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Effect of liberal glucose control on critically ill patients: a systematic review and meta-analysis

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Abstract

Background Most current guideline statements support some level of unrestricted glycemic management in critically ill adult patients. Nevertheless, the effectiveness of liberal glucose control is currently not well-supported by evidence. Therefore, our objective is to investigate the influence of liberal glucose control (> 180 mg/dl) on critically ill patients in the intensive care unit (ICU).

Methods Until November 23, 2023, English language literature was thoroughly and systematically searched through multiple databases, including PubMed, Embase, Cochrane Library, and Web of Science. Our primary endpoints of interest were the occurrence of hypoglycemia, mortality in the ICU, and mortality during hospitalization. In addition, our secondary outcomes comprised of 90-day mortality, bloodstream infections, the proportion of patients necessitating renal replacement therapy (RRT), the length of time under mechanical ventilation, duration of stay in the ICU, and length of the overall hospitalization. Weighted mean difference (WMD) and relative risk (RR) were respectively computed as overall effect size for continuous and dichotomous data and reported with their 95% confidence intervals (95% CI).

Results A total of 9 studies were incorporated, which included 14,878 patients in the ICU. Compared with other blood glucose target control groups, liberal glucose control significantly reduced the incidence of hypoglycemia (RR = 0.41; 95% CI:0.25 to 0.69; $P = 0.001$), but increased ICU mortality (RR = 1.23; 95% CI:1.03 to 1.48; $P = 0.023$), in-hospital mortality risk (RR = 1.18; 95% CI:1.03 to 1.35; $P = 0.020$), and the risk of requiring RRT (RR = 1.26; 95% CI:1.11 to1.42; $P < 0.001$).

Conclusion Liberal glucose control can reduce the risk of hypoglycemia but increases the risks of ICU mortality, in-hospital mortality, and the requirement for RRT. To confirm the outcomes further, large-scale, high-quality clinical trials are necessary.

Keywords Liberal glucose control, Blood glucose, Hypoglycemia, Mortality, Meta-analysis

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Introduction

Diabetes imposes a significant economic burden on the global economy, with costs expected to increase from 1.8% of global GDP in 2015 to 2.2% by 2030 [1]. Among admitted patients, the prevalence of hyperglycemia and diabetes is estimated to be between 38% and 40% [2]. It should be noted that in critically ill adults, hyperglycemia and diabetes can reach 70 to 80% [3, 4]. Previous research has demonstrated a positive correlation between hyperglycemia in critically ill adults and increased mortality rates [5–7]. Therefore, monitoring and controlling blood glucose levels is crucial for the prognosis of critically ill patients. The current management of hyperglycemia is primarily achieved through insulin therapy [8]. Although it has become the standard approach for hyperglycemia management in critically ill patients, the target blood glucose levels have been fluctuating since 2000, and poor blood glucose control in critically ill patients significantly increases both ICU and hospital stay times [9].

Preliminary evidence has indicated that stringent blood glucose control (ranging from 80 to 110 mg/dl) could decrease the occurrence and fatality rates of critically ill patients, while avoiding hypoglycemia-related complications [10, 11]. However, subsequent studies showed minimal clinical benefit in critically ill patients under strict blood glucose control, and a higher incidence of hypoglycemia and mortality [12, 13]. A recent meta-analysis revealed that strict blood glucose control was associated with reduced overall mortality, shortened length of ICU stay, and a lower incidence of sepsis and hospital-acquired infections. Nevertheless, it also increased the probability of severe hypoglycemic events [14]. Song et al. [15], in their meta-analysis of 12 RCTs, found that intensive blood glucose management (≤150 mg/dL)and routine blood glucose control had similar therapeutic effects on septic hyperglycemic patients. However, the strict blood glucose management group had a higher occurrence of hypoglycemia.

Due to stress response, cytokine levels, nutritional intake and activity levels, more personalized treatment approaches are recommended for critical patients with glucose abnormalities [16]. A multicenter, parallel-group, randomized clinical trial compared unrestricted glycemic management (ranging from 180 to 252 mg/dl) with conventional blood glucose control (ranging from 108 to 180 mg/dl) among type 2 diabetic adult patients who were hospitalized in the ICU for a minimum of three consecutive days. The investigation revealed that unrestricted glycemic management resulted in a lower frequency of hypoglycemia (5% vs. 18%). In addition, there was no significant difference in 90-day mortality rate between the strict blood glucose control group and the conventional glucose control group [17]. In a recent multicenter randomized parallel-group controlled clinical trial, 9230 ICU patients were arbitrarily allocated to either strict blood glucose control (ranging from 80 to 110 mg/dl) or unrestricted glycemic management (ranging from 180 to 215 mg/dl), which did not affect ICU length of stay or 90-day mortality [18]. However, a meta-analysis is currently lacking to demonstrate the true efficacy of liberal glucose control. Therefore, the main purpose of this meta-analysis is to scrutinize the consequences of unrestricted glycemic management on patients who are critically ill in the ICU, and to examine the efficiency and safety of this strategy.

Methods

This report was executed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19] and registered on the Prospero website for meta-analysis (registration number: CRD42023489410).

Search strategy

PubMed, Embase, Cochrane Library, and Web of Science databases were systematically retrieved to collect English studies published from the inception of each database up to November 23, 2023. We employed a hybrid of Medical Subject Headings (MeSH) and relevant free-text terms as search criteria, including the following medical subject headings: Critical Illness, Intensive Care Units, critical care, and Blood Glucose. Detailed information about the exact search strategies used is available in Supplementary Table 1. Additionally, to ensure the comprehensiveness of our literature search, we also carried out a secondary search of the reference lists of systematic reviews that were published previously.

Study selection

Inclusion criteria: (1) Study population: critically ill patients in the ICU (age > 18 years); (2) Intervention: liberal glucose control (180–252 mg/dl); Comparison: other blood glucose control targets (108–180 mg/dL or 80–110 mg/dL); (3) Study design: randomized controlled trials (RCTs); (4) Outcomes reported: incidence of hypoglycemia (defined as < 40 mg/dl or < 72 mg/dl), ICU mortality, in-hospital mortality, length of ICU stay, duration of mechanical ventilation, etc.

Exclusion criteria: (1) Reviews, case reports, study protocols, or conference abstracts; (2) Animal or in vitro studies; (3) Duplicate publications or documents that cannot be accessed in full text; (4) Studies that cannot report or provide outcome measures.

The literature was screened independently by two reviewers based on the aforementioned criteria. Any discrepancies encountered during the selection process were clarified either by discussion or by engaging an independent third reviewer.

Data extraction and quality assessment

Two reviewers independently extracted data from the eligible studies. The extracted information included essential details like author name, publication year, study design, interventions and comparison interventions, demographic information such as age and gender of participants, outcome measures, and more.

Two reviewers utilized the Cochrane Collaboration's risk of bias tool (RoB 2.0) [20] to evaluate the potential of bias in the included RCTs. The tool consists of five domains, including randomization process bias, intervention deviations bias, missing outcome data bias, outcome measurements bias, and selective reporting. The level of risk in each of the five domains was rated as "low risk", "high risk", or "some concerns". In case of any discrepancies, they were reconciled by discussing with a third reviewer. The results of this assessment were subsequently presented in a risk of bias diagram.

The Methodological Index for Non-Randomized Studies (MINORS) was utilized to evaluate non-randomized studies included in our analysis [21]. MINORS involves 12 items, including (1) clear aim of the study; (2) consecutive patient inclusion; (3) prospective data collection; (4) endpoints relevant to the study aim; (5) objective endpoint evaluation; (6) follow-up long enough for outcomes to occur; (7) follow-up loss < 5%; (8) calculating the sample size prospectively; (9) contemporary control group; (10) control group not subject to the intervention; (11) equivalent baseline characteristics among groups; (12) appropriate statistical analysis. A score of 0 points is assigned for items that are not reported, 1 point for those that are reported but considered inadequate, and 2 points for items that are reported and considered adequate. The maximum total score is 24 points. Each study was independently evaluated by two reviewers as "low quality", "moderate quality", or "high quality" based on the total score. Based on their score, studies were assessed as being of low quality if they scored below 8. Studies with scores ranging from 8 to 12 were considered to have moderate quality. Studies that received scores above 12 were classified as high quality.

Data integration and statistical analysis

The primary outcome measures of interest were the incidence of hypoglycemia, ICU mortality rate, and in-hospital mortality rate. The secondary outcome measures included the 90-day mortality rate, incidence of bacteremia, proportion of patients requiring renal replacement therapy (RRT), duration of mechanical ventilation, length of ICU stay, and total length of hospital stay. In the context of this study, hypoglycemia was defined as a blood glucose level below 72 mg/dl, while a level below 40 mg/dl was categorized as severe hypoglycemia.

The meta-analysis was executed using STATA 15.0. For continuous data measured on the same scale, we calculated the weighted mean difference (WMD) and reported the 95% confidence interval (CI). Dichotomous variables were displayed as the relative risk (RR). The Q test and I^2 statistic were used to evaluate the heterogeneity of the included studies. I^2 is an important indicator of heterogeneity, with a score of 25%, 50%, and 75% denoting low, moderate, and high degrees of heterogeneity, respectively [22]. When there was no significant heterogeneity detected among the studies ($I2 < 50\%$ and $P > 0.1$), the meta-analysis was conducted using a fixed-effect model. When a considerable level of heterogeneity was present in the studies ($I2 \geq 50\%$ or $P \leq 0.1$), we implemented a random-effects model for conducting the meta-analysis. Subgroup and regression analyses were conducted based on study design (RCT or non-RCT), whether the subjects are all diabetes patients, and the blood glucose control target range of the control group (80–110 mg/dl or 108–180 mg/dl) to clarify the size and source of the heterogeneity between studies. Sensitivity analysis was used to investigate the consistency and reliability of the meta-analysis results, which was performed by systematically excluding individual studies from the pooled analysis. To evaluate possible publication bias, funnel plots were generated, and statistical tests (Egger or Begg method) were performed for outcomes that were reported in at least 5 studies. A P-value below 0.05 was suggestive of significant publication bias. In the presence of publication bias, the trim-and-fill method was utilized to assess its impact on the meta-analysis results.

Results

Literature screening results and flowchart

From the original database search, a total of 15,165 papers were retrieved. No other studies were found through a manual search of references. Following the removal of duplicates, 11,429 irrelevant articles were excluded after reading their titles and abstracts. The full texts of only 18 articles were read, and a total of 9 studies met the inclusion criteria and were incorporated into the meta-analysis [10, 17, 18, 23–28]. The literature screening process is depicted in Fig. 1.

Basic characteristics of included studies

The 9 included studies were from two countries, namely Belgium and Australia. These studies were composed of 5 randomized controlled trials and 4 non-randomized controlled trials. A total of 14,878 ICU patients were involved, among whom 7,465 received liberal glucose control and 7,413 received other blood glucose control targets. The included population consisted of 9,593 males and 5,285 females, with an average age ranging from 61 to 69 years. Five studies included only critically

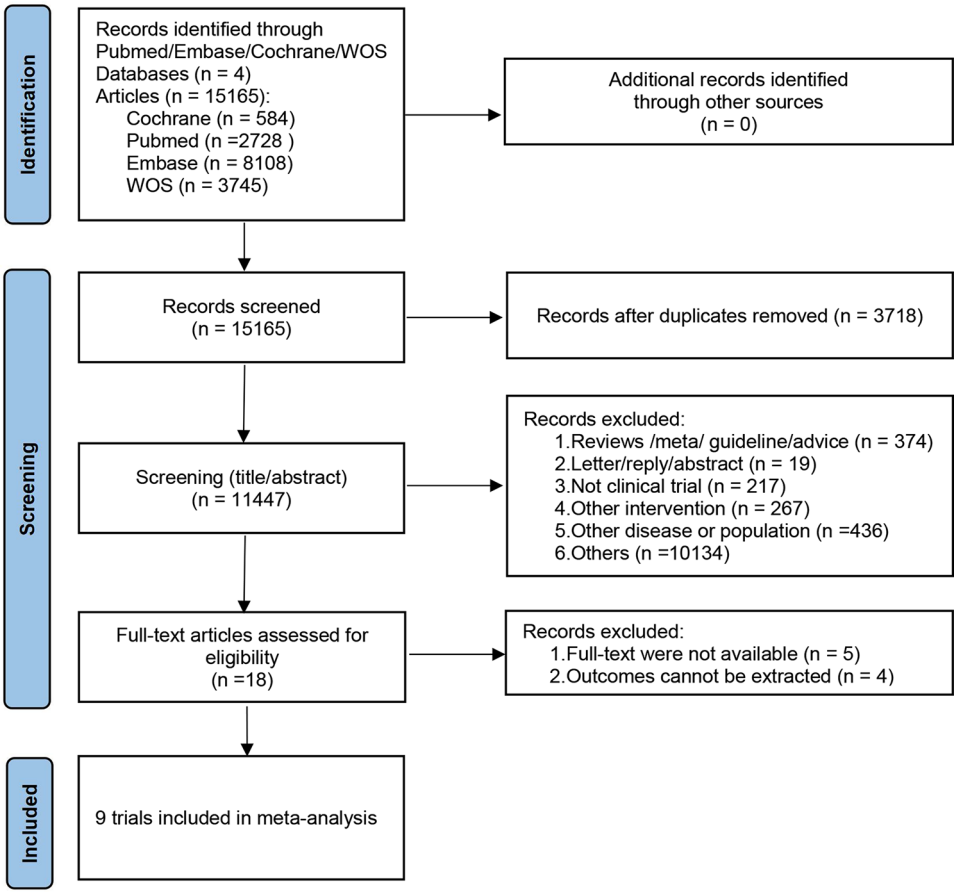

Fig. 1 Flow chart for study selection

ill diabetes patients in the ICU. Regarding the control group, the blood glucose control target range was 108–180 mg/dl in 5 studies and 80–110 mg/dl in 4 studies. Regarding the liberal glucose control group, the target range was 180–200 mg/dl in 3 studies, 180–215 mg/dl in 1 study, and 180–252 mg/dl in 5 studies. Table 1 provides detailed characteristics of the included studies.

Quality assessment

Figure 2 displays the results of the Cochrane risk of bias assessment for the 5 included RCTs. All of these RCTs had a low risk of bias in terms of the randomization process, intervention deviations, outcome data missingness, and outcome domain measurement. However, the risk of selective reporting was unclear in 3 studies. Overall, the 5 included RCTs demonstrated a low risk of bias.

To appraise the quality of the 4 non-RCTs, we applied the MINORS tool. Two studies scored 12 points (moderate quality) and the other 2 studies scored 14 points and 15 points, respectively (high quality). Table 2 shows the detailed results of the quality assessment.

Meta-analysis results

Hypoglycemia incidence

A total of 8 studies reported the incidence of hypoglycemia [10, 17, 18, 24–28].The results showed that liberal glucose control significantly decreased the incidence of hypoglycemia compared to other blood glucose control targets (RR = 0.41; 95%CI:0.25 to 0.69; $P = 0.001$; $I^2 = 80.5\%$; $P < 0.001$), as presented in Fig. 3.

Due to the considerable heterogeneity, we conducted subgroup analyses on the incidence of hypoglycemia based on diagnostic criteria for hypoglycemia, study design, whether all study subjects were diabetic patients, and the blood glucose control target range of the control group (Table 3; Figs. 4, 5, 6 and 7). When subgroup analyses were conducted based on the diagnostic criteria for hypoglycemia (below 40 mg/dl or below 72 mg/dl), the results showed that regardless of whether the hypoglycemia diagnostic criterion was below 40 mg/dl (RR = 0.29; 95% CI: 0.14 to 0.59) or below 72 mg/dl (RR = 0.63; 95% CI: 0.43 to 0.95), free blood glucose control was found to significantly reduce the risk of hypoglycemia when compared to other glycemic control regimens. The results of the regression analysis indicated that differences in the diagnostic criteria for hypoglycemia led to variations in

Table 1 Detailed characteristics of included studies comparing liberal glucose control with other glycemic target control groups in critically ill patients

No.	First Author	Publication Year	Country	Study Design	Diabetic *n*(%)	Sample size	Sex (male/female)	Age	Blood glucose level at ICU admission, mmol/L	Blood glucose values starting with insulin	Treatment		Clinical scores						Follow-up (days)
											Experimental group Target glucose (mg/dL)	Control group Target glucose (mg/dL)	APACHE II during first 24 h	TISS-28 during first 24 h	APACHE II during second 24 h	TISS-28 during second 24 h	APACHE III score	Baseline APACHE II score	
1	Vanhorebeek et al.	2006	Belgium	RCT	E: 25 (10%) C: 21 (10%)	E: 243 C: 208	E: 164/79 C: 144/64	E: 61 ± 16 C: 62 ± 15	E: 147.6 ± 55.6 C: 144.2 ± 52.9	E:>215 mg/dl C: NA	180–200 mg/dl	80–110 mg/dl	E: 12 (8, 15) C: 11 (7, 15)	E: 39 (33, 45) C: 40 (35, 45)	NA	NA	NA	NA	NA
2	Luethi et al.	2019	Australia	Non-RCT	E: 189(94.5%) C: 189 (94.5%)	E: 200 C: 200	E: 154/46 C: 130/70	E: 66(59,74) C: 67(60,75)	E: 8.6(6.7,11.0) C: 8.6(7.0,12.0)	E: >252 mg/dl C: >180 mg/dl	180–200 mg/dl	108–180 mg/dl	NA	NA	NA	NA	E:61 (46, 81) C: 56 (43, 72)	NA	NA
3	van den Berghe et al.	2001	Belgium	RCT	E: 103(13) C: 101(13)	E: 783 C: 765	E: 557/226 C: 544/221	E: 62.2 ± 13.9 C: 63.4 ± 13.6	NA	E:>215 mg/dl C:>110 mg/dl	180–200 mg/dl	80–110 mg/dl	E: 9 (7, 13) C: 9 (7, 13)	E: 43 (36, 47) C: 43 (37, 46)	E: 9 (6, 13) C: 9 (6, 13)	E: 38 (32, 44) C: 38 (31, 43)	NA	NA	NA
4	van den Berghe et al.	2006	Belgium	RCT	E: 97(16.0) C: 106(17.8)	E: 605 C: 595	E: 382/223 C: 356/239	E: 64 ± 16 C: 63 ± 16	E: 162 ± 70 C: 162 ± 71	E:>215 mg/dl C:>110 mg/dl	180–200 mg/dl	80–110 mg/dl	NA	NA	NA	NA	NA	E: 23 ± 9 C: 23 ± 10	90
					E: 58(15.2) C: 59(15.3)	E: 381 C: 386	E: 243/138 C: 224/162	E: 64 ± 16 C: 62 ± 16	E: 164 ± 68 C: 163 ± 67				NA	NA	NA	NA	NA	E: 24 ± 9 C: 24 ± 10	
5	Luethi et al.	2018	Australia	Non-RCT	E: 350(100%) C: 350 (100%)	E: 350 C: 350	E: 256/94 C: 232/118	E: 67(59,75) C: 68(60,75)	E: 8.6(6.7,11.0) C: 8.6(7.0,12.0)	E: >252 mg/dl C: >180 mg/dl	180-252 mg/dl	108–180 mg/dl	NA	NA	NA	NA	E:60 (45, 75) C: 56 (43, 70)	NA	30
6	Di Muzio et al.	2016	Australia	Non-RCT	E: 40(100%) C: 40 (100%)	E: 40 C: 40	E: 28/12 C: 25/15	E: 69(61,73) C: 68(60,77)	NA	NA	180-252 mg/dl	108–180 mg/dl	NA	NA	NA	NA	E:52 (40, 77) C:59 (46, 72)	NA	NA
7	Kar et al.	2016	Australia	Non-RCT	E: 31(100%) C: 52 (100%)	E: 31 C: 52	E: 18/13 C: 30/22	E: 62.8 ± 11.5 C: 63.7 ± 14.5	NA	E: >252 mg/dl C: >180 mg/dl	180-252 mg/dl	108–180 mg/dl	NA	NA	NA	NA	E: 72.9 ± 22.6 C: 74.7 ± 26.9	E: 19.9 ± 6.4 C: 20.4 ± 7.1	90
8	Poole et al.	2022	Australia	RCT	E: 210(100%) C: 209(100%)	E: 210 C:209	E: 138/72 C: 136/73	E: 67(58,75) C: 66(58,73)	NA	E: >252 mg/dl C: >180 mg/dl	180-252 mg/dl	108–180 mg/dl	NA	NA	NA	NA	E:74 (55, 95) C:71 (58, 93)	E:20 (16, 26) C: 20 (16, 26)	90
9	Gunst et al.	2023	Belgium	RCT	E: 955(20.7%) C: 933(20.2%)	E: 4622 C:4608	E: 2902/1720 C: 2930/1678	E: 67(56,75) C: 67(57,75)	NA	E:>215 mg/dl C:>180 mg/dl	180-215 mg/dl	80–110 mg/dl	NA	NA	NA	NA	NA	E:21 (15, 30) C:21 (15, 30)	90

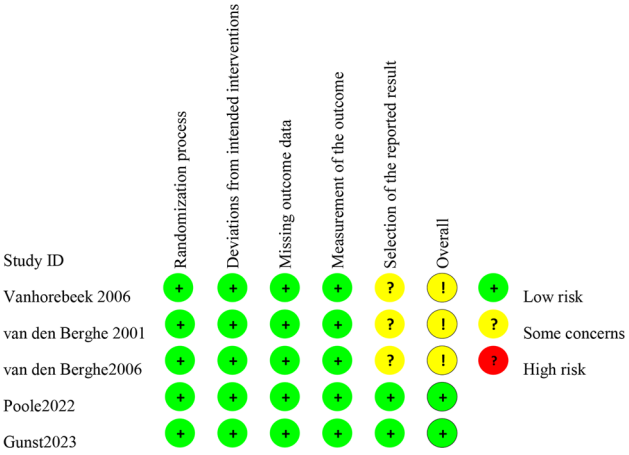

Fig. 2 The Cochrane risk of bias assessment for the included RCTs

the incidence of hypoglycemia ($P = 0.047$). When subgroup analyses of the incidence of hypoglycemia were conducted based on study design (RCT or Non-RCT), the results showed that in RCT studies, the incidence of hypoglycemia in the free blood glucose control group was significantly reduced (RR = 0.25; 95% CI: 0.13 to 0.47). However, in Non-RCT studies, there was no significant difference between the two groups (RR = 0.77; 95% CI: 0.54 to 1.11). Further regression analysis indicated a significant difference in the occurrence of hypoglycemia ($P = 0.003$). When subgroup analyses of the incidence of hypoglycemia were conducted based on the blood glucose control targets of the control group (tight blood glucose control: 80–110 mg/dl; conventional blood glucose control: 108–180 mg/dl), the results showed that regardless of whether the control group practiced strict blood glucose control (RR = 0.23; 95% CI: 0.11 to 0.51) or conventional blood glucose control (RR = 0.65; 95% CI: 0.46 to 0.92), the risk of hypoglycemia was lower in the free blood glucose control group. There was a significant difference in the risk of hypoglycemia between different blood glucose control targets (for the control group) ($P = 0.012$). After subgroup analysis of the incidence of hypoglycemia based on whether all the study subjects were diabetic patients, the results showed that regardless of whether all the study subjects were diabetic patients (RR = 0.65; 95% CI: 0.46 to 0.92) or not all were diabetic patients (RR = 0.23; 95% CI: 0.11 to 0.51), free blood glucose control significantly reduced the incidence of hypoglycemia compared to other blood glucose control targets. In the regression analysis, we also found that whether all the study subjects were diabetic patients had a significant effect on the occurrence of hypoglycemia ($P = 0.012$).

ICU mortality rate

Eight studies reported ICU mortality rate [10, 17, 18, 23, 25–28]. The heterogeneity test demonstrated a significant

Table 2 Quality evaluation of MINORS for the included non-RCTs

Author	Year	A	B	C	D	E	F	G	H	I	J	K	L	Total
Luethi et al.	2019	2	2	0	2	0	0	0	0	2	0	2	2	12
Luethi et al.	2018	2	2	0	2	0	1	2	0	2	0	1	2	14
Di Muzio et al.	2016	2	2	0	2	0	0	0	0	2	0	2	2	12
Kar et al.	2016	2	2	0	2	0	1	2	0	2	0	2	2	15

Numbers A-H in heading signified: A,clearly stated study objectives; B,Inclusion of consecutive patientss; C, Prospective collection of data; D, Endpoints appropriate to the aim of the study; E, Unbiased assessment of the study endpoint; F, Follow-up period appropriate to the aim of the study; G, Loss to follow up less than 5%; H, Prospective calculation of the study size; I, A control group having the gold standard intervention; J, Contemporary groups; K, Baseline equivalence of groups; L, Statistical analyses adapted to the study design

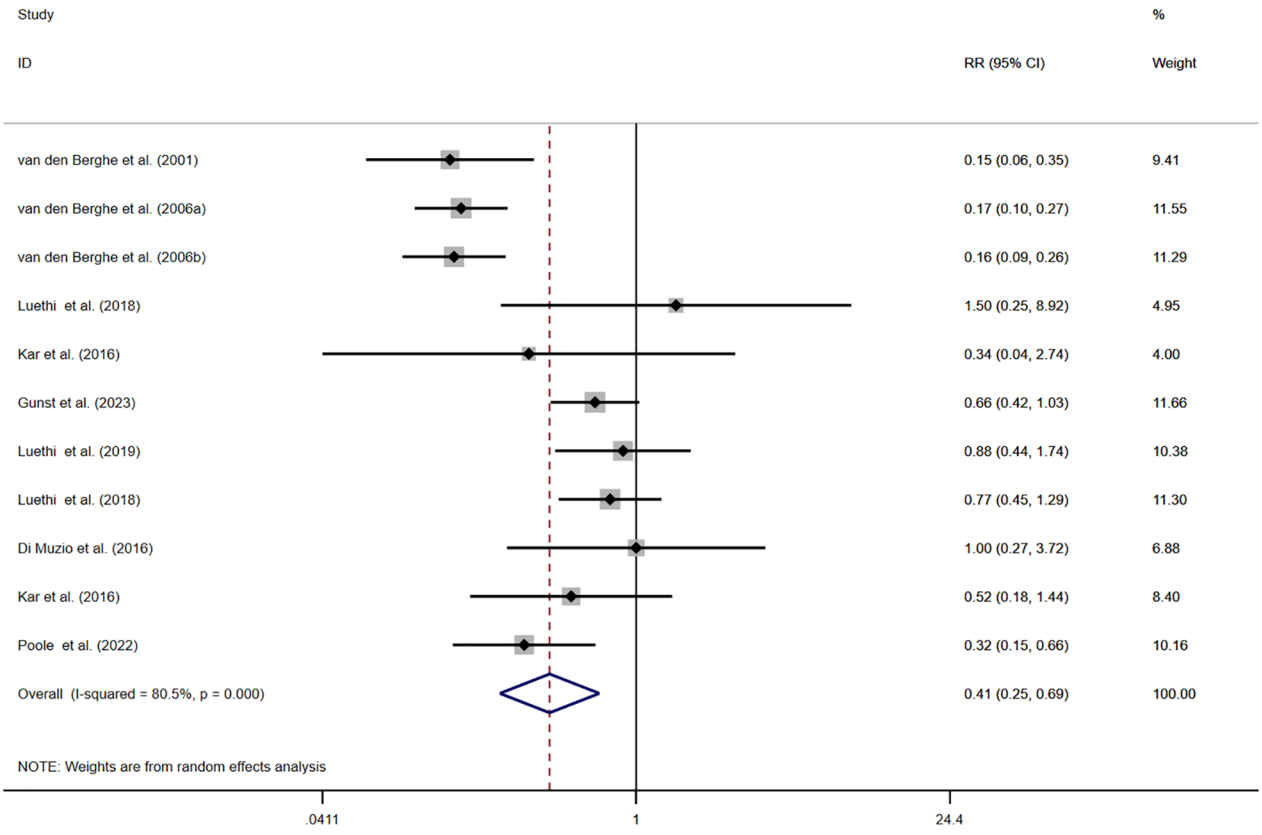

Fig. 3 Forest plot of Hypoglycemia incidence between liberal glucose control and other blood glucose target control groups. (CI, confidence interval; 2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days, RR, relative risk)

degree of heterogeneity ($I^2 = 61.4\%$, $P = 0.008$). According to the random-effect model analysis, it was observed that liberal glucose control was linked to a greater likelihood of ICU mortality, when compared to other blood glucose control targets (RR = 1.23; 95%CI:1.03 to 1.48; $P = 0.023$), as displayed in Fig. 8.

Due to notable heterogeneity, we conducted subgroup analyses of ICU mortality rates based on study design, whether all study subjects were diabetic patients, and the range of blood glucose control targets in the control group (Table 4; Figs. 9, 10 and 11). When subgroup analysis was performed based on whether all study subjects were diabetic patients for ICU mortality rates, the results showed that regardless of whether the study subjects were all diabetic patients (RR = 1.23; 95% CI: 0.86 to 1.77) or not all were diabetic patients (RR = 1.24; 95% CI: 1.00 to 1.54), there was no significant increase in ICU mortality rates in either group. In the regression analysis, we found that whether all study subjects were diabetic patients may not be the source of the heterogeneity in ICU mortality rates ($P = 0.924$). After performing subgroup analyses of ICU mortality rates based on the range of blood glucose control targets in the control group (strict glucose control: 80–110 mg/dl; routine glucose control: 108–180 mg/dl), it was found that regardless of whether the control group's blood glucose control target was routine (RR = 1.23; 95%CI: 0.86 to 1.77) or strict (RR = 1.24; 95%CI: 1.00 to 1.54), it did not significantly increase ICU mortality rates. In the regression analysis, we found that the range of blood glucose control targets in the control group may not be the source of the heterogeneity in ICU mortality rates ($P = 0.924$). When subgroup analyses of ICU mortality rates were conducted based on study design (RCT or Non-RCT studies), the results showed that in RCT studies (RR = 1.25; 95%CI: 1.03 to 1.52), there was a significant increase in ICU mortality risk in the group with free glucose control. However, in Non-RCT studies (RR = 0.99; 95%CI: 0.47 to 2.08), no significant difference in mortality risk between the groups with free glucose control was found. In the regression analysis results, study design may also not be the source of the heterogeneity in ICU mortality rates ($P = 0.654$).

In-hospital mortality rate

Seven studies reported in-hospital mortality rate [10, 18, 24–28]. The data analysis was conducted using the random-effects model. The liberal glucose control

Table 3 Subgroup analysis of hypoglycemia incidence

Subgroup	Studies	RR (95% CI),*P*	I^2,$P_{Heterogeneity}$	$P_{regression}$
All studies	8	1.23 (1.03, 1.48),0.001	61.4%,0.008	
The diagnostic criteria for hypoglycemia				0.047
< 40 mg/dL	5	0.29(0.14,0.59),0.001	82.6%,<0.001	
< 72 mg/dL	5	0.63(0.43,0.95),0.026	25.8%,<0.001	
Control group target blood glucose				0.012
80–110 mg/dl	3	0.23 (0.11,0.51),<0.001	88.0%,<0.001	
108–180 mg/dl	5	0.65(0.46, 0.92),0.015	9.4%,0.357	
Diabetes				0.012
Partial diabetic	3	0.23 (0.11,0.51),<0.001	88.0%,<0.001	
Diabetic	5	0.65(0.46, 0.92),0.015	9.4%,0.357	
Study type				0.003
RCT	4	0.25 (0.13, 0.47),<0.001	84.2%,<0.001	
Non-RCT	4	0.77 (0.54, 1.11),0.161	0.0%,0.849	

Abbreviations: RR, relative risk; CI, confidence interval

group exhibited a significantly greater risk of in-hospital mortality relative to other blood glucose control targets (RR = 1.18; 95%CI:1.03 to 1.35; $P = 0.020$; $I^2 = 55.2\%$, $P = 0.029$), as presented in Fig. 12.

Due to high heterogeneity, we conducted subgroup analyses of in-hospital mortality rates based on study design, whether the study subjects were all diabetics, and the range of blood glucose control targets in the control group (Table 5; Figs. 13, 14 and 15). After subgroup analysis of in-hospital mortality rates based on whether the study subjects were all diabetics, the results showed that there was no significant difference in the risk of in-hospital mortality between the group of study subjects who were all diabetics (RR = 1.16; 95%CI: 0.90 to 1.49) and the group where not all the study subjects were diabetics (RR = 1.19; 95%CI: 0.99 to 1.43). In the regression analysis, we found that whether the study subjects were all diabetics may not be the source of the heterogeneity in in-hospital mortality rates ($P = 0.846$). After conducting subgroup analyses of in-hospital mortality rates based on the range of blood glucose control targets in the control group (strict glucose control: 80–110 mg/dl; routine glucose control: 108–180 mg/dl), it was found that regardless of whether the blood glucose control target in the control group was routine (RR = 1.16; 95%CI: 0.90 to 1.49) or strict (RR = 1.19; 95%CI: 0.99 to 1.43), it would not significantly increase the in-hospital mortality rate in either group. In the regression analysis, we observed that the range of blood glucose control targets in the control group may not be the source of the heterogeneity in in-hospital mortality rates ($P = 0.846$). The subgroup analysis of in-hospital mortality rates based on study design (RCT or Non-RCT studies) revealed that no significant difference in the risk of in-hospital death was found between RCT studies (RR = 1.19; 95%CI: 0.99 to 1.43) and Non-RCT studies (RR = 1.16; 95%CI: 0.90 to 1.49). The regression analysis results also suggest that study design may not be the source of the heterogeneity in in-hospital mortality rates ($P = 0.846$).

90-day mortality rate

Four studies reported the 90-day mortality rate [17, 18, 25, 28]. The data analysis was conducted using the random-effects model. The results demonstrated that there was no statistically significant difference in the 90-day mortality rate between the group receiving liberal glucose control and the group receiving other blood glucose control targets (RR = 1.03; 95%CI:0.95 to 1.11; $P = 0.504$; $I^2 = 15.9\%$, $P = 0.313$), as demonstrated in Fig. 16.

Bacteremia incidence

Four studies reported the incidence of bacteremia [10, 23–25]. The incidence of bacteremia was found to be similar between the liberal glucose control group and other blood glucose control targets, with no significant difference observed (RR = 1.35; 95%CI: 0.90 to 2.00; $P = 0.145$; $I^2 = 62.7\%$, $P = 0.045$), as shown in Fig. 17.

Proportion of patients requiring RRT

Seven studies reported the proportion of patients requiring RRT [10, 18, 23, 25–28]. A fixed-effect model was employed to combine data ($I^2 = 49.2\%$, $P < 0.066$). Compared to other blood glucose control targets, the liberal glucose control group had a greater percentage of patients who needed RRT, based on the results (RR = 1.26; 95%CI: 1.11 to 1.42; $P < 0.001$), as illustrated in Fig. 18.

Due to considerable heterogeneity, we conducted subgroup analyses based on study design, whether the study population included only diabetics, and the range of blood glucose control targets in the control group, to assess the ratio of patients requiring RRT (Table 6; Figs. 19, 20 and 21). After subgroup analysis based on whether the study population included only diabetics, the results showed that no significant difference in the ratio of patients requiring RRT was found between the groups where the study population was entirely diabetic (RR = 1.26; 95%CI: 0.73 to 2.16) and where the study population was not entirely diabetic (RR = 1.25; 95%CI: 1.11 to 1.42). After performing subgroup analyses on

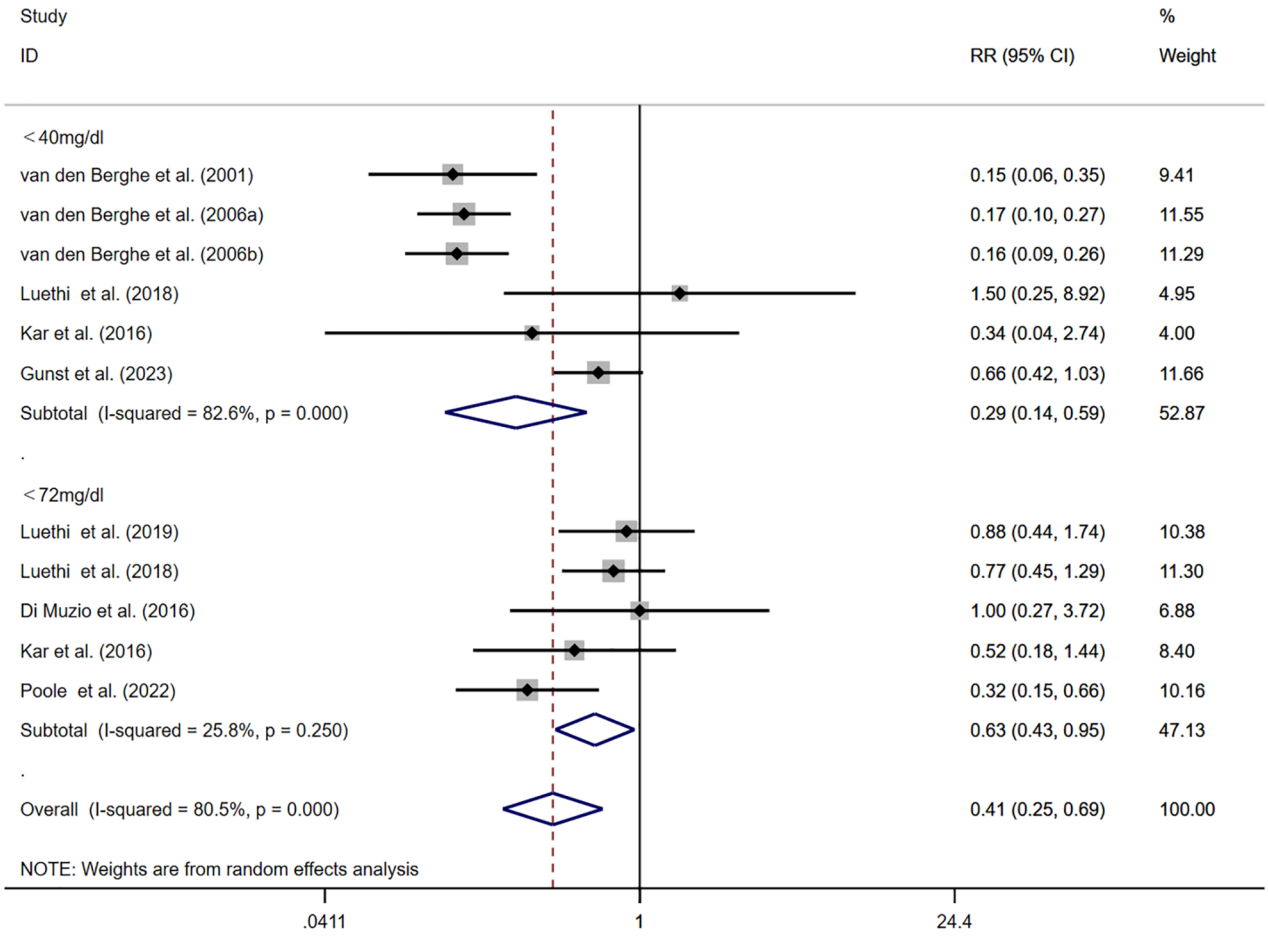

Fig. 4 Forest plot of subgroup analysis of hypoglycemia incidence based on the diagnostic criteria for hypoglycemia. (CI, confidence interval; 2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days; RR, relative risk)

the ratio of patients requiring RRT based on the range of blood glucose control targets in the control group (strict glucose control: 80–110 mg/dl; conventional glucose control: 108–180 mg/dl), it was found that no significant difference in the ratio of patients requiring RRT was observed between the groups with conventional (RR = 1.26; 95%CI: 0.73 to 2.16) or strict (RR = 1.25; 95%CI: 1.11 to 1.42) glucose control in the control group. When subgroup analyses of the ratio of patients requiring RRT were conducted based on study design (RCT or Non-RCT), the results showed that no significant difference in the ratio of patients requiring RRT was found between RCT studies (RR = 1.25; 95%CI: 1.11 to 1.42) and Non-RCT studies (RR = 1.26; 95%CI: 0.73 to 2.16). Based on the subgroup heterogeneity and the results of regression analysis, we found that study design, whether the study population included only diabetics, and the range of blood glucose control targets in the control group were not likely sources of heterogeneity among patients requiring RRT ($P = 0.815$).

Mechanical ventilation duration

Four studies reported the mechanical ventilation duration [10, 23, 26, 27]. Non-significant heterogeneity was noted across the included studies, as indicated by the heterogeneity test ($I^2 = 41.1\%$, $P = 0.165$). The meta-analysis was conducted using the random-effects model. The results demonstrated that there was no statistically significant difference in the mechanical ventilation duration between the group receiving liberal glucose control and the group receiving other blood glucose control targets (WMD = 0.08; 95%CI: -0.09 to 0.26; $P = 0.545$), as presented in Fig. 22.

Length of ICU stay and total length of stay

Six studies reported the length of stay in ICU [10, 17, 18, 23, 24, 27]. The random-effects meta-analysis results revealed that there was no significant difference observed between the group receiving liberal glucose control and the group receiving other blood glucose control targets, in terms of both the length of ICU stay and total length of stay (WMD = 0.34; 95%CI: -0.32 to 1.01; $P = 0.309$ and

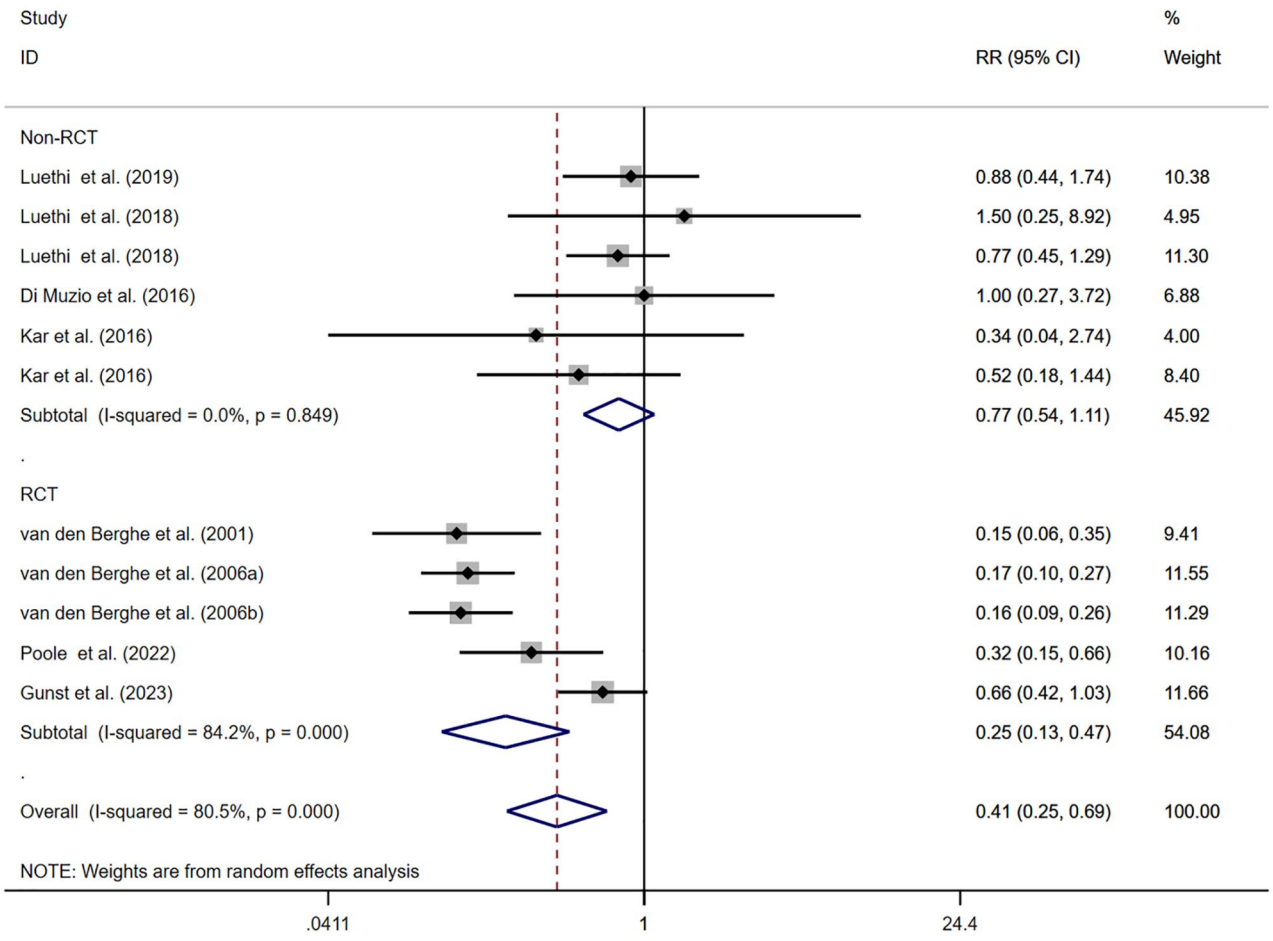

Fig. 5 Forest plot of subgroup analysis of hypoglycemia incidence based on the study design (RCT or non-RCT). (CI, confidence interval; 2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days; RR, relative risk)

WMD = 2.84; 95%CI: -0.46 to 6.12; $P = 0.092$; respectively), as illustrated in Figs. 23 and 24.

Due to significant heterogeneity, we performed subgroup analyses on the duration of ICU hospitalization based on study design, whether the study population consisted solely of diabetic patients, and the range of blood glucose control targets in the control group (Table 7; Figs. 25, 26 and 27). After subgroup analysis based on whether the study population consisted solely of diabetic patients, the results showed that no significant difference in the duration of ICU hospitalization was found between the groups where all subjects were diabetic patients (WMD=-0.14; 95%CI: -1.19 to 0.91) or where not all subjects were diabetic patients (WMD = 0.90; 95%CI: -0.17 to 1.97). In the regression analysis, we found that whether the study population consisted solely of diabetic patients may not be a source of heterogeneity in the duration of ICU hospitalization ($P = 0.191$). When subgroup analyses were conducted based on the blood glucose control target range of the control group (tight control: 80–110 mg/dl; routine control: 108–180 mg/dl) for ICU hospitalization days, it was found that there was no significant difference in ICU hospitalization days between the groups with routine (WMD=-0.14; 95%CI: -1.19 to 0.91) or strict (WMD = 0.90; 95%CI: -0.17 to 1.97) control of blood glucose targets. In the regression analysis, we observed that the range of blood glucose control targets in the control group may not be a source of heterogeneity in ICU hospitalization days ($P = 0.191$). The subgroup analysis based on the study design (RCT or Non-RCT) of ICU hospitalization days revealed that no significant difference in ICU hospitalization days was observed between RCT studies (WMD = 0.42; 95% CI: -0.63 to 1.46) and Non-RCT studies (WMD = 1.26; 95% CI: -0.08 to 0.96). Furthermore, in the regression analysis, it was found that the study design may not be a source of heterogeneity in ICU hospitalization days ($P = 0.889$). This suggests that the type of study design does not appear to influence the variability in ICU hospitalization lengths.

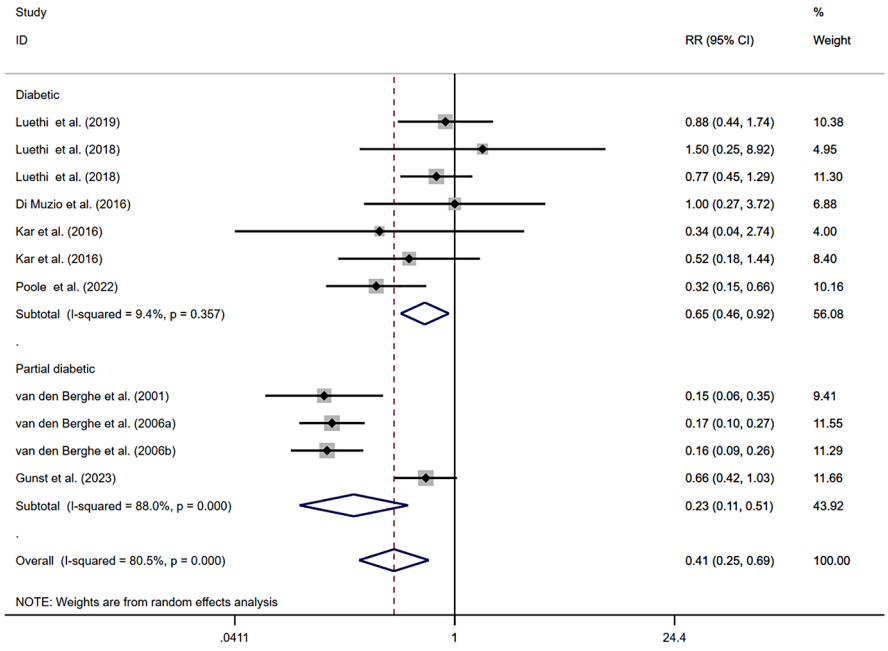

Fig. 6 Forest plot of subgroup analysis of hypoglycemia incidence based on the blood glucose control target range of the control group. (CI, confidence interval; 2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days; RR, relative risk)

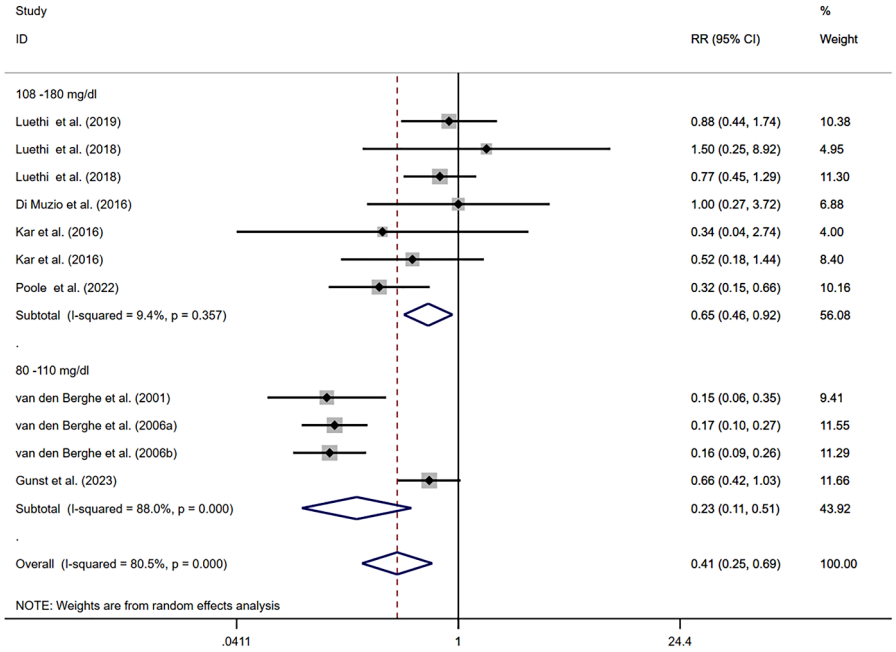

Fig. 7 Forest plot of subgroup analysis of hypoglycemia incidence based on whether the study population included only diabetes patients. (CI, confidence interval; 2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days; RR, relative risk)

Sensitivity analysis

To evaluate the impact of each individual study on the overall findings, sensitivity analysis was conducted on ICU mortality rate, hypoglycemia incidence, and length of ICU stay using a one-by-one exclusion method. The results demonstrated that none of the combined findings were considerably impacted by any single study. Based on this, it can be inferred that the outcomes obtained from this meta-analysis are generally reliable and robust. The sensitivity analysis results are presented in Figs. 28, 29 and 30.

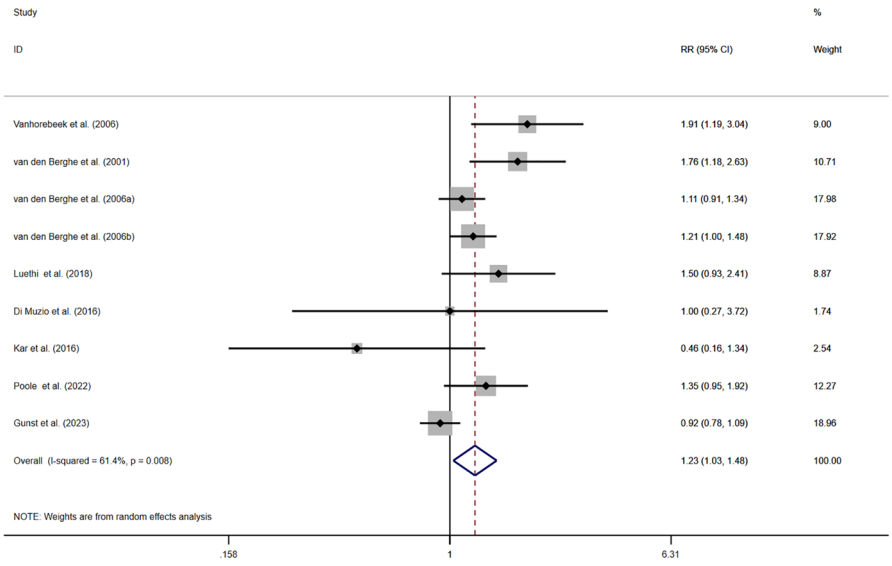

Fig. 8 Forest plot of ICU mortality rate between liberal glucose control and other blood glucose target control groups. (CI, confidence interval; 2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days, RR, relative risk)

Table 4 Subgroup analysis of ICU mortality rate

Subgroup	Studies	RR (95% CI),*P*	I^2,$P_{Heterogeneity}$	$P_{regression}$
All studies	8	1.23 (1.03, 1.48),0.023	61.4%,0.008	
Control group target blood glucose				0.924
80–110 mg/dl	4	1.24 (1.00, 1.54),0.055	74.4%,0.004	
108–180 mg/dl	4	1.23 (0.86, 1.77),0.258	28.0%,0.244	
Diabetes				0.924
Partial diabetic	4	1.24 (1.00, 1.54),0.055	74.4%,0.004	
Diabetic	4	1.23 (0.86, 1.77),0.258	28.0%,0.244	
Study type				0.654
RCT	5	1.25 (1.03, 1.52),0.025	70.0%,0.005	
Non-RCT	3	0.99 (0.47, 2.08),0.988	50.1%,0.135	

Abbreviations: RR, relative risk; CI, confidence interval

Publication bias

We employed funnel plots, Egger's test, and Begg's test to detect publication bias in the main outcome measures, in an effort to ensure the validity of our meta-analysis results. The result indicated that there was no significant evidence of publication bias in any of the outcome measures ($P > 0.05$).

Discussion

In our meta-analysis, various studies comparing liberal glucose control in critically ill patients with other blood glucose control targets were incorporated. The results showed that liberal glucose control could reduce the risk of hypoglycemia, but increase the ICU mortality rate, in-hospital mortality rate and the proportion of patients requiring RRT. In terms of clinical outcomes, no significant difference was detected between the implementation of liberal glucose control and other blood glucose control targets in terms of bacteremia rate, 90-day mortality rate, duration of mechanical ventilation, length of ICU stay, and total length of hospital stay. Although this is a hypothesis-generating study, this meta-analysis represents the first attempt to compare liberal glucose control to other target ranges of blood glucose control in a comprehensive and systematic manner. Therefore, our findings may be novel and warrant detailed discussion.

Interestingly, our meta-analysis drew different conclusions compared to previous meta-analyses that have been published [14, 29–32]. Previous meta-analyses have evaluated the potential risks and benefits associated with strict blood glucose control(<150 mg/dL) in adult patients who are critically ill [30, 31]. Previous analyses have established that strict blood glucose control does not significantly reduce the in-hospital mortality rate in critically ill adult patients. Yao et al. [14] found that strict blood glucose control (80–120 mg/dL) significantly reduced all-cause mortality rate in their meta-analysis. However, these analyses did observe an increased incidence of severe hypoglycemia in critically ill adult patients subjected to strict blood glucose control

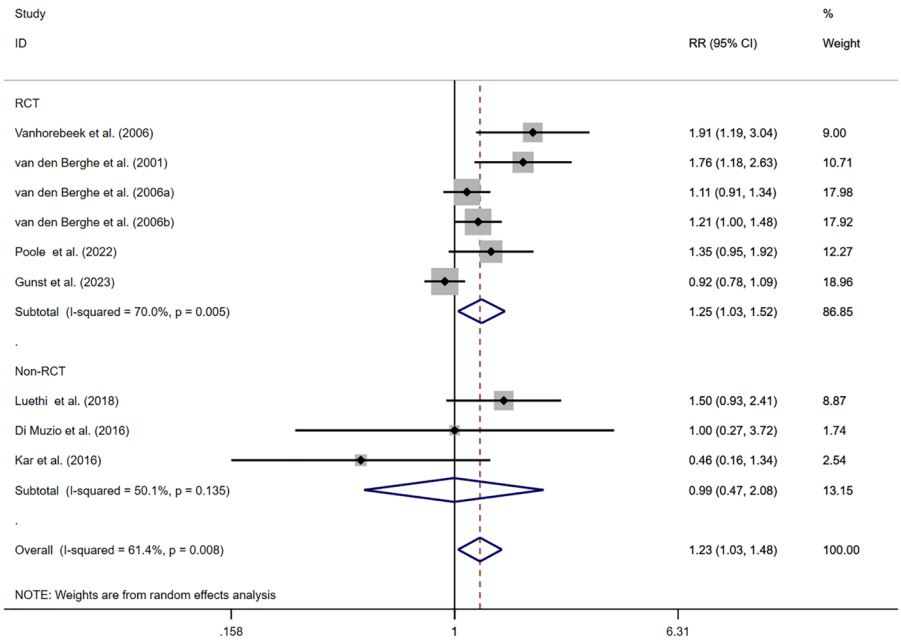

Fig. 9 Forest plot of subgroup analysis of ICU mortality rate based on the study design (RCT or non-RCT). (CI, confidence interval; 2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days; RR, relative risk)

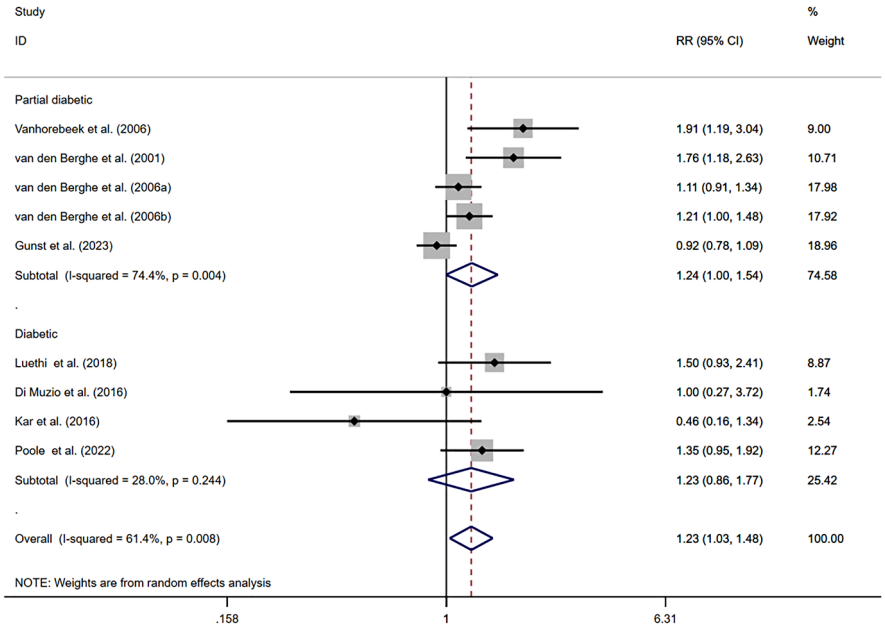

Fig. 10 Forest plot of subgroup analysis of ICU mortality rate based on whether the study population included only diabetes patients. (CI, confidence interval; 2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days; RR, relative risk)

[33, 34]. In 2001, Van den Berghe et al. [10] conducted the first study on liberal glucose control (180–220 mg/dL). The study was a prospective, randomized controlled trial that enrolled adult patients undergoing mechanical ventilation in surgical ICUs. The participants were randomly assigned to either a strict blood glucose control group (target range of 80–110 mg/dL) or a liberal glucose control group (target range of 180–200 mg/dL). The study found that the liberal glucose control group had a reduced risk of hypoglycemia compared to the strict blood glucose control group (0.8% vs. 5.1%). The American College of Physicians [35] recommends that the blood glucose level for ICU patients undergoing insulin therapy should be controlled within 140–200 mg/dL,

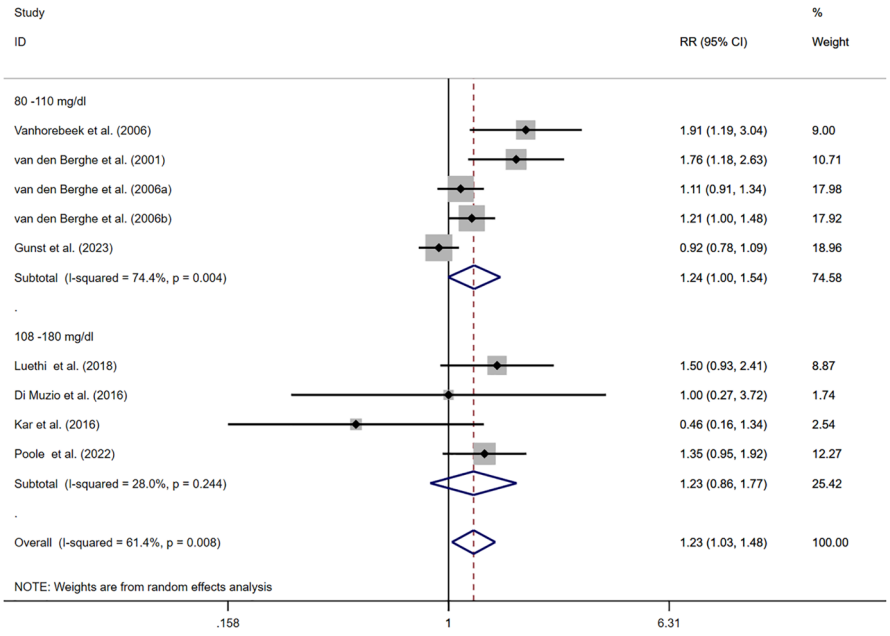

Fig. 11 Forest plot of subgroup analysis of ICU mortality rate based on the blood glucose control target range of the control group. (CI, confidence interval; 2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days; RR, relative risk)

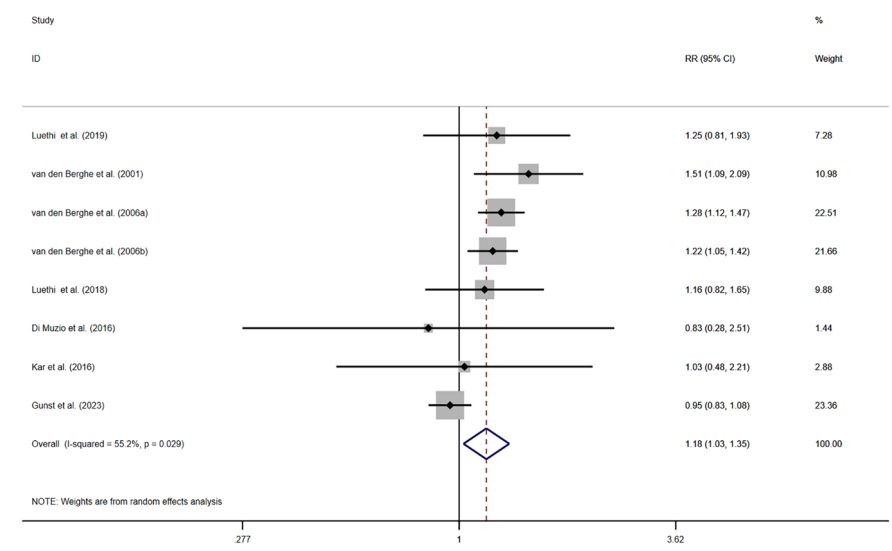

Fig. 12 Forest plot of In-hospital mortality rate between liberal glucose control and other blood glucose target control groups. (CI, confidence interval; 2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days, RR, relative risk)

and to prevent risks, patients should avoid having blood glucose levels less than 140 mg/dL. As per the guidelines of the Surviving Sepsis Campaign, insulin therapy should be initiated when blood glucose levels surpass 180 mg/dL [36]. Yamada et al. [37] and Yatabe et al. [32] performed network meta-analysis of four intervention measures to compare the effectiveness of insulin therapy in critically ill hyperglycemic adult patients with specific blood glucose control target ranges: tight control (80–100 mg/dL), moderate control (110–140 mg/dL), mild control

Table 5 Subgroup analysis of in-hospital mortality rate

Subgroup	Studies	RR (95% CI),*P*	I^2,$P_{Heterogeneity}$	$P_{regression}$
All studies	7	1.18 (1.03, 1.35),0.020	55.2%,0.029	
Control group target blood glucose				0.846
80–110 mg/dl	3	1.19 (0.99,1.43),0.062	80.2%,0.002	
108–180 mg/dl	4	1.16 (0.90, 1.49),0.258	0.0%,0.908	
Diabetes				0.846
Partial diabetic	3	1.19 (0.99,1.43),0.062	80.2%,0.002	
Diabetic	4	1.16 (0.90, 1.49),0.258	0.0%,0.908	
Study type				0.846
RCT	3	1.19 (0.99,1.43),0.062	80.2%,0.002	
Non-RCT	4	1.16 (0.90, 1.49),0.258	0.0%,0.908	

Abbreviations: RR, relative ratio; CI, confidence interval

(140–180 mg/dL), and extreme mild control (>180 mg/dL). As per the study results, the liberal glucose control group demonstrated a lower likelihood of hypoglycemia when compared to the strict blood glucose control group. However, very few studies have directly compared blood glucose target ranges of >180 mg/dL with 80–110 mg/dL or 108–180 mg/dL. Our meta-analysis mainly studied the effects of liberal glucose control (>180 mg/dL) on critically ill patients, providing evidence for the selection of blood glucose control target ranges in critically ill patients.

High blood glucose can have adverse effects on the body, such as fluid imbalance, acidosis, and impaired immune functions [38]. Previous meta-analyses have revealed that adopting strict blood glucose control in critically ill adult patients can increase the likelihood of experiencing hypoglycemia as a side effect [14, 29–32]. Consistent with our study results, our meta-analysis found a lower risk of hypoglycemia in liberal glucose control. The occurrence of hypoglycemia could potentially serve as a standalone risk factor leading to higher mortality rates [12, 39, 40] and is linked with prolonged patient hospitalization, increased 30-day mortality, and increased risk of one-year mortality [41].

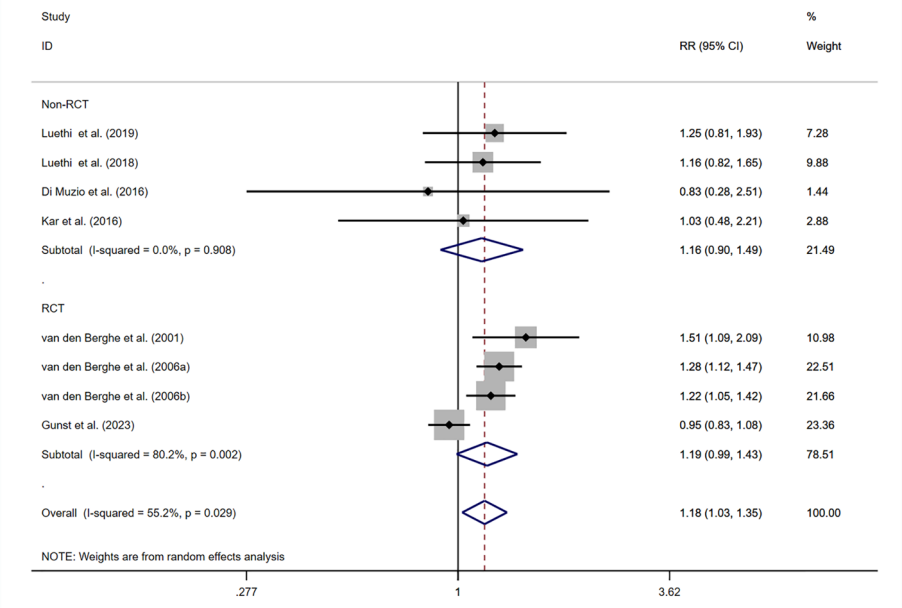

Fig. 13 Forest plot of subgroup analysis of In-hospital mortality rate based on the study design (RCT or non-RCT). (CI, confidence interval; 2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days; RR, relative risk)

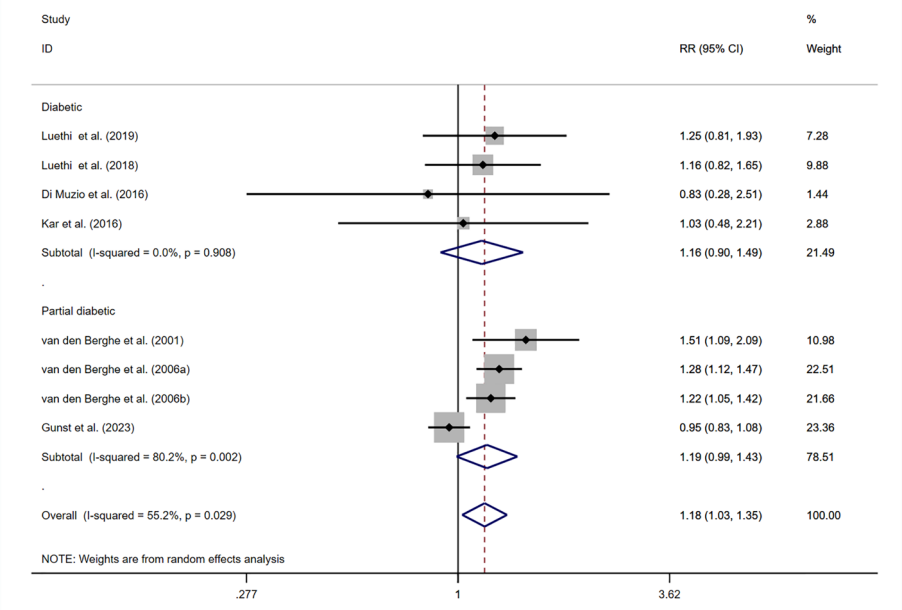

Fig. 14 Forest plot of subgroup analysis of In-hospital mortality rate based on whether the study population included only diabetes patients. (CI, confidence interval; 2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days; RR, relative risk)

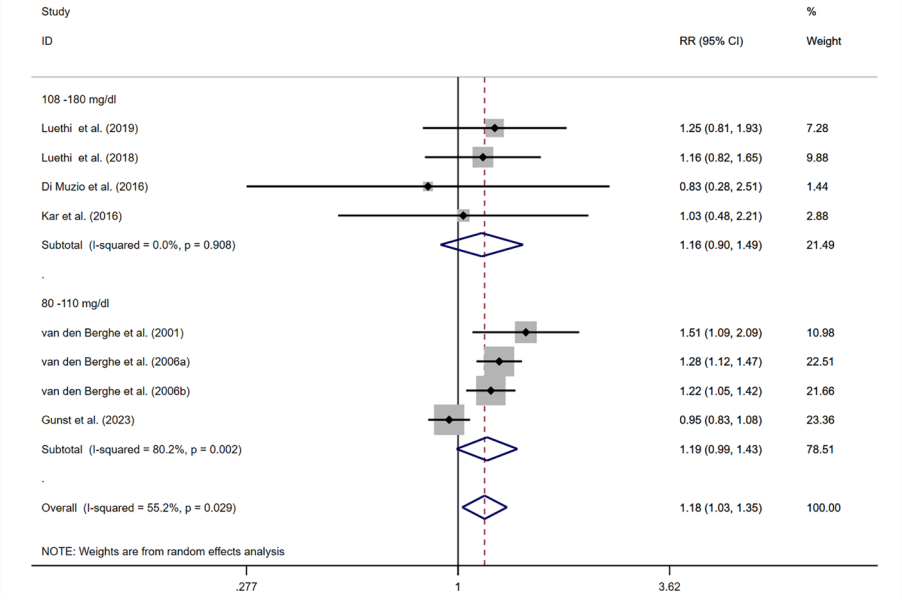

Fig. 15 Forest plot of subgroup analysis of In-hospital mortality rate based on the blood glucose control target range of the control group. (CI, confidence interval; 2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days; RR, relative risk)

In subgroup analysis, we found that in RCT studies, compared to other blood glucose control target ranges, the liberal glucose control group had a significantly lower risk of hypoglycemia, a significantly increased risk of ICU mortality, and a significantly increased proportion of patients requiring RRT. Because non-RCT studies lack random allocation of exposure/interventions, they may suffer from confounding and bias, resulting in lower quality evidence compared to RCTs.

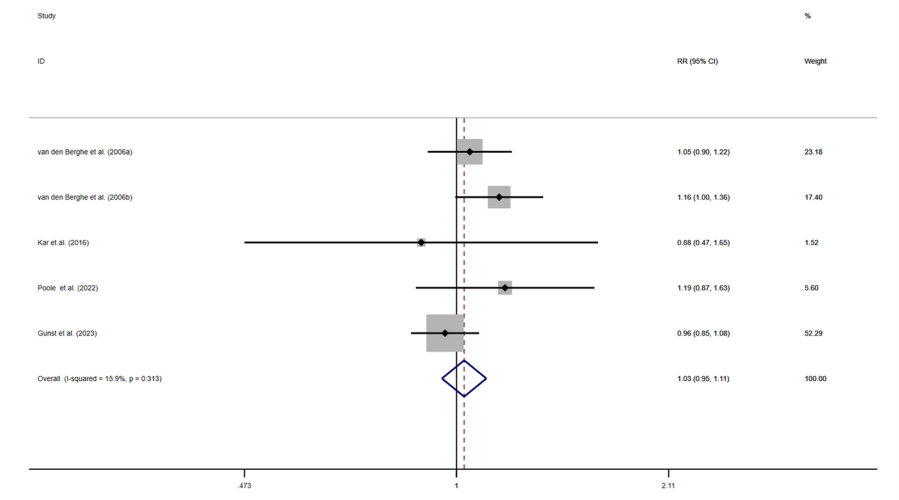

Fig. 16 Forest plot of 90-day mortality rate between liberal glucose control and other blood glucose target control groups. (CI, confidence interval; 2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days, RR, relative risk)

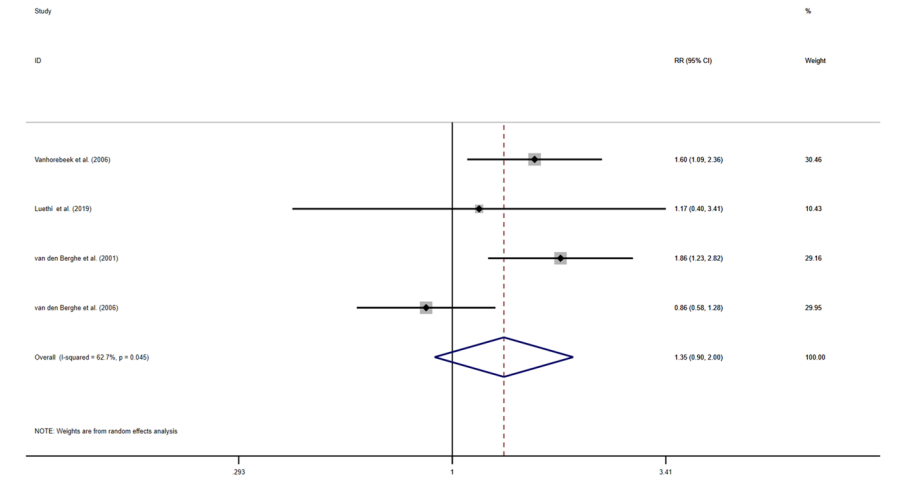

Fig. 17 Forest plot of Bacteremia incidence between liberal glucose control and other blood glucose target control groups. (CI, confidence interval; RR, relative risk)

This study is subject to several limitations, which are inevitable. Firstly, the number of the included studies is limited, with only 9 studies included, including non-RCT studies. In addition, two studies had a sample size of less than 60 individuals in either the intervention or control group [27, 28], which may affect the evaluation of the combined data. Secondly, the studies included in our analysis had different blood glucose control targets for liberal and other glucose control groups. Despite performing stratified analysis, we were unable to analyze the potential impact of certain factors, such as the duration of diabetes, timing of intervention, and intervention

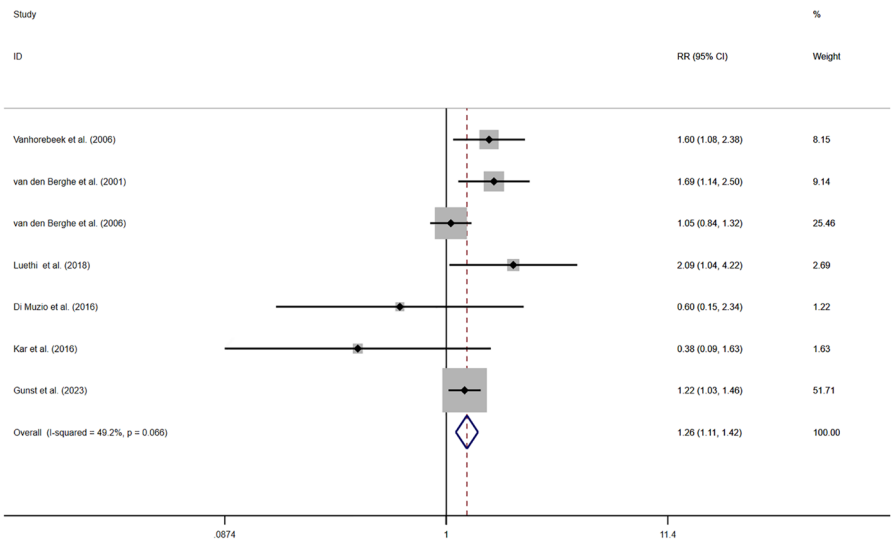

Fig. 18 Forest plot of Proportion of patients requiring RRT between liberal glucose control and other blood glucose target control groups (CI, confidence interval; RR, relative risk)

Table 6 Subgroup analysis of proportion of patients requiring RRT

Subgroup	Studies	RR (95% CI),*P*	I^2,$P_{Heterogeneity}$	$P_{regression}$
All studies	7	1.32 (1.15, 1.53),<0.001	43.7%,0.114	
Control group target blood glucose				0.815
80–110 mg/dl	4	1.25 (1.11,1.42),<0.001	50.6%,0.108	
108–180 mg/dl	3	1.26 (0.73, 2.16),0.405	65.1%,0.057	
Diabetes				0.815
Partial diabetic	4	1.25 (1.11,1.42),<0.001	50.6%,0.108	
Diabetic	3	1.26 (0.73, 2.16),0.405	65.1%,0.057	
Study type				0.815
RCT	4	1.25 (1.11,1.42),<0.001	50.6%,0.108	
Non-RCT	3	1.26 (0.73, 2.16),0.405	65.1%,0.057	

Abbreviations: RR, relative ratio; CI, confidence interval; RRT, renal replacement therapy

duration, due to the insufficient number of studies that examined these variables. Thirdly, it has been previously proven that computerized protocols have a lower incidence of hypoglycemia compared to paper protocols. However, since most of the included studies did not provide relevant information, the current study did not consider the impact of different types of protocols on our results. Future research can further explore and uncover findings in this area. Finally, factors such as patient glucose control methods, glucose monitoring methods, and patient feeding plans may help to explain the heterogeneity between studies.

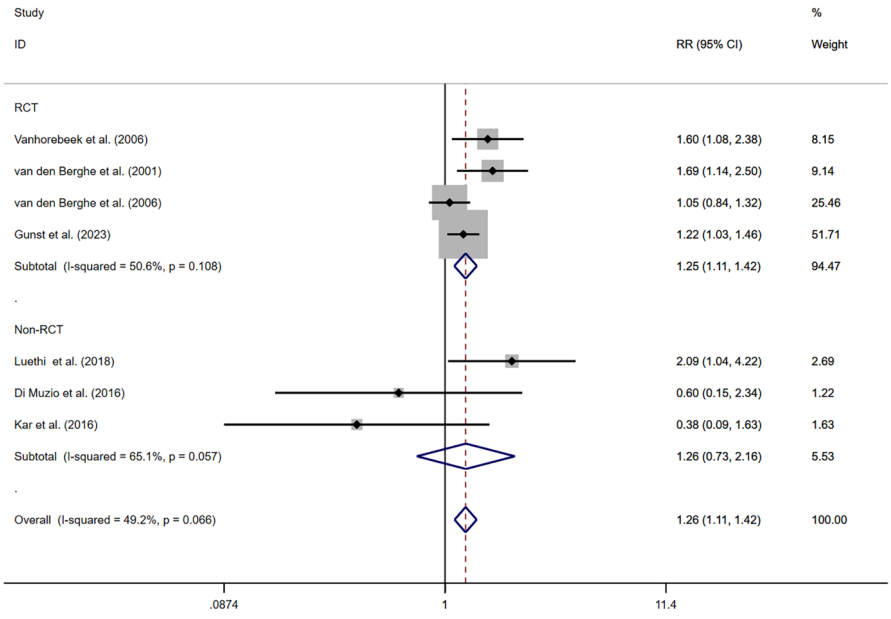

Fig. 19 Forest plot of subgroup analysis of Proportion of patients requiring RRT based on the study design (RCT or non-RCT). (CI, confidence interval RR, relative risk)

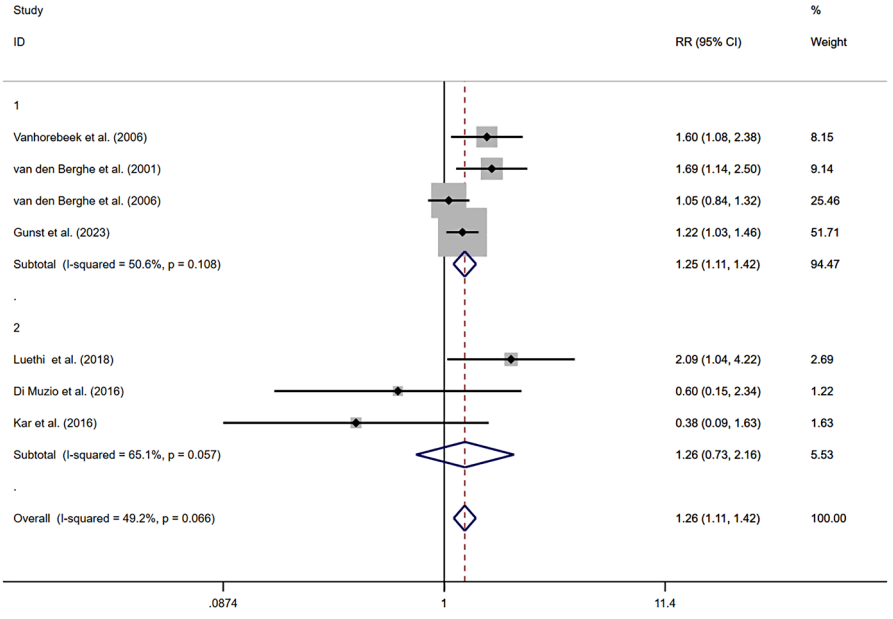

Fig. 20 Forest plot of subgroup analysis of Proportion of patients requiring RRT based on whether the study population included only diabetes patients. (CI, confidence interval RR, relative risk)

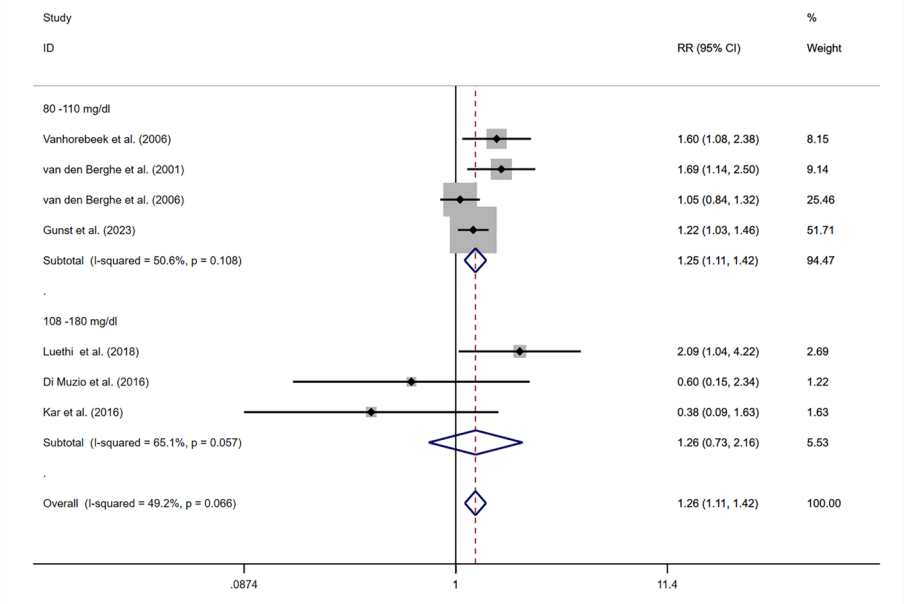

Fig. 21 Forest plot of subgroup analysis of Proportion of patients requiring RRT based on the blood glucose control target range of the control group. (CI, confidence interval; RR, relative risk)

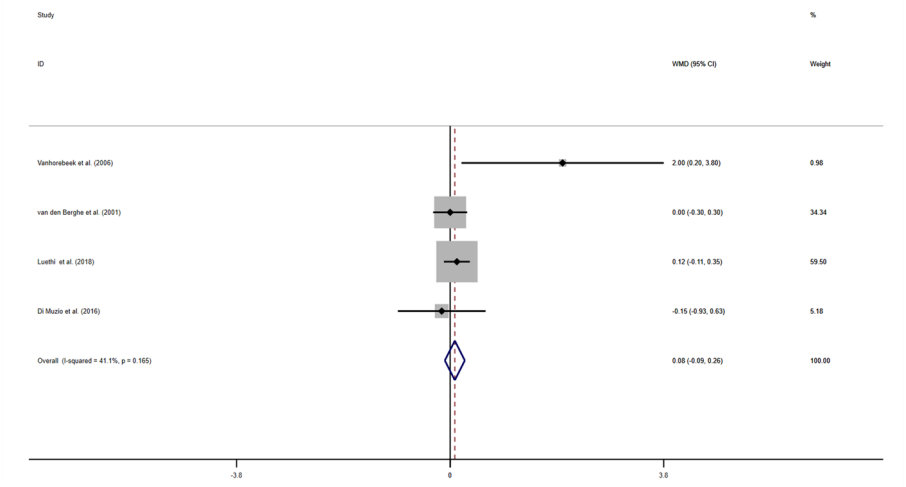

Fig. 22 Forest plot of Mechanical ventilation duration between liberal glucose control and other blood glucose target control groups. (WMD, weighted mean difference; CI, confidence interval)

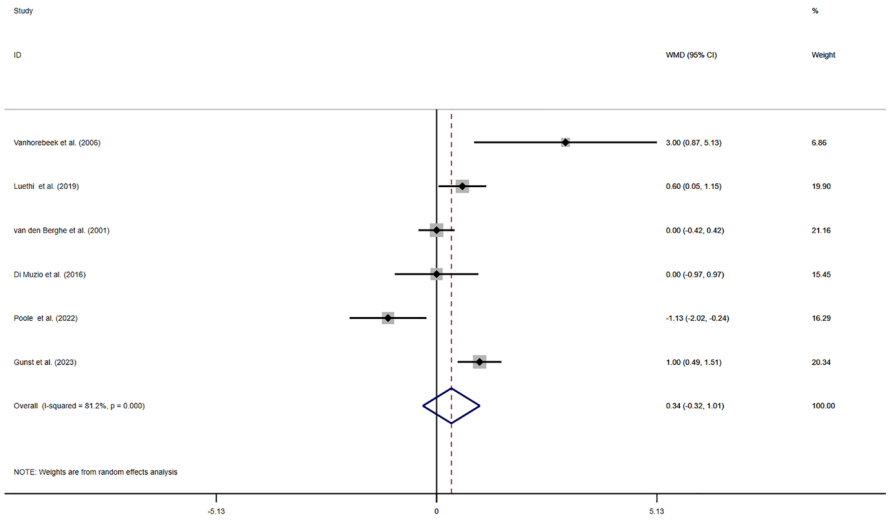

Fig. 23 Forest plot of Length of ICU stay between liberal glucose control and other blood glucose target control groups. (WMD, weighted mean difference; CI, confidence interval)

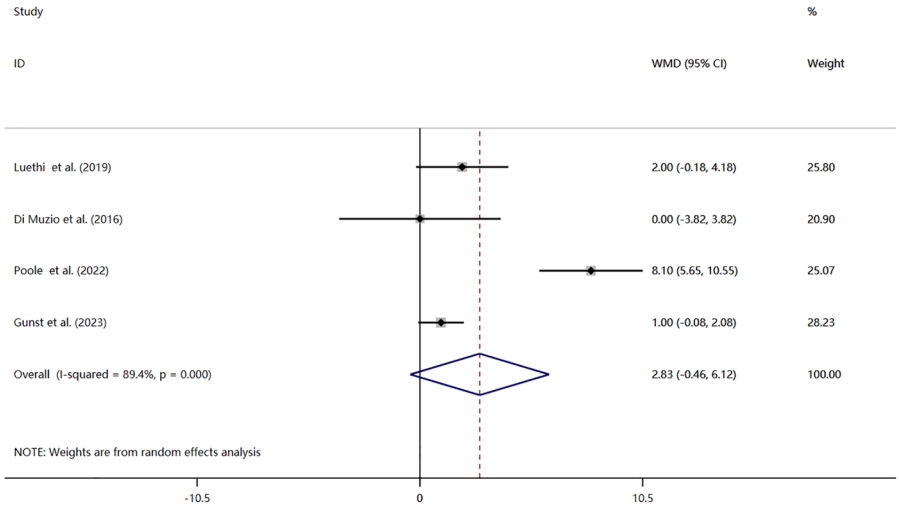

Fig. 24 Forest plot of Total length of stay between liberal glucose control and other blood glucose target control groups. (WMD, weighted mean difference; CI, confidence interval)

Table 7 Subgroup analysis of length of ICU stay

Subgroup	Studies	WMD (95% CI), *P*	I^2,$P_{Heterogeneity}$	$P_{regression}$
All studies	6	0.34(-0.32, 1.01),0.309	81.2%,<0.001	
Control group target blood glucose				0.191
80–110 mg/dl	3	0.90(-0.17, 1.97),0.099	86.1%,0.001	
108–180 mg/dl	3	-0.14 (-1.19, 0.91)0.0.797	80.8%,0.005	
Diabetes				0.191
Partial diabetic	3	0.90(-0.17, 1.97),0.099	86.1%,0.001	
Diabetic	3	-0.14 (-1.19, 0.91)0.0.797	80.8%,0.005	
Study type				0.889
RCT	4	0.42(-0.63, 1.46),0.433	88.1%<0.001	
Non-RCT	2	0.44 (-0.08, 0.96),0.099	9.3%,0.294	

Abbreviations: WMD, weighted mean difference; CI, confidence interval

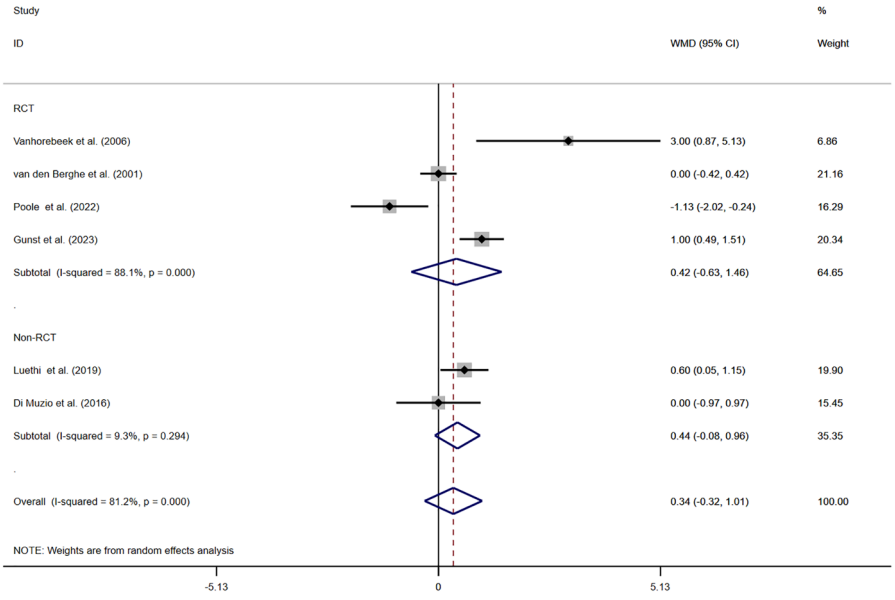

Fig. 25 Forest plot of subgroup analysis of Length of ICU stay based on the study design (RCT or non-RCT). (WMD: weighted mean difference; CI: confidence interval)

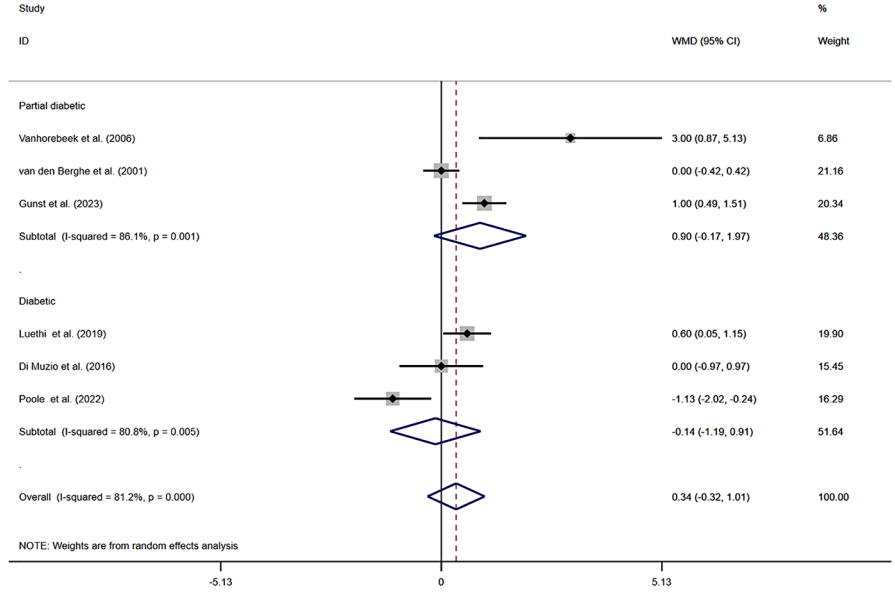

Fig. 26 Forest plot of subgroup analysis of Length of ICU stay based on whether the study population included only diabetes patients. (WMD: weighted mean difference; CI: confidence interval)

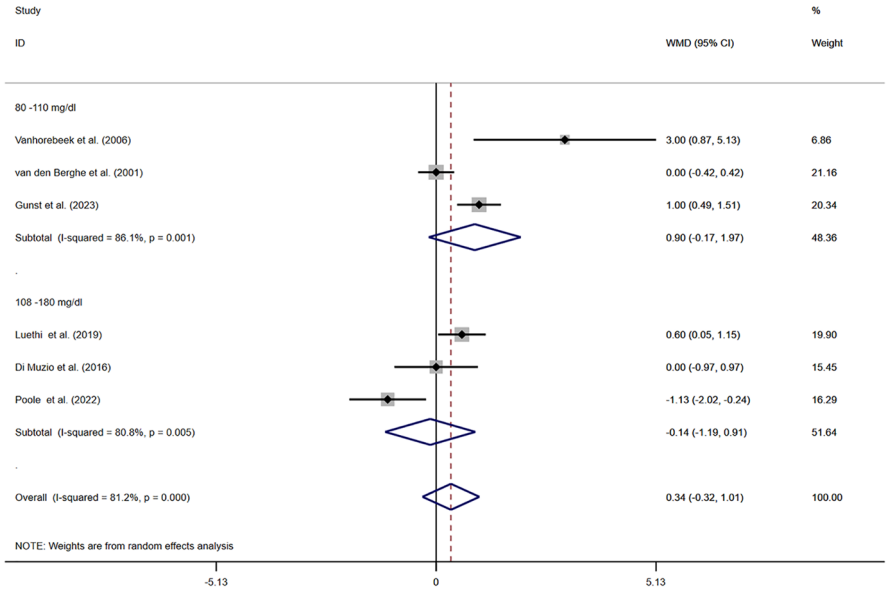

Fig. 27 Forest plot of subgroup analysis of Length of ICU stay based on the blood glucose control target range of the control group. (WMD: weighted mean difference; CI: confidence interval)

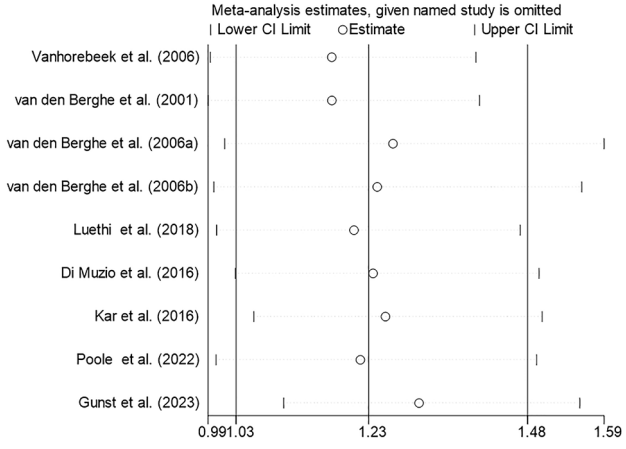

Fig. 28 Sensitivity analysis of ICU mortality rate. (2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days)

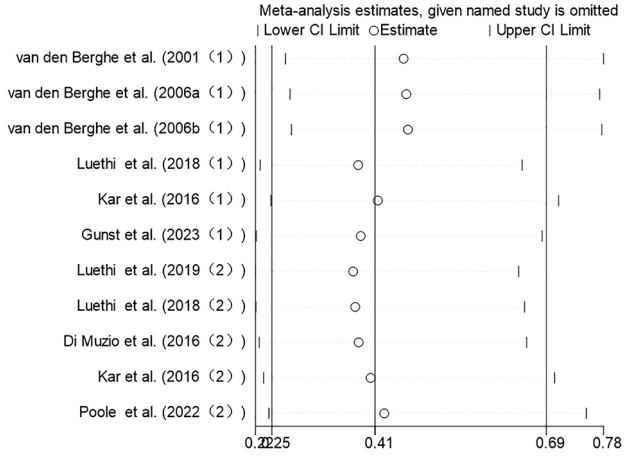

Fig. 29 Sensitivity analysis of Hypoglycemia incidence(2006a: Intention-to-Treat Group; 2006b: Group in ICU for ≥ 3 Days)

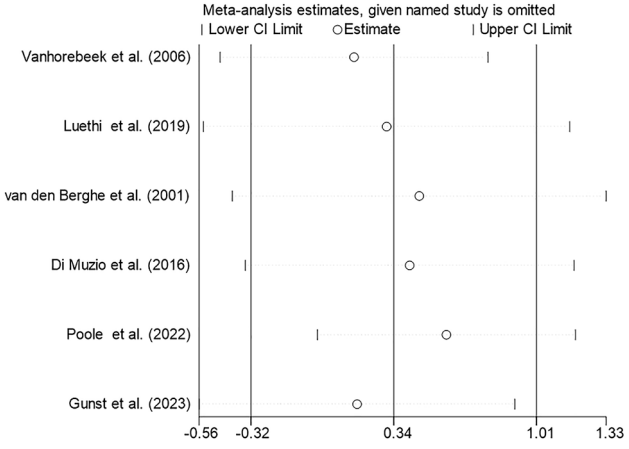

Fig. 30 Sensitivity analysis of Length of ICU stay

Conclusion

In conclusion, current evidence suggests that liberal glucose control (>180 mg/dL), as compared with other blood glucose control targets (80–110 mg/dL or 108–180 mg/dL), reduces the risk of hypoglycemia, but increases ICU mortality rate, in-hospital mortality rate, and the proportion of patients requiring RRT. Our findings provide guidance for glycemic management of critically ill patients in ICU. Moreover, conducting large-scale, high-quality clinical trials is crucial to confirm and strengthen our conclusions.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions
Jiahui Ma: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft preparation. Xu Wang: Methodology, Formal analysis, Writing - review and editing. Yan Zhang: Formal analysis, Writing - review and editing. Chunyan Ge: Conceptualization, Formal analysis, Writing - review and editing. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
An ethics statement is not applicable because this study is based exclusively on published literature.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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