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ORIGINAL ARTICLE

Association between comorbid diabetes mellitus and mortality of patients with sepsis: A meta-analysis

Qingxia Du[1] · Xuelian Yin[1] · Hong Zhao[1] · Jiebin Li[1] · Jing Zhang[1]

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Abstract

Objective Although diabetes patients have a higher propensity to develop infection and sepsis, it is still controversial whether the mortality of sepsis patients is affected by diabetes (DM). We conducted a systematic review and meta-analysis to determine the relationship between diabetes and mortality in patients with sepsis.

Methods We comprehensively searched for relevant studies in PubMed, MEDLINE, EMBASE, and the Cochrane Library database from January 2000 to December 2021. Two reviewers independently selected studies, extracted data, and assessed quality. We used random-effects modeling to calculate the summary of risk ratios and confidence interval (CI) of mortality. Study quality was assessed using NOS score, and publication bias was assessed using Egger's statistic.

Results A total of 23 studies were included in the analyses, comprising 14,521,791 septic patients, including 2,866,429 DM patients. We stratified the in-hospital mortality data by duration for 30 days, 90 day, and mixed days. Meta-analysis of 23 studies showed slightly increased overall mortality among the patients with DM (RR, 1.12; 95% CI 1.00 – 1.25; I^2 96.1%; $p = 0.000$) by pooling of all data in the random effects model. Subgroup analysis did not demonstrate a statistically significant increase either in 30-day mortality (RR, 1.07; 95% CI 0.97–1.18; I^2 0.0%; p 0.963), 90-day mortality (RR, 1.00; 95% CI 0.95–1.07; I^2 0.0%; $p = 0.735$), or mixed-day mortality (RR, 1.16; CI 0.98–1.37; I^2 97.9%; $p = 0.000$). The quality of the included studies was good, and the median NOS score was 7.1 (range, 6–9).

Conclusions This systematic review and meta-analysis of studies suggests that DM does slightly increase sepsis overall mortality, however with statistical heterogeneity. Due to the limitations of the analysis, more well-designed clinical studies are still necessary in future.

Keywords Meta-analysis · Diabetes · Sepsis · Outcome · Mortality

Abbreviations

CI	Confidence interval
RR	Relative risk
DM	Diabetes mellitus

Introduction

Sepsis is a life-threatening organ dysfunction caused by over activation of inflammatory reaction and coagulation dysfunction response to severe systemic infection. It is a major medical problem worldwide and accounts for 20% of the global death [1]. Diabetes mellitus (DM) is a common and increasing comorbidity in sepsis patients. The incidence rate of DM is rising and has become a major public health problem worldwide [2], especially in low and middle-income countries. Sepsis is closely related to DM; in fact, Sepsis 2.0 used hyperglycemia (blood glucose > 7.7 mmol/L) in patients without a previous history of diabetes as one of the diagnostic criteria for sepsis, which shows the close relationship between sepsis and DM.

It is clear that DM patients are more prone to infection and sepsis, but the impact of diabetes on the outcome of sepsis is still uncertain. Two meta-analyses about this topic showed that presence of diabetes does not increase the risk of mortality in patients with sepsis [3, 4]. Neither of these two meta-analyses included Zoppini's study [5], a large-size observational study, which proved that diabetic patients had a twofold increased mortality for sepsis compared to non-diabetic patients. Due to the increase of relevant research in recent years, we searched studies January 2000 to December 2021 and conducted a systematic review and meta-analysis on this topic to determine the association between preexisting DM and mortality in humans with sepsis.

✉ Jing Zhang
zhangjing68519@sohu.com

[1] Department of Emergency, Beijing Tongren Hospital of Capital Medical University, Beijing 100730, China

Materials and methods

This study protocol was implemented following the Meta-analysis of Preferred Reporting Items for Systematic Reviews (PRISMA) [6].

Data sources and search strategy

We searched PubMed, MEDLINE, EMBASE, and the Cochrane Library database from January 2000 to December 2021. We use medical heading terms and cross search the following three categories for term search: (1) diabetes ("diabetes" or "diabetic"); (2) disease ("sepsis," "septic shock," "septic," or "septicemia"); and (3) others related ("outcome," "intensive care unit," "ICU," "critically ill patients," "death", "mortality," or "prognosis"). We limited the types of studies to "human" and "English" languages. Only studies that reported a comparison between diabetes patients and non-diabetes patients, whose ages were over 18 years of age, were included. All retrieved studies and recent bibliographies were screened to further expand the search scope.

Inclusion criteria

Two researchers independently read the titles and abstracts to determine eligible study. Studies were included if (1) the study population came from a well-established retrospective, prospective cohort, or case–control study, including a group of diabetic patients and a group of non-diabetic patients with sepsis; (2) the 28-day mortality, 90-day mortality, or hospitalization mortality was clearly reported on both group or provided sufficient data to calculate these parameters.

Data extraction and methodological quality

Two researchers (XY and QD) independently collected data from the included studies into a data standardized collection form. The following elements were extracted from the included studies: first author, year of publication, study design, study country, severity of sepsis, and number of diabetes patients and non-diabetic patients. The primary outcome was 28-, 30-, or 90-day mortality and mixed-day mortality. We equated 28-day mortality with 30-day mortality. The day of mortality not specified was assigned to mixed-day mortality. Newcastle–Ottawa Scale tool (available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) was used to evaluate the quality of the included studies.

Data synthesis and statistical methods

Stata Software (version 12.0 Stata Corporation, College Station, TX, USA) was used for statistical analysis. The dichotomous data of relative risk (RR) with 95% confidence intervals (CI) for in-hospital mortality in each study were pooled using the random-effects model; results were expressed by Forest plots.

In order to evaluate the effect of DM on the mortality of sepsis patients, we performed a subgroup analysis to evaluate the influence of DM. The first subgroup was sixteen studies that reported the day of mortality not specified. The second subgroup was studies that reported 30-day mortality, and the third subgroup was studies that reported 90-day mortality. Publication bias was assess by Egger's test [7]. A RR > 1 suggested that DM was associated with an increased risk of mortality.

We proposed to use Cochran's Q test and reported as I^2 to assess and calculate statistical heterogeneity between studies. Sensitivity analysis was used to determine the robustness of the data and the impact of individual research on the summary effect. In addition, p value < 0.05 was considered statistically significant.

Results

Search results

According to the initial search strategy, 5856 unique records were yielded, 1908 duplicates were removed, and 3796 records were eliminated by screening titles and abstracts. Full-text assessment was conducted in the last 156 articles. Of these articles, 23 studies satisfied the inclusion criteria. The study selection process was shown in Fig. 1.

Characteristics of included studies

All the studies were published from 2000 to 2021. There were a total of 14,521,791 septic patients, including 2,866,429 DM patients and 11,646,162 non-DM patients, ages ranging from 45 to 80 years and mostly older than 60 in these studies. Except for 5 prospective studies, the others are retrospective studies. The effect estimations of relative ratios (RRs) of mortality for diabetic patients were provided in each study. What should be mentioned is that four cohorts were included in Russell's study [8]. Four studies included six cohorts provided relative ratios (RRs) of 30-day mortality for diabetic patients. Four studies provided relative ratios (RRs) of 90-day mortality for diabetic patients. Of these studies, 8 studies enrolled patients with severe sepsis, septic shock patients, or ICU septic patients [8–15], 2 contained non-ICU patients [16, 17], and the left 14 studies enrolled sepsis patients with all stages. The sources of infection in the included studies were not limited to any specific systems or organs. The characteristics of each included study were presented in Table 1.

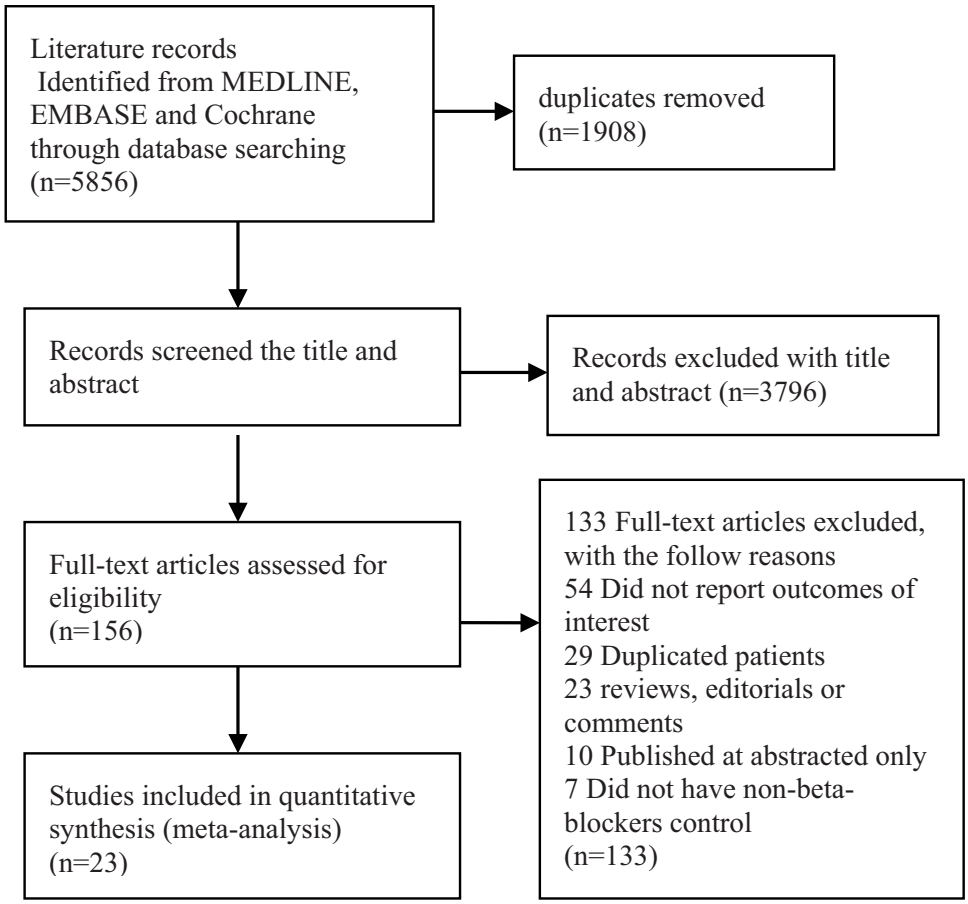

Fig. 1 Study flow diagram in this meta-analysis

The quality of each included study, assessed by the Newcastle–Ottawa Scale tool, was good. The NOSs was displayed in Table S1 (median score, 7.1; range from 6 to 9).

Quantitative data synthesis

The mortality RR was estimated using a random-effect model meta-analysis, and heterogeneity was evaluated by I^2. Meta-analysis of 23 studies showed that DM did slightly increase sepsis overall mortality (RR, 1.12; 95% CI 1.00–1.25; I^2 96.1%; $p = 0.000$) according to the random effects model, however with large heterogeneity. Subgroup analysis did not demonstrate a statistically significant increase either in 30-day mortality (RR, 1.07; 95% CI 0.97–1.18; I^2 0.0%; $p = 0.963$), 90-day mortality (RR, 1.00; 95% CI 0.95–1.07; I^2 0.0%; $p = 0.735$), or mixed-day mortality (RR, 1.16; 95% CI 0.98–1.37; I^2 97.9%; $p = 0.000$).

Inter-study variability

The pooled relative risk of DM related overall mortality in patients with sepsis was 1.12 (95% CI 1.00–1.25; $I^2 = 96.1\%$; $p = 0.000$). In subgroup analysis, no evidence of heterogeneity was observed in the analysis of 30-day mortality group ($I^2 = 0.0\%$; $p = 0.963$) and 90-day mortality group ($I^2 = 0.0\%$; $p = 0.735$), but a high degree of heterogeneity was observed among mixed-day mortality subgroup ($I^2 = 97.9\%$; $p = 0.000$) and among all the included studies (Fig. 2).

The leave-one-out sensitivity analyses by removing one study per time were used to test the replicability of the results. Two studies [14, 17] were identified as the source of heterogeneity (Fig. 3), and after the exclusion of these two studies, de Miguel-Yanes' [17] ($I^2 = 96.7\%$; $p = 0.000$) or Shah's study [14] ($I^2 = 96.0\%$; $p = 0.000$), only a little heterogeneity was removed in the mixed-day mortality subgroup. The omission of de Miguel-Yanes' [17] or Shah's study [14] seems to be not drastically changed in this analysis, and the RRs were in the range from 1.13 (95% CI 0.99–1.29) to 1.08 (95% CI 0.98–1.18). All the results were of marginal significance (Fig. 4).

Publication bias

We used Egger's regression asymmetry test to access the publication bias of included literatures, and no evidence of publication bias could be found ($t = 1.64$, $p = 0.113$) (Fig. 4).

Table 1 Characteristics of clinical studies investigating the association between diabetes and mortality for sepsis included in the meta-analysis

Authors	Year	Country	Study design	Participant	Mortality diabetes vs. no diabetes
Zohar [18]	2021	Israel	Retrospective cohort	Patients with community-onset sepsis 1527 (DM: 469; non-DM: 10,58)	Mort1ality (in-hospital): RR 1.21 (0.80–1.71) Mortality at 30 days: RR 1.10 (0.79–1.54) Mortality at 90 days: RR 1.13 (0.86–1.49)
Akinosoglou [19]	2021	Greece	Retrospective cohort study	The Hellenic Sepsis Study Group Registry non-ICU patients 812 (406 in each of the DM and non-DM groups)	Post-discharge: RR 1.04 (0.75–1.44)
Lin et al. [13]	2021	China	Retrospective analysis data	China mean age of 66.7 years; 51% males; Majority with bloodstream (44%) and urinary tract infection (21%) 5774 (2887 in each of the DM and non-DM groups)	Mortality (in-hospital): RR 0.73 (0.62– 0.87) Mortality at 28 days post-discharge: RR 0.86 (0.77–0.97)
Kushimoto et al. [20]	2020	Japan	Retrospective analysis of prospectively collective data	Mean age of 73 years; 60% males; majority with pulmonary (31%) and gastrointestinal infection (26%); 63% with septic shock 1127 (DM: 261; non-DM: 866)	In-hospital mortality: RR 1.32 (0.96– 1.81)
Russell [21]	2019	Canada		UK Biobank Cohort 1 Single Centre Cohort 2 Inflammation Mechanism Cohort 3 Lipid Mechanism Cohort 4 484,857 (DM: 25,430; non-DM: 459,407) 727 (DM: 37; non-DM: 690) 779 (DM: 165; non-DM: 614) 200 (DM: 9; non-DM:15)	Mortality at 28-days OR 1.18 (0.91– 1.54, $p=0.21$) Mortality at 28-days OR 1.35 (0.63–2.92, $p=0.452$) Mortality at 28-days OR 1.09 (0.76–1.55, $p=0.651$) Mortality at 90-days OR 1.59 (0.70–3.65, $p=0.28$)
Sathananthan [22]	2019	USA	Analysis of retrospective cohort data	Majority with age > 60 years; > 55% males; majority with severe sepsis (> 80%); 1698 (DM: 508; non-DM: 1190)	Mortality at 30 days *p*: RR 1.00 (0.81– 1.25)
Zoppini [5]	2018	Italy	Retrospective cohort study on a regional electronic archive	185,341 diabetic individuals	Increased risk of death from infection-related causes in diabetic people (especially in female and people aged between 30 and 64 years): RR for septicemia 1.91 (1.76–2.06)
Van Vught [16]	2017	Netherlands	Retrospective large national database review	41,492 ICU septic patients (8085 with diabetes)	Mortality (in-hospital): RR 1.14 (1.07–1.21) Mortality at 90-days post-discharge: RR 1.09 (0.72–1.66)
Van Vught [23]	2016	Netherlands	Prospective observational study	1104 ICU septic patients (241 with diabetes)	No association between diabetes and 90-day mortality: HR 0.90 (0.69–1.15) after correction for BMI, age, gender, hypertension, cardiovascular, and renal insufficiency HR 1.02 (0.81–1.29) after correction for APACHE IV score

Table 1 (continued)

Authors	Year	Country	Study design	Participant	Mortality diabetes vs. no diabetes
Venot [24]	2015	France	Case–control study based on a multicenter database	10,911 patients (3728 with severe sepsis or septic shock; among them, 451 with diabetes)	No difference in mortality between diabetic and non-diabetic septic patients (19.8% vs. 15% in the matched case–control analysis; $p=0.08$) Mortality (in-hospital): RR 1.32 (91.00–1.74)
De Miguel-Yanes [8]	2015	Spain	Retrospective cohort study	Mean age of 72 years; > 55% males; majority one or more organ failure 217,280 All sepsis (DM: 50,611; non-DM: 166,669)	In-hospital mortality 0.97 (0.96–0.98)
Schuetz [11]	2012	USA	Prospective cohorts study	Mean age of 60 years; around 48% were females; majority with pneumonia (22%) or skin/soft tissue infection (27%) or urinary tract infections (11%) 1849 (DM: 539; non-DM: 1310)	In-hospital mortality 0.95 (0.48–1.90)
Chang C et al. [25]	2012	Taiwan	Nationwide population-based retrospective cohort study	Mean age of 67 years; > 50% males; majority with pneumonia (43%) or gastrointestinal infection (34%) or urinary tract infections (26%); majority with severe sepsis/septic shock 16,497 (DM: 4573; non-DM: 11,924)	90-day mortality (in-hospital): RR 1.00 (0.94–1.07)
Schuetz [9]	2011	USA	Prospective cohorts study	Patients admitted to the hospital from the ED with suspected infection; mean age of 59 years; around 49% were males; around one-third (37%) had severe sepsis/septic shock 7754 (DM: 1844; non-DM: 5910)	0.85 (0.71–1.01)
Yang et al. [10]	2011	Singapore	Retrospective large database review	Mean age of 60 years; around 50% were males; majority with respiratory, urinary tract or gastrointestinal infections 9221 (DM: 2943; non-DM: 6278)	Mortality (in-hospital): RR 0.96 (0.88–1.05)
Stegenga [26]	2010	Multicentric study	Retrospective analysis of a previously published RCT	ICU patients with septic shock (188 with diabetes) 830 (DM: 188; non-DM: 642)	Mortality at 28 days: RR 1.03 (0.81–1.31) Mortality at 90 days: RR 1.00 (0.71–1.41)
Vincent [27]	2010	Belgium	Prospective study	3147 ICU septic patients (226 with insulin-treated diabetes) 3147	No difference in ICU and hospital mortality between diabetic and non-diabetic septic patients
Chen Y [28]	2009			121 Severe sepsis and septic shock, 34 with diabetes	Hospital mortality 0.97 (0.59–1.59)
Esper [14]	2009		Retrospective large national registry review	12,500,459 septic patients (2,070,459 with diabetes)	Lower hospital mortality in diabetic vs. non-diabetic patients (18.5% vs. 20.6%, $p<0.05$) Mortality 0.90 (0.81–1.0)

Table 1 (continued)

Authors	Year	Country	Study design	Participant	Mortality diabetes vs. no diabetes
Moutzouri [29]	2008	Greece	A prospective cohort study	64 severe sepsis or septic shock; mean age of around 60 years; around 50% were females; majority with urinary tract infections; most had severe sepsis/septic shock 64 (DM: 24; non-DM: 40)	In-hospital mortality1.30 (0.56–3.03)
Shah [12]	2003	Canada	Retrospective cohort study on population-based administrative data	513,749 diabetic individuals (matched to an equal number of non-diabetics)	Higher global infection-related mortality in diabetic patients (including home and hospital) risk ratio up to 1.92 (1.79–2.05) No significant difference in term of infection-related hospital mortality risk ratio up to 0.94 (0.87–1.01)
Bertoniet [30]	2001	USA	Retrospective cohort study on a national registry	9208 individuals (533 with diabetes)	Higher infection-related mortality in diabetic patients with cardiovascular disease RR 3.0 (1.8–5.0)
Moss [31]	2000	USA	A prospective cohort study	113 septic shock	0.67 (0.36–1.23)

Discussion

DM is the main comorbidity of sepsis because of its high prevalence; about 10–30% of septic patients have diabetes. However, the effect of diabetes on outcome of sepsis is not completely clear. There are two meta-analyses about this topic: one showed that the mortality rate of septic patients with DM was slightly lower than that of non-diabetic patients [30]; the other (included four loosely defined sepsis studies) demonstrated that there were no significant differences in the risk of mortality [6]. In a recent meta-analysis, it was reported that DM was associated with mortality, severe COVID-19, ARDS, and disease progression in patients with COVID-19 [30].

In these 23 included studies, the results by Zoppini et al. [7] and Bertoni [18] found increased mortality rate related to sepsis in diabetic compared to the general population, whereas others [9–13, 16, 19–29] failed to demonstrate such association, and four studies [8, 14, 17, 31] reported decreased mortality rates among DM patients during sepsis. The following factors have been proposed to explain this heterogeneity in mortality: different study populations (including different the duration, severity of diabetes, lack of stratification into type 1 and type 2 diabetes, different adjustments for comorbidities, sepsis etiology, stages, and severity) [32], anti-diabetic medication to control blood glucose, degree of glycemic control of during hospital, medical treatment, and nursing. The main finding of our meta-analysis is that pre-existing DM slightly significantly increased overall mortality in sepsis patients, but not 30-day mortality, 90-day, or mixed-day mortality in sepsis patients. From this meta-analysis, it is certain that presence of DM is not associated with reduced risk of mortality in sepsis patients.

To clarify the risk of DM in sepsis mortality, we need to clarify blood glucose level control and the risk of sepsis mortality. As an important cellular energy, blood glucose must be controlled at a specific level and kept relatively stable. Whether it is low or high, it is not conducive to cell survival. It has been demonstrated that hyperglycemia, irrespective of the DM status, is a major independent risk factor for in-hospital sepsis mortality [33], while hypoglycemia is associated with an increased risk of mortality too [15]. Dose–response analysis showed that the effect of blood glucose on mortality may differ in patients with DM versus without [34]. Critically ill patients undergoing intensive glucose control showed significantly reduced all-cause mortality, length of ICU stay, and incidence of acquired infection and sepsis compared to the same parameters in patients treated with the usual care strategy, while the intensive glucose control strategy was associated with higher occurrence of severe hypoglycemic events [35]. Septic patients with higher acute glycemic variability had significantly increased mortality risk compared to those with lower acute glycemic variability; higher acute glycemic variability may

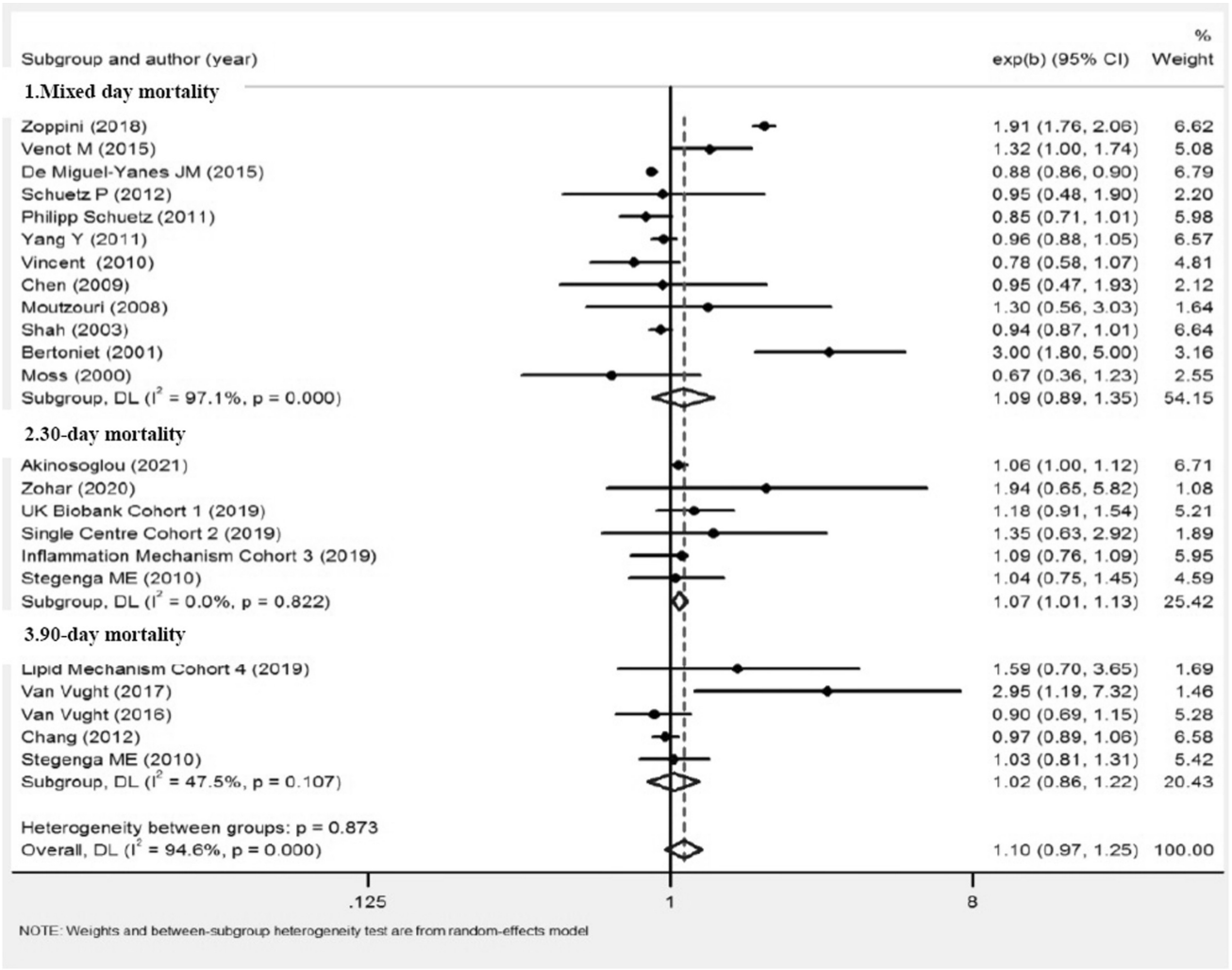

Fig. 2 Meta-analysis of the overall pooled odds ratios (ORs) of studies investigating the mortality of patients with diabetes mellitus in sepsis. Forest plot showing lightly increased risk of sepsis-related overall mortality according to the random effects model

be a predictor of mortality risk in patients with sepsis [36]. From these studies, we can draw conclusion that DM should impair the outcome of patients with sepsis; at least, it will not improve the prognosis of sepsis.

In this meta-analysis, the included studies showed a low-risk publication bias. Therefore, the heterogeneity was not considered statistically. The heterogeneity may be derived from methodological and clinical causes, such as the sample sizes, ethnically diverse, anti-diabetic medications, different DM type, different glucose control level, different adjustments for comorbidities, sepsis etiology, and disease severity. The relation between DM and risk mortality is weak across all three subgroups. Due to the weak nature of the association between DM and mortality, drawing conclusions about the practical significance of this relationship should be treated with caution.

This meta-analysis has several strengths. First, the risk publication bias assessment by using Egger's test showed a low risk of bias among the included studies. All the studies fulfilled the diagnostic criterion proposed by sepsis, and most of the included studies were of high NOS score, which demonstrated the relatively high quality of the included studies. Second, we pooled data for the primary outcome by the random effects model, which allows for more accurate representation of data that arise from complicated multilevel study designs. Finally, the outcome of the sensitivity analysis showed that this result slightly varies.

Study limitations

There are also several limitations in our study which are similar to other meta-analysis. First, there is a marked heterogeneity noted in study design, size, duration, the mean ages, severity, and DM type of the patients among the included studies.

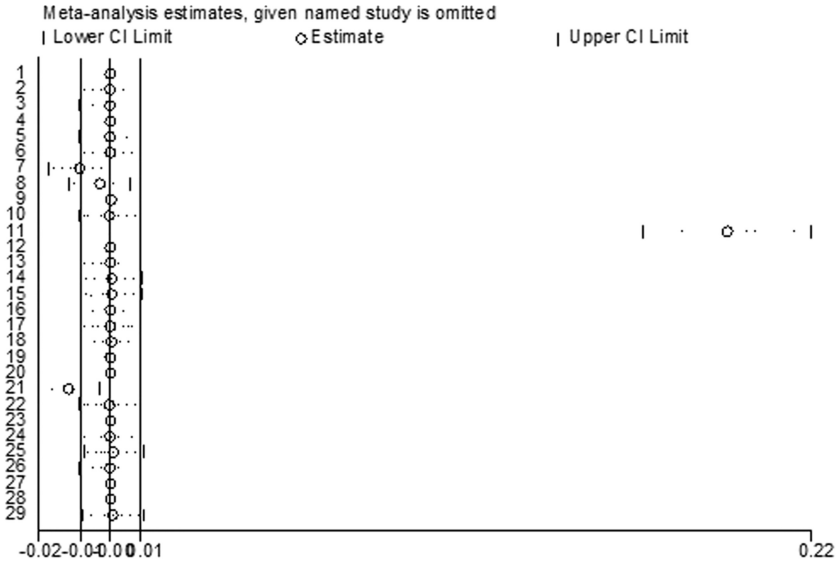

Fig. 3 Sensitivity analysis of the meta-analysis of the association between diabetes mellitus and mortality risk in sepsis patients. The meta-analysis is dominated by De Miguel-Yanes' study and Shah's study

Furthermore, most used a retrospective design, and the effect estimate was adjusted for different level confounders. For example, the diagnosis of diabetes in most of the studies depended on the medical history record and did not provide severity, duration, and anti-diabetic medication of diabetics. These heterogeneity might have an effect on the outcome. Second, our analysis only includes the articles published in full text and in English, so the publication bias is unavoidable. Finally, all these limitations of the available data make it hard to reach definitive conclusions of the effect of DM on mortality of sepsis.

Conclusions

Despite diabetes does not increase risk of 28-day mortality or 90-day mortality, it slightly does increase risk of sepsis-related overall mortality. Diabetes is not associated with beneficial survival outcomes in patients with sepsis. Considering the limitations of the meta-analysis, more high-quality original designed studies are required to confirm the association. Future research should aim to gain a deeper understanding of the relationship between DM and mortality using more reliable measures and accurate prospective research to elicit the truth.

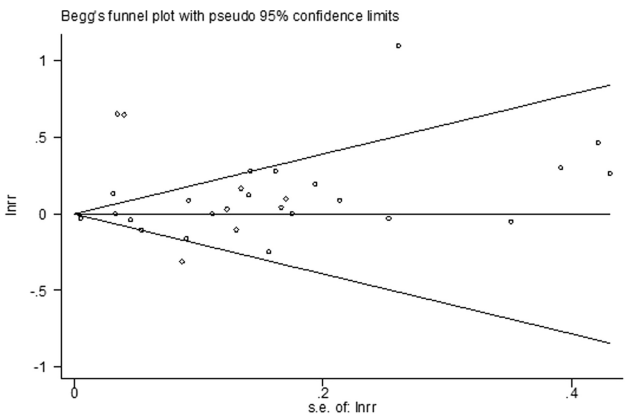

Fig. 4 Egger's funnel plots test with pseudo 95% confidence limits for studies reporting diabetes mellitus and mortality in sepsis patients. There is no evidence of bias in the test or the formal plot ($t=1.64$, $p=0.113$)

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13410-023-01225-0.

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Data Availability The data that support the findings of this study are openly available within the article or its supplementary materials.

Declaration

Conflict of interest The authors declare no conflict of interest related to this work.

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