mortality risk among patients with sepsis or septic shock and associated hypoglycemia or euglycemia on admission by searching for observational studies in PubMed, Embase and Scopus databases. The eligible studies included patients with sepsis and/or severe sepsis/septic shock and compared mortality rates between those with hypoglycemia on admission and those who were euglycemic. A stratified analysis based on sepsis or severe sepsis/septic shock and diabetes on admission included 14 studies. Patients with hypoglycemia had a significantly higher risk of in-hospital mortality and mortality during the 1st month after discharge. In addition, hypoglycemic patients with sepsis had a slightly increased risk of in-hospital mortality, but no increase in the mortality risk was observed within 1 month of follow-up. However, in patients with severe sepsis and/or septic shock, hypoglycemia was associated with a higher risk of both in-hospital mortality and mortality during 1 month of follow-up. In patients with diabetes, hypoglycemia was not associated with an increased risk of in-hospital mortality or mortality within 1 month of follow-up. Patients with sepsis or severe sepsis/septic shock and hypoglycemia had an increased mortality risk, and the association was stronger in cases of severe sepsis/septic shock. Hypoglycemia in diabetic patients did not correlate with increased mortality risk. Careful monitoring of blood glucose in sepsis and/or severe sepsis/septic shock patients is required.

Key words: sepsis, severe sepsis, septic shock, blood glucose, hypoglycemia, mortality, meta-analysis

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Introduction

Over 48 million cases of sepsis and 11 million sepsis-related deaths were reported in 2017, making it one of the leading causes of mortality.¹ Data from Europe, North America and Australia show that 30-day and 90-day mortality rates due to sepsis were 25% and 32%, respectively.² The highest sepsis burden and related mortality were found in Sub-Saharan Africa and Southeast Asia.¹

Due to changes in endocrinal metabolism, patients with sepsis and/or septic shock have fluctuations in blood glucose levels that negatively impact the internal milieu and worsen their clinical condition.^{3,4} Sepsis is associated with higher levels of oxidative stress and the secretion of interleukin (IL)-1, IL-6 and tumor necrosis factor alpha (TNF- α) by inflammatory cells. This, in turn, damages pancreatic β -cells,^{3–5} affects the production of insulin, and leads to a state of stress hyperglycemia.⁵ Hyperglycemia may result in several complications, such as increased predisposition to infections, oxidative stress and increased mortality risk.^{6,7} However, studies have also indicated that patients with sepsis and/or septic shock are at an increased risk of hypoglycemia,^{5,8} though its mechanisms are still unclear. Some studies suggest that the increased utilization of peripheral glucose, depletion of glycogen reserves, reduction in gluconeogenesis, and a comparatively decreased nutrient supply may play a role in sepsis-induced hypoglycemia.^{5,9,10} Another crucial contributor could be the strict measures for blood glucose control in such patients.¹¹

The effect of hypoglycemia on the survival of patients with sepsis is still unclear. Although studies have examined the impact of hypoglycemia on the mortality of these patients, only a few have summarized the available data.^{12,13} A meta-analysis by Wang et al. pooled findings from 5 studies and found increased mortality in patients with decreased blood glucose levels.¹² Recently, several new studies provided updated clinical evidence, and these findings should also be considered.

Objectives

The primary objective of this meta-analysis was to synthesize evidence from available studies to estimate the risk of mortality in patients with sepsis and/or septic shock and associated hypoglycemia at the time of hospital admission.

Materials and methods

Database search and strategy

We searched PubMed, Embase and Scopus databases for English-language papers published until April 30, 2022, using the following key words: (“hypoglycaemia” OR “hypoglycemia” OR “low blood glucose” OR “low blood sugar”) AND (“sepsis” OR “severe sepsis” OR “septic shock” OR

“septicemia”) AND (“mortality” OR “death” OR “survival”). We based our review on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,¹⁴ and the paper was registered at PROSPERO with the number CRD42022336895.

Study selection criteria and process

Observational studies with either retrospective or prospective designs concerning subjects with sepsis and/or severe sepsis/septic shock were considered. Furthermore, the analyzed studies had to compare the mortality risk among patients with hypoglycemia or euglycemia at the time of hospital admission. We excluded case reports and review articles, as well as studies that did not have the exposure of interest (blood glucose assessment at the time of admission) or did not compare the risk of mortality between hypoglycemic and euglycemic patients.

After removing duplicates, the list of potentially eligible studies was screened by 2 independent reviewers following pre-defined inclusion and exclusion criteria. The articles that met the inclusion criteria were subject to a full-text assessment. Any disagreements between the 2 reviewers were resolved by discussion. The bibliography of the included studies was thoroughly screened for additional relevant publications. The study selection process is shown in Fig. 1.

Data extraction and statistical analysis

We used a pretest data extraction sheet to fill in relevant data from the included studies. The data extraction process was carried out independently by 2 authors. The quality of the studies was assessed using the Newcastle-Ottawa Quality Assessment Scale for observational studies.¹⁵ Statistical analysis employed STATA software v. 16.0 (StataCorp LLC, College Station, USA). The pooled effect sizes and 95% confidence intervals (95% CIs) were reported as odds ratios (ORs). The selection of the final analytical model was based on the observed I^2 value (used to denote the degree of heterogeneity). We used a random effects model for outcomes with $I^2 > 40\%$, and a fixed effects model was used for $I^2 \leq 40\%$.¹⁶ Egger's test assessed publication bias.¹⁷ Wherever reported, we considered a p-value of less than 0.05 to denote statistical significance. We used the method reported by Chyou to calculate the p-value for the reported pooled effect sizes in the meta-analysis.¹⁸ First, we calculated the standardized z statistic using the following formula: $z = (b/sb)$, where $b = \log(\text{OR})$ and $sb = \ln(\text{upper confidence limit/OR})/1.96$. Second, we derived p-values corresponding to the obtained z-statistic and reported the z-statistic and its corresponding p-value in the results. A subgroup analysis based on the clinical condition studied, i.e., sepsis or severe sepsis/septic shock, as well as the presence or absence of diabetes on admission, was also carried out.

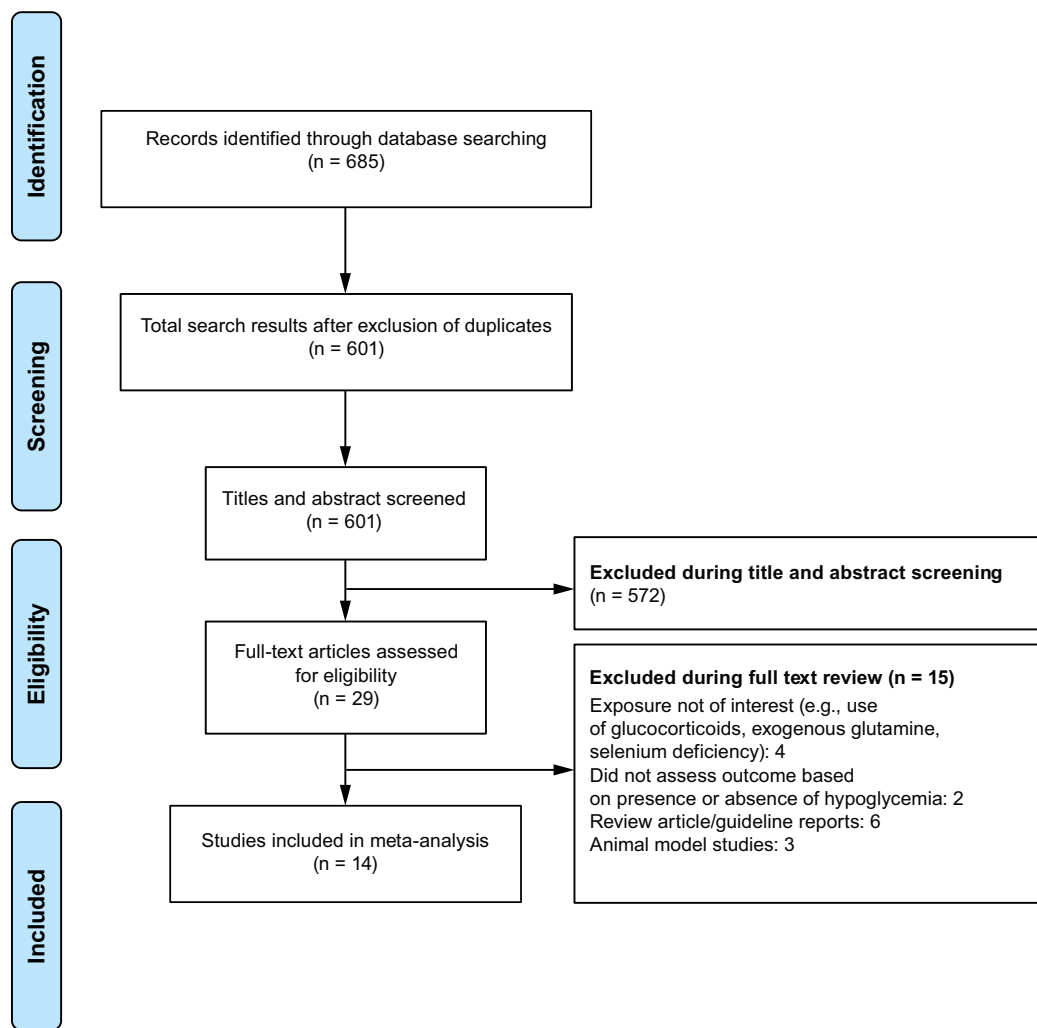


Fig. 1. The selection process of the studies included in the review

Results

A total of 14 studies were selected for this meta-analysis.^{19–32} The specific details of the included studies are summarized in Table 1. All studies were observational, including 12 retrospective and 2 prospective in design. Three studies

were conducted in Japan and Australia. Two studies were from Taiwan and the USA, and China, Uganda and South Korea conducted 1 study each. Eight studies included patients with severe sepsis and/or septic shock, and 6 included patients with sepsis. There was a difference in the operational definition adopted for the classification of hypoglycemia

Table 1. Characteristics of the studies included in the meta-analysis

Author, year, reference	Study design	Country	Characteristics of the participants	Operational definition for hypoglycemia	Sample size	Outcome (mortality) (hypoglycemia compared to euglycemia)
Furukawa et al. (2019) ¹⁹	retro-spective	Japan	patients included in the study had sepsis; mean age: 74 years; males: 61%; infection focus (pneumonitis: 53%; pyelonephritis: 16%)	blood glucose on admission: <80 mg/dL	336	in-hospital: OR: 3.50 (95% CI: 1.78–6.94)
Mitsuyama et al. (2022) ²⁰	retro-spective	Japan	patients included in the study had sepsis; median age: 71 years; males: 63%; infection focus (lung: 38%; abdomen: 23%; skin and soft tissue: 17%); pre-existing diabetes: 26%, hypertension: 34%	blood glucose on admission: ≤70 mg/dL	265	day 28: OR: 12.18 (95% CI: 4.35–34.2)
Wei et al. (2021) ²¹	retro-spective	China	patients included in the study had sepsis; mean age: approx. 65 years; males: 55%; hypertension: 30%, chronic heart disease: 10%, chronic kidney disease: 13%	blood glucose on admission: <70 mg/dL	2948	day 30: OR: 1.91 (95% CI: 1.35–2.72); with diabetes on admission, day 30: OR: 1.40 (95% CI: 0.86–2.29)

Table 1. Characteristics of the studies included in the meta-analysis – cont.

Author, year, reference	Study design	Country	Characteristics of the participants	Operational definition for hypoglycemia	Sample size	Outcome (mortality) (hypoglycemia compared to euglycemia)
Chan et al. (2016) ²²	retrospective	Taiwan	patients included in the study had severe sepsis; median age: approx. 74 years; males: 79%; primary reason for sepsis (pneumonia: 83%); mean APACHE II score: 27	blood glucose on admission: <80 mg/dL	127	in-hospital: OR: 3.60 (95% CI: 1.24–10.50) day 14: OR: 6.81 (95% CI: 2.43–19.1) with diabetes on admission, day 14: OR: 0.70 (95% CI: 0.10–4.87)
Schuetz et al. (2011) ²³	prospective	USA	majority of patients included in the study had sepsis (57.5%); mean age: 59 years; males: 49%; white race: 70%; associated diabetes: 24%; associated prior congestive heart failure: 10%	blood glucose on admission: <100 mg/dL	7754	in-hospital: OR: 1.09 (95% CI: 1.03–1.14) with diabetes on admission, in-hospital: OR: 2.30 (95% CI: 1.61–3.30)
Ssekitoleko et al. (2011) ²⁴	prospective	Uganda	patients included in the study had severe sepsis; mean age: approx. 35 years; males: 46%; bacteremia/fungemia present in 21%; HIV-positive: 83%	blood glucose on admission: <80 mg/dL	418	in-hospital: OR: 1.60 (95% CI: 0.92–2.78)
Park et al. (2012) ²⁵	retrospective	South Korea	patients included in the study had septic shock (around 60%); mean age: approx. 70 years; males: 53%; associated diabetes: 33%; insulin therapy: 70%; bacteremia/fungemia present in 21%; HIV-positive: 83%	blood glucose on admission: <40 mg/dL	313	in-hospital: OR: 6.37 (95% CI: 2.31–17.55) day 30: OR: 5.30 (95% CI: 2.04–13.78) 1 year: OR: 6.48 (95% CI: 1.89–22.21)
Magee et al. (2018) ²⁶	retrospective	Australia	patients included in the study with sepsis; mean age: approx. 66 years; males: 56%; associated chronic renal failure: 6%; immunosuppression: 9%; APACHE III mean score: approx. 66	blood glucose on admission: <120 mg/dL	90,644	in-hospital: OR: 0.99 (95% CI: 0.95–1.04) with diabetes on admission, in-hospital: OR: 1.71 (95% CI: 1.36–2.14)
Kushimoto et al. (2020) ²⁷	retrospective	Japan	majority of patients included in the study had severe sepsis/septic shock; mean age: approx. 73 years; males: 60%; mean BMI: 22 kg/m ² ; associated diabetes: 23%; site of infection (lung: 31%, abdomen: 26%)	blood glucose on admission: <70 mg/dL	1158	in-hospital: OR: 2.06 (95% CI: 1.22–3.50) day 28: OR: 2.37 (95% CI: 1.38–4.08) with diabetes on admission, in-hospital: OR: 1.71 (95% CI: 0.51–5.72)
Chao et al. (2017) ²⁸	retrospective	Taiwan	patients included in the study had sepsis; median age: approx. 66 years; males: 54%; associated diabetes: 58%; chronic kidney disease: 12%	blood glucose on admission: ≤100 mg/dL	6165	in-hospital: OR: 1.39 (95% CI: 1.08–1.78) with diabetes on admission, in-hospital: OR: 0.74 (95% CI: 0.59–0.93)
Bagshaw et al. (2009) ²⁹	retrospective	Australia	majority of patients included in the study had severe sepsis/septic shock; mean age: approx. 65 years; males: 59%	blood glucose on admission: <72 mg/dL	66,184	in-hospital: OR: 1.60 (95% CI: 1.40–1.80)
Liang and Ty (2018) ³⁰	retrospective	USA	patients included in the study had severe sepsis and/or septic shock; age >18 years; patients with DKA or hyperosmolar hyperglycemic state were excluded from the study	blood glucose on admission: <140 mg/dL	150	in-hospital: OR: 0.65 (95% CI: 0.29–1.46)
Shahab et al. (2011) ³¹	retrospective	no data provided	patients included in the study had severe sepsis and/or septic shock; patients with DKA and/or hyperosmolar nonketotic coma were excluded from the study	blood glucose on admission: <150 mg/dL	115	in-hospital: OR: 1.08 (95% CI: 0.48–2.45)
Tiruvoipati et al. (2013) ³²	retrospective	Australia	patients included in the study had severe sepsis and/or septic shock; mean age: 67 years; males: 50%; mean APACHE III score: 75; 16% with associated chronic renal failure and 20% with diabetes mellitus	blood glucose on admission: ≤124 mg/dL	297	in-hospital: OR: 1.20 (95% CI: 0.64–2.23)

APACHE II – Acute Physiology and Chronic Health Evaluation II; HIV – human immunodeficiency virus; DKA – diabetic ketoacidosis; OR – odds ratio; 95% CI – 95% confidence interval; BMI – body mass index.

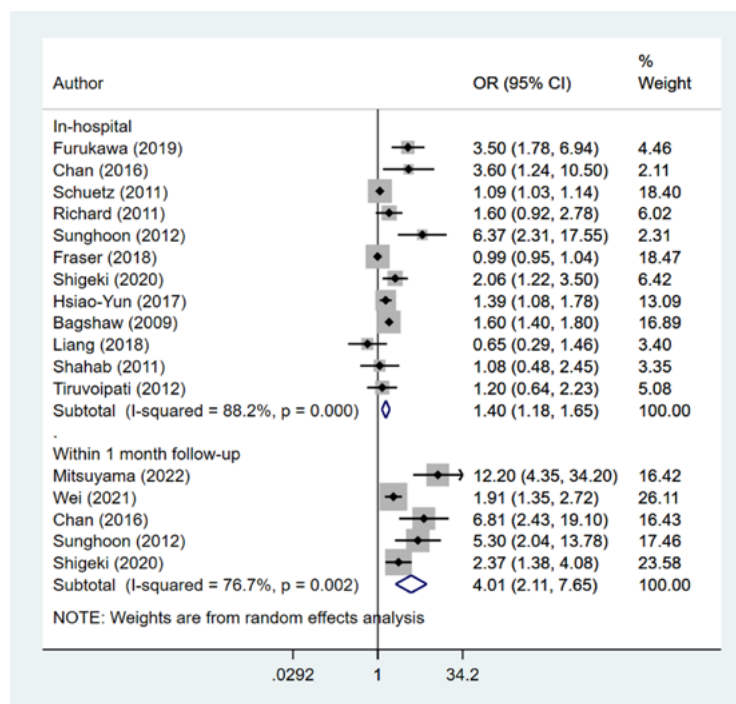


Fig. 2. Mortality risk in patients with sepsis or severe sepsis/septic shock and associated hypoglycemia, compared to those with euglycemia at the time of admission

OR – odds ratio; 95% CI – 95% confidence interval.

in the included studies. Supplementary Tables 2 and 3 summarize the findings of the quality assessment of the 14 included studies. All studies were of moderate to good quality.

Hypoglycemia and mortality risk

The pooled findings suggested an increased risk of in-hospital mortality (OR = 1.40, 95% CI: 1.18–1.65, $I^2 = 88.2\%$, $n = 12$, z -statistic = 4.25, $p = 0.0001$) and mortality within 1 month of hospital discharge (OR = 4.01, 95% CI: 2.11–7.65, $I^2 = 76.7\%$, $n = 5$, z -statistic = 4.21, $p = 0.0001$) among patients with hypoglycemia compared to patients with euglycemia (Fig. 2). There was no evidence of publication bias ($p > 0.05$) for mortality outcomes at either timepoint (Supplementary Table 3).

Analysis based on the presence of sepsis or severe sepsis/septic shock

In patients with sepsis, hypoglycemia was not significantly correlated with a higher risk of in-hospital mortality (OR = 1.15, 95% CI: 1.00–1.32, $I^2 = 88.1\%$, $n = 4$, z -statistic = 1.99, $p = 0.05$) or with an increased risk for mortality within 1 month of follow-up (OR = 4.52, 95% CI: 0.74–27.7, $I^2 = 91.0\%$, $n = 2$, z -statistic = 1.64, $p = 0.10$), compared to euglycemic patients (Fig. 3). In patients with severe sepsis and/or septic shock, hypoglycemia was associated with a significantly higher risk of in-hospital mortality (OR = 1.64, 95% CI: 1.20–2.25, $I^2 = 58.1\%$, $n = 8$, z -statistic = 3.06, $p = 0.002$) and mortality within 1 month of follow-up (OR = 3.94, 95% CI: 1.96–7.89, $I^2 = 53.2\%$, $n = 3$, z -statistic = 3.88, $p = 0.0001$) (Fig. 4), with no evident publication bias ($p > 0.05$) (Supplementary Table 3).

Analysis of patients with diabetes at the time of admission

In patients who were diabetic at the time of admission, hypoglycemia did not correlate with increased in-hospital mortality risk (OR = 1.45, 95% CI: 0.79–2.66, $I^2 = 92.3\%$, $n = 4$, z -statistic = 1.19, $p = 0.23$) or mortality within 1 month of follow-up (OR = 1.34, 95% CI: 0.84–2.16, $I^2 = 0.0\%$, $n = 2$, z -statistic = 1.16, $p = 0.25$) (Fig. 5), with no evident publication bias ($p > 0.05$) for any of these 2 outcomes (Supplementary Table 3).

Discussion

The findings of the current review showed a higher mortality risk in patients with hypoglycemia, and this risk was predominant in patients with severe sepsis and/or septic shock. However, hypoglycemia was not associated with a higher mortality risk in patients with pre-existing diabetes. These findings are consistent with a previous review by Wang et al., where a similar association of hypoglycemia with mortality was noted (OR = 1.68).¹² Similarly, the association between mortality and hyperglycemia was stronger in patients with severe sepsis/septic shock (OR = 1.98).

Previous studies showed that patients with severe infection/sepsis usually have elevated blood glucose levels (stress hyperglycemia) due to the enhanced release of glucocorticoids, epinephrine and norepinephrine.^{33–35} These higher glucose levels may lead to an inflammatory state, endothelial cell dysfunction, oxidative stress, and immunosuppression.^{34–36} Studies have also noted an increased risk

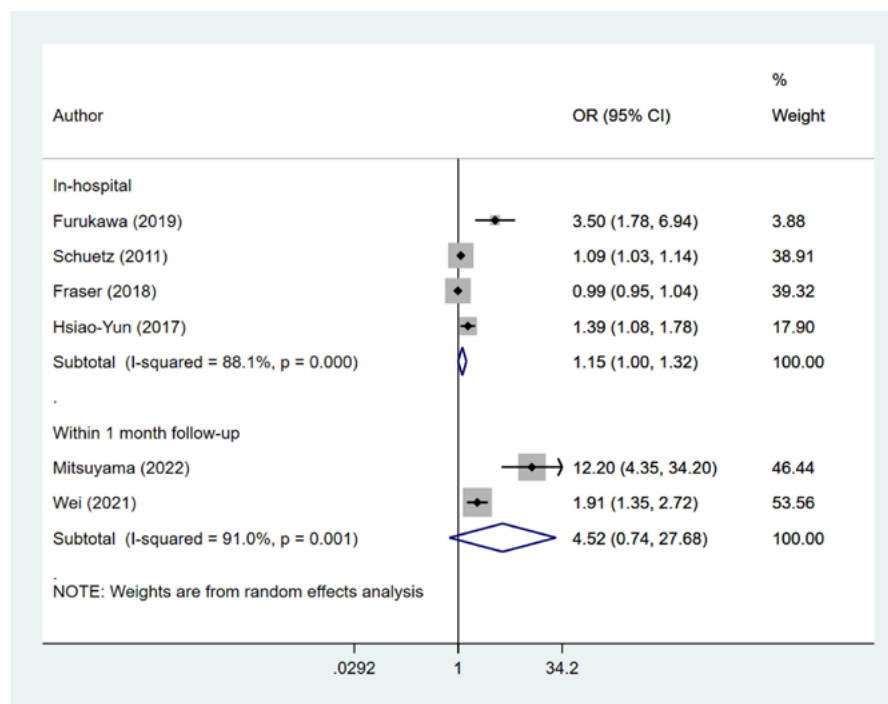


Fig. 3. Mortality risk in patients with sepsis and associated hypoglycemia, compared to those with euglycemia at the time of admission

OR – odds ratio; 95% CI – 95% confidence interval.

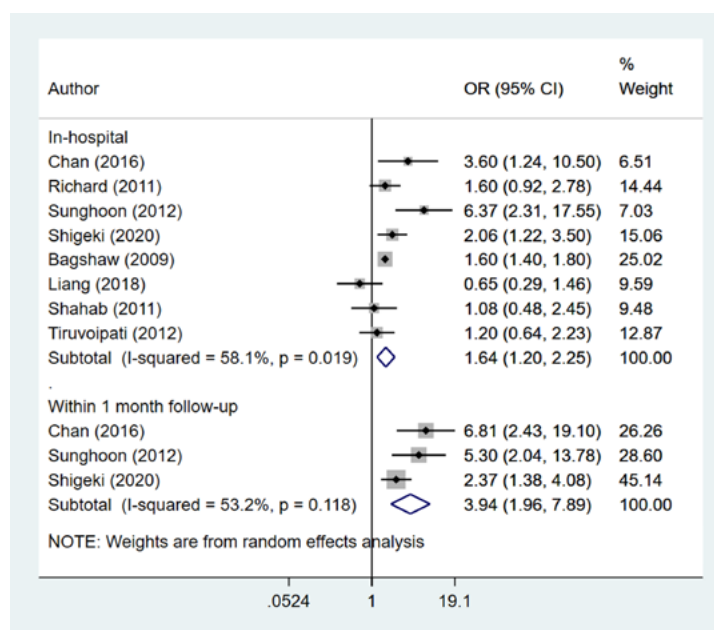


Fig. 4. Mortality risk in patients with severe sepsis/septic shock and associated hypoglycemia, compared to those with euglycemia at the time of admission

OR – odds ratio; 95% CI – 95% confidence interval.

of mortality in patients with hyperglycemia and associated sepsis.^{6,7,37} However, there is also a possible risk of hypoglycemia due to either strict glycemic control strategies or the upregulation of cytokines that increase the utilization of peripheral blood glucose and downregulate gluconeogenesis.^{5,8–11} Additionally, the metabolic rate in patients with sepsis is higher, which may lead to excessive glucose consumption and glycogen reserve depletion.^{5,38,39} Another vital pathway through which hypoglycemia may occur in patients with sepsis is the inhibition of the prosecretory effects of adrenocorticotrophic hormone (ACTH) on adrenal cortisol production,^{39,40} leading to corticosteroid insufficiency.^{39,40}

Hypoglycemia may lead to the activation of sympathoadrenal mechanisms, abnormal cardiac repolarization, dysregulation of hemostatic mechanisms such as accelerated thrombogenesis and vasoconstriction, and elevated levels of inflammatory cytokines.⁴¹ All of these processes could worsen the outcome for patients with sepsis. The higher mortality risk, especially in patients with severe sepsis/septic shock, could be due to increased glycemic variability, as documented in some studies.^{42,43} The current meta-analysis found no significant association between hypoglycemia and mortality among diabetic patients, which is contrary to the findings of a meta-analysis by Wang et al. showing

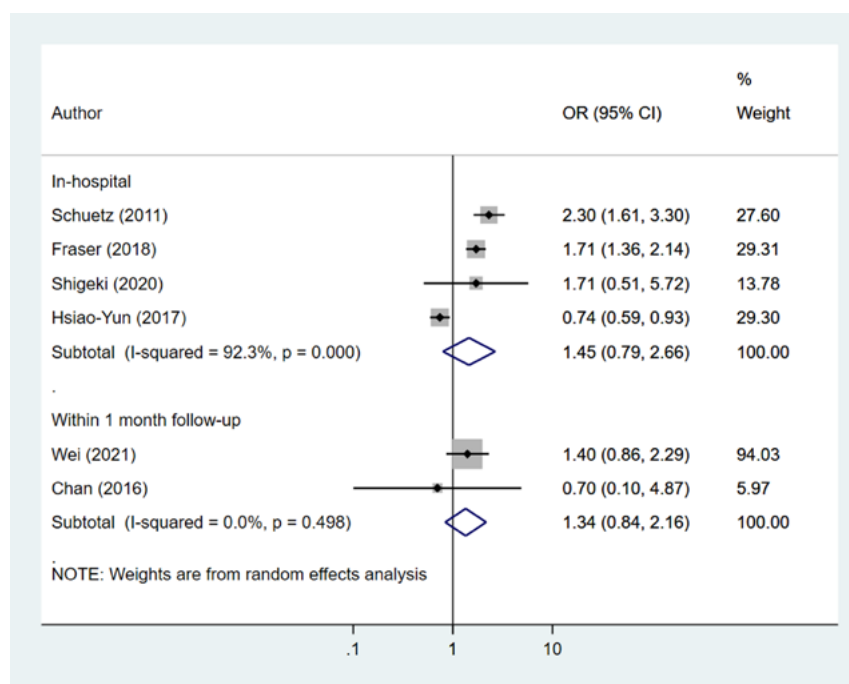


Fig. 5. Mortality risk in diabetic subjects with associated hypoglycemia, compared to those with euglycemia on admission

OR – odds ratio; 95% CI – 95% confidence interval.

that hypoglycemia (defined as a blood glucose level of <145 mg/dL) correlated with increased mortality risk in patients with diabetes and associated sepsis.¹³ The authors suggested that this could be due to the relative intolerance in diabetic subjects to hypoglycemic episodes.^{12,23} The noted difference in the findings could be partially explained by the difference in the cutoff level defining hypoglycemia. Most studies included in the current meta-analysis adopted a comparatively lower cutoff level. These contrasting findings underscore the complex nature of the interactions between blood glucose levels and adverse clinical outcomes among patients with pre-existing diabetes and call for more research on this issue.

Limitations

Our study had some limitations. First, all included studies were observational, meaning that a causal relationship could not be established between hypoglycemia and mortality. Furthermore, there is a possibility that crucial variables and confounders were not adjusted for, or data on these variables were not collected. Second, there was a high heterogeneity in the findings, which could be due to the differences in methodologies and variation in the participant characteristics. The included studies used various blood sugar cutoff values for hypoglycemia, and there were differences in the operational definitions adopted for sepsis. We conducted our analysis using a random effects model to partly address the high heterogeneity.

Conclusions

Our findings indicate that hypoglycemia might correlate with increased mortality risk in sepsis and/or severe sepsis/septic shock patients. Therefore, monitoring of blood glucose in these patients may be required. We noted that different blood sugar cutoff values were used to label hypoglycemia for both euglycemic and diabetic patients. It is important to develop harmonized diagnostic criteria that are reliable and practical enough to be implemented routinely in order to avoid such heterogeneity. Such criteria need to be updated when new evidence becomes available, with new developments necessitating changes in the criteria for sepsis informed by findings from prospectively conducted studies. More research is needed to clarify the link between low blood glucose levels and the mortality risk in sepsis patients with diabetes.

Supplementary data

The supplementary materials are available at <https://doi.org/10.5281/zenodo.7967501>. The package contains the following files:

Supplementary Table 1. Authors' judgements about study quality using the adapted Newcastle-Ottawa risk of bias assessment tool.

Supplementary Table 2. Authors' judgements about study quality using the adapted Newcastle-Ottawa risk of bias assessment tool.

Supplementary Table 3. Results of Egger's test for the outcomes.

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