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Acute Glycemic Variability and Early Outcomes After Cardiac Surgery: A Meta-Analysis

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ABSTRACT

The influence of acute glycemic variability (GV) on early outcomes of patients after cardiac surgery remains not fully determined. We performed a systematic review and meta-analysis to evaluate the association between acute GV and in-hospital outcomes of patients after cardiac surgery. Relevant observational studies were obtained by search of electronic databases including Medline, Embase, Cochrane Library, and Web of Science. A randomized-effects model was selected to pool the data by incorporating the influence of potential heterogeneity. Nine cohort studies involving 16 411 patients after cardiac surgery were included in this meta-analysis. Pooled results showed that a high acute GV was associated with an increased risk of major adverse events (MAE) during hospitalization for patients after cardiac surgery [odds ratio [OR]: 1.29, 95 % CI: 1.15 to 1.45, $p < 0.001$, $I22 = 38$ %]. Sensitivity analysis limited to studies of on-pump surgery and GV evaluated by coefficient of variation of blood glucose showed similar results. Subgroup analysis suggested that a high acute GV was related to an increased incidence of MAE in patients after coronary artery bypass graft, but not for those after isolated valvular surgery ($p = 0.04$), and the association was weakened after adjustment of glycosylated hemoglobin ($p = 0.01$). Moreover, a high acute GV was also related to an increased risk of in-hospital mortality (OR: 1.55, 95 % CI: 1.15 to 2.09, $p = 0.004$; $I22 = 0$ %). A high acute GV may be associated with poor in-hospital outcomes in patients after cardiac surgery.

Introduction

Glycemic disorder has been suggested to be related to a poor prognosis of patients after cardiac surgery [1]. Accumulating evidence suggests that compared to those without preexisting diabetes, patients with diabetes are associated with poor clinical outcomes after cardiac surgery [2]. A previous meta-analysis including 12 965 patients from 11 cohort studies showed that diabetes may be an independent risk factor of mortality in patients after coronary artery bypass graft (CABG) [3]. Subsequent studies indicated that the influence of diabetes on the prognosis of patients after cardiac surgery is complicated, which may also be influenced by the strategy of blood control [4, 5]. It was shown that compared with moderate glycemic control strategy (7.8–10.0 mmol/l) in patients with diabetes undergoing cardiac surgery, who maintained strict glycemic control (7.8 mmol/l), was associated with lower risk of atrial fibrillation (AF) and sternal wound infection, although there was no significant differences in postoperative mortality, stroke, and hypoglycemic episodes [6]. However, results of previous studies were not consistent, and a recent study suggested that strict glucose control was associated with an increased risk of in-hospital mortality among patients with diabetes after CABG, whereas it reduced the risk of major complications among non-previous diabetic patients [7]. The potential adverse influence of strict glucose control on survival of patients after cardiac surgery may be related to the

increased risk of hypoglycemia [8]. Collectively, these findings suggest the complexity of the influences of glycemic disorders and glycemic control strategies on the clinical outcomes of patients after cardiac surgery.

Since persistent hyperglycemia and incidental hypoglycemia have both been suggested to be associated with adverse outcomes of patients after cardiac surgery, it was hypothesized that acute glycemic fluctuation may be an important predictor of poor prognosis of these patients [9]. The concept of glycemic variability (GV) was proposed during the research of glycemic disorder in recent decades. By definition, GV reflects the extent of glucose fluctuation within days (acute GV) or months/years (long-term GV). Increasing evidence suggests that for patients with acute clinical conditions, a high acute GV may be a risk factor of poor prognosis, such as in hospitalized patients with acute stroke [10], sepsis [11], acute coronary syndrome [12], and intracranial hemorrhage [13]. However, the influence of acute GV in perioperative period on the in-hospital outcomes of patients after cardiac surgery remains not fully determined [14, 15]. Although several pilot studies have been performed, the results of these studies are not always consistent [16–24]. Accordingly, we performed a systematic review and meta-analysis to evaluate the association between acute GV and in-hospital outcomes of patients after cardiac surgery.

Materials and Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) [25, 26] and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) [27] guidelines in conducting and reporting of the meta-analysis.

Search of electronic databases

We identified relevant studies by a systematic search of Medline, Embase, Cochrane Library, and Web of Science electronic databases using the following terms: (1) “glycemic variability” OR “glyceamic variability” OR “glucose variability” OR “glucose fluctuation” OR “standard deviation of blood glucose” OR “coefficient of variation of blood glucose” OR “glycemic lability index” OR “GLI” OR “mean amplitude of glycemic excursion” OR “MAGE” OR “largest amplitude of glycemic excursion” OR “LAGE”; and (2) “cardiac surgery” OR “heart surgery” OR “coronary artery bypass” OR “CABG” OR “cardiopulmonary bypass” OR “valve surgery” OR “tricuspid valve replacement” OR “mitral valve replacement” OR “aortic valve replacement”. The search was performed from the inception of the databases to the date of last search (February 20, 2023). Only studies involving human subjects and published in English were selected. According to the aim of the meta-analysis, only original studies were included. However, we also performed a manual check-up for the reference lists of the related original and review articles for potential identification of non-included original studies.

Selection of eligible studies

The PICOS criteria were used for study inclusion.

1. P (Participants): Adult patients who received cardiac surgery.
2. I (Intervention/exposure): Patients with a high acute GV during the perioperative period of the surgery. The parameters, protocols, and cutoff values for measuring acute GV were consistent of the methods used in the original studies.
3. C (Control/comparator): Patients with a low acute GV during the perioperative period of the surgery.
4. O (Outcome): The primary outcome was the incidence of major adverse events (MAE) during hospitalization, which generally included a composite of in-hospital mortality, myocardial infarction, pneumonia, stroke, renal failure, surgical site infection requiring operative intervention and mediastinal reexploration for reintervention for bleeding/tamponade, valvular dysfunction, graft dysfunction, or other complications. The secondary outcome was the incidence of in-hospital all-cause mortality.
5. S (Study design): Observational studies with longitudinal follow-up, such as cohort studies, nested case-control studies, and post-hoc analysis of clinical trials. Only studies published as full-length articles peer-reviewed journals in English were included in the meta-analysis. Grey literatures such as conference abstracts or unpublished data were excluded because these literatures are mostly not peer-reviewed.

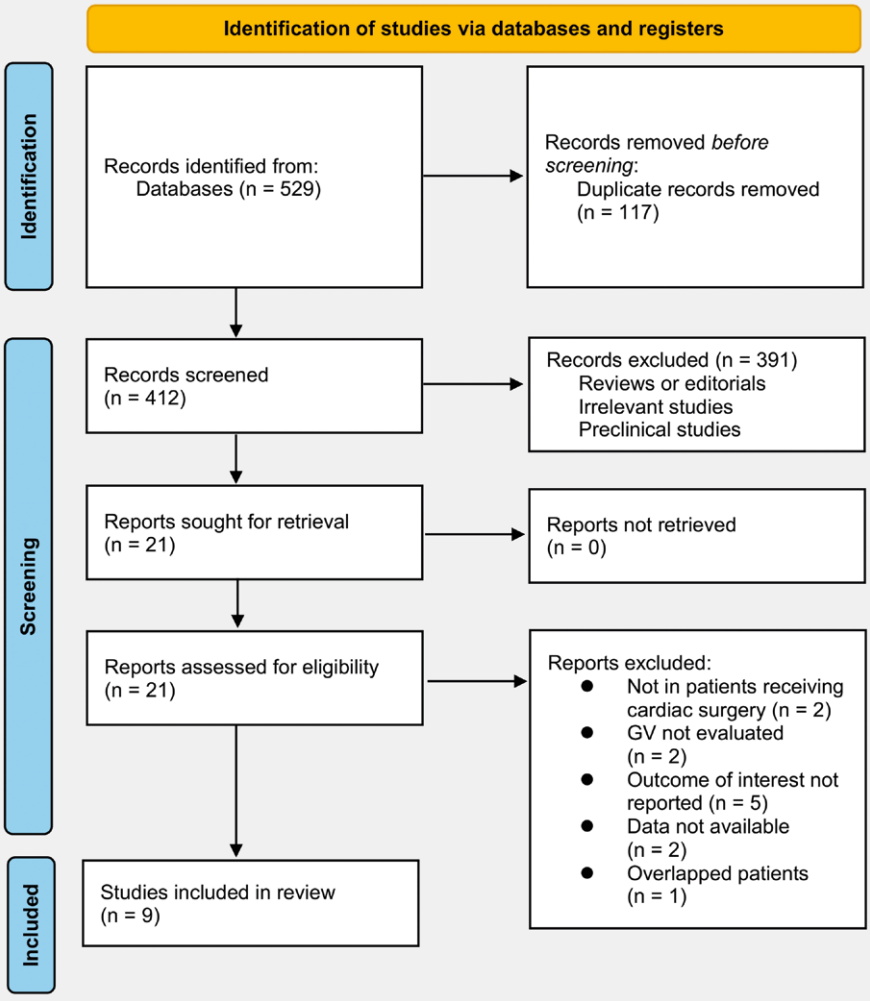
Reviews, editorials, meta-analyses, preclinical studies, studies that did not include patients after cardiac surgery, without measuring acute GV as exposure, or not reporting the outcomes of interest were excluded.

Study quality evaluation and data collection

The Newcastle-Ottawa Scale (NOS) [28] was used for study quality assessment, which included three domains such as defining of study groups, between-group comparability, and validation of the outcome. A total of nine criteria were incorporated for the NOS, and one point was given if a certain criterion was met by the individual study. This scale totally scored from 1 to 9 stars, with 9 stars indicating the highest study quality level. Two of the authors independently conducted electronic database search, extraction of study data, and assessment of study quality according to the inclusion criteria described above. If there were discrepancies, discussion with the corresponding author was indicated to resolve them. The extracted data included the following: (1) study information (authors, countries, publication year, and study design); (2) numbers of patients included, type of surgery, mean age, sex, and diabetic status of the patients; (3) parameters and durations for measuring GV; (4) detailed definition of MAE and number of patients who had MAE during hospitalization; and (5) variables included in the multivariate regression analysis for the association between acute GV and in-hospital outcomes of patients after cardiac surgery.

Statistical methods

Odds ratios (ORs) and 95 % confidence intervals (CIs) were selected as the general outcome variable for the relationship between acute GV and in-hospital outcomes of patients after cardiac surgery. Data of ORs and standard errors (SEs) were calculated from 95 % CIs or p-values, and an additional logarithmical transformation was performed to stabilize variance and normalize to the distribution [25]. The Cochrane Q-test was used to evaluate the heterogeneity, and the I^2 statistic was also estimated [29]. Heteroge-



▶ **Fig. 1** Flowchart of database search and study inclusion.

neity was deemed to be significant if $I^2 > 50\,\%$. We used a randomized-effects model for data synthesis because this model has incorporated the potential between-study heterogeneity and could provide a more generalized result [25]. Sensitivity and subgroup analysis were performed to evaluate the influences of patient or study characteristics on the outcome of the meta-analysis. Funnel plots were constructed, and a visual inspection of the symmetry was conducted to reflect the publication bias. The Egger's regression asymmetry test was further performed for the evaluation of potential publication bias [30]. We used the RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and Stata (version 12.0; Stata Corporation, College Station, TX, USA) software for the statistical analyses.

Results

Results of database search

The database search process is summarized in ▶ **Fig. 1**. Briefly, 529 articles were found in the initial literature search of the databases; after excluding the duplications, 412 studies remained. An additional 391 were excluded through screening of the titles and abstracts mainly because of the irrelevance to the meta-analysis. The remaining 21 studies underwent a full-text review, of which 12 were further excluded for the reasons listed in ▶ **Fig. 1**. Finally, nine observational studies [16–24] were included in the meta-analysis.

Characteristics of the included studies

As shown in ▶ **Table 1**, three prospective cohort studies [17, 18, 21], and six retrospective cohort studies [16, 19, 20, 22–24] were included in the meta-analysis. These studies were published between 2010 and 2023 and performed in the United States, Korea, and China, respectively. Overall, 16 411 patients after cardiac surgery were included. The surgery type included CABG, valvular surgeries, and other types of cardiac surgery, which were mainly on-pump cardiac surgeries (95.6 %). The mean ages of the patients were 42 to 68 years, and the proportions of men were 54 % to 84 %. The prevalence of diabetes was 8 % to 100 % among the included patients. The coefficient of variation of blood glucose (CVBG) was used to evaluate acute GV in eight studies [16–23], which was de-

▶ **Table 1** Characteristics of the included studies.

Study [Ref]	Country	Design	Surgery	On-pump (%)	No. of patients	Mean age (years)	Men (%)	DM (%)	Parameters for GV	Duration for GV	Definition of MAE	No. of patients with MAE	Variables adjusted
Duncan 2010 [16]	USA	RC	Any on-pump cardiac surgery	100	4302	64.2	66.9	23.8	CVBG	During ICU stay	Cardiac and neurologic morbidities, prolonged intubation, renal morbidity and infection, and death	367	Age, sex, hypoglycemia, histories of HTN, DM, COPD, AF, procedural and perioperative characteristics
Subramaniam 2014 [17]	USA	PC	CABG with or without valvular surgery	100	1461	68	74.8	38.6	CVBG	During the first 24 h in ICU after surgery	In-hospital mortality, MI, pneumonia, stroke, renal failure, SSI requiring operative intervention and mediastinal reexploration for reintervention for bleeding/tamponade, valvular dysfunction, graft dysfunction, or other complications	143	Age, sex, history of MI, CHF and COPD, HbA1c levels (above vs. below 6.5 %), STS score, and valvular surgery
Bardia 2017 [18]	USA	PC	Isolated valve surgery	100	763	67	54.8	19	CVBG	During the first 24 h in ICU after surgery	In-hospital death, MI, reoperations, sternal infection, cardiac tamponade, pneumonia, stroke, or renal failure	87	Age, sex, HbA1c, dialysis, STS score, dyslipidemia, and cross-clamp time
Clement 2019 [19]	USA	RC	Isolated CABG	96	2215	64.9	83.5	48.5	CVBG	During the first 24 h in ICU after surgery	Postoperative cardiac arrest, pneumonia, renal failure, stroke, sepsis, reoperation, and mortality	260	Age, sex, HbA1c, EF, hyperlipidemia, HTN, time of CPB, and total blood transfusion
Rangasamy 2020 [21]	USA	PC	Any on-pump cardiac surgery	100	1963	67.8	70.8	35.4	CVBG	During the first 24 h in ICU after surgery	Death, reoperation, deep sternal infection, stroke, pneumonia, renal failure, tamponade, and MI	170	Age, sex, comorbidities, DM, STS score, and surgery type

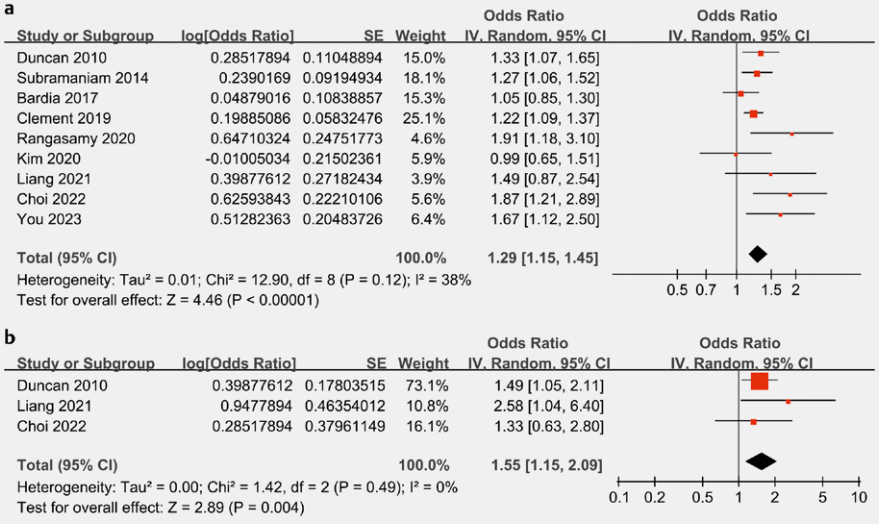
▶ **Table 1** Continued

Study [Ref]	Country	Design	Surgery	On-pump (%)	No. of patients	Mean age (years)	Men (%)	DM (%)	Parameters for GV	Duration for GV	Definition of MAE	No. of patients with MAE	Variables adjusted
Kim 2020 [20]	Korea	RC	Off-pump CABG	0	703	65.8	71	100	CVBG	During the first 24 h in ICU after surgery	Postoperative permanent stroke, prolonged ventilation, deep sternal wound infection, renal failure, reoperation, and mortality	128	Age, sex, CHF, CKD, PAD, previous PCI, MR, HbA1c
Liang 2021 [22]	China	RC	Cardiac surgery for IE	100	381	42	63.1	8.5	CVBG	During the first 24 h in ICU after surgery	All-cause death, stroke, myocardial infarction, acute heart failure, IE recurrence, acute renal failure and sepsis	79	Age, sex, HbA1c, systemic emboli, staphylococcus infection, uncontrolled infection, prosthetic valve endocarditis, mitral and aortic involvement
Choi 2022 [23]	Korea	RC	CABG and/or valvular surgery	100	705	66	59.1	30.9	CVBG	During surgery and post-operative period	Mortality, permanent stroke, pneumonia, renal failure, prolonged ventilation, deep sternal wound infection, and reoperation	121	Age, sex, education, eGFR, surgery type, CPB time, and VIS at end of surgery
You 2023 [24]	China	RC	CABG	100	3918	60.9	74.5	100	LAGE	During post-operative period	Mortality, acute MI, strokes and acute kidney injuries	126	Age, sex, BMI, smoking, LDL-C, CRF, CHF, previous MI, and PAD

GV: Glycemic variability; MAE: Major adverse events; CPB: Cardiopulmonary bypass; CABG: Coronary artery bypass graft; HbA1c: glycosylated hemoglobin; DM: Diabetes mellitus; RC: Retrospective cohort; PC: Prospective cohort; IE: Infective endocarditis; CVBG: Coefficient of variation of blood glucose; LAGE: Largest amplitude of glycemic excursion; ICU: Intensive care unit; MI: Myocardial infarction; SSI: Surgical site infection; HTN: Hypertension; AF: Atrial fibrillation; COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure; STS: Society of Thoracic Surgeons; EF: Ejection fraction; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtrating rate; PAD: Peripheral artery disease; PCI: Percutaneous coronary intervention; MR: Mitral regurgitation; CRF: Chronic renal failure; BMI: Body mass index; LDL-C: Low-density lipoprotein cholesterol; VIS: Vasoactive-inotropic score.

▶ **Table 2** Study quality evaluation with the Newcastle-Ottawa Scale.

Study [Ref]	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age and sex	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Duncan 2010 [16]	0	1	1	1	1	1	1	1	1	8
Subramaniam 2014 [17]	1	1	1	1	1	1	1	1	1	9
Bardia 2017 [18]	1	1	1	1	1	1	1	1	1	9
Clement 2019 [19]	0	1	1	1	1	1	1	1	1	8
Rangasamy 2020 [21]	1	1	1	1	1	1	1	1	1	9
Kim 2020 [20]	0	1	1	1	1	1	1	1	1	8
Liang 2021 [22]	1	1	1	1	1	1	1	1	1	9
Choi 2022 [23]	0	1	1	1	1	1	1	1	1	8
You 2023 [24]	0	1	1	1	1	1	1	1	1	8



▶ **Fig. 2** Forest plots for the meta-analysis of the association between acute GV and in-hospital outcome of patients after cardiac surgery. **a**: Forest plots for the association between acute GV and the risk of MAE in patients after cardiac surgery; and **b**: Forest plots for the association between acute GV and the risk of in-hospital mortality in patients after cardiac surgery.

fined as the standard deviation divided by the mean values of the blood glucose during the observational duration [31]. For another study, the largest amplitude of glycemic excursion (LAGE) was used to define acute GV, which was calculated as the difference between the maximum and minimum blood glucose levels in a day [31]. The duration for measuring acute GV varied from during the first 24 hours to several days after surgery. During hospitalization, MAE occurred in 1481 (9.1 %) patients. Variables including maternal age, sex, comorbidities, surgery characteristics, diabetic status, and glycemic levels, etc. were adjusted to a different degree among the

▶ **Table 3** Sensitivity and subgroup analyses for the association between GV and MAEs after cardiac surgery.

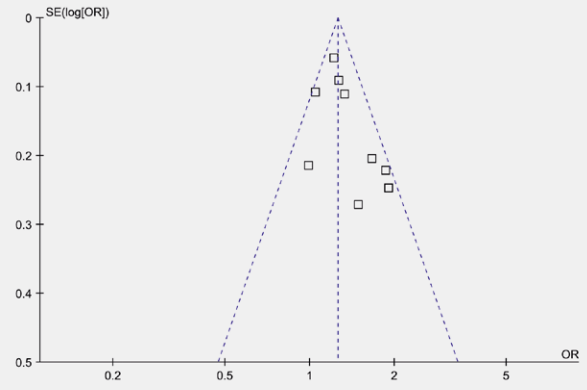
	MAE				
Study characteristics	**Dataset number**	**OR [95 % CI]**	**I^2**	**p for subgroup effect**	**p for subgroup difference**
Use of CPB					
Only on-pump surgeries	7	1.37 [1.18, 1.60]	45 %	< 0.001	–
Parameters for GV					
Only studies with CVBG	8	1.27 [1.13, 1.42]	36 %	< 0.001	–
Study location					
America	5	1.24 [1.11, 1.38]	33 %	< 0.001	
Asia	4	1.46 [1.10, 1.94]	39 %	0.009	0.29
Study design					
Prospective	3	1.27 [1.01, 1.61]	63 %	0.04	
Retrospective	6	1.32 [1.15, 1.52]	30 %	< 0.001	0.75
Surgery type					
CABG	4	1.24 [1.12, 1.38]	11 %	< 0.001	
Valvular surgery	1	1.05 [0.85, 1.30]	–	0.65	
Mixed cardiac surgery	4	1.49 [1.25, 1.78]	3 %	< 0.001	0.04
Prevalence of diabetes					
< 35 %	4	1.32 [1.05, 1.66]	55 %	0.03	
≥ 35 %	5	1.29 [1.12, 1.49]	36 %	< 0.001	0.87
Duration of GV measurements					
First 24 h after surgery	6	1.22 [1.09, 1.36]	27 %	< 0.001	
Longer than 24 h	3	1.49 [1.22, 1.83]	16 %	< 0.001	0.08
Adjustment of HbA1c					
Yes	5	1.20 [1.10, 1.30]	0 %	< 0.001	
No	4	1.54 [1.28, 1.85]	11 %	< 0.001	0.01
Quality scores					
NOS = 8	5	1.32 [1.13, 1.55]	41 %	< 0.001	
NOS = 9	4	1.28 [1.04, 1.58]	49 %	0.02	0.81

GV: Glycemic variability; MAE: Major adverse events; OR: Odds ratio; CI: Confidence interval; CPB: Cardiopulmonary bypass; CABG: Coronary artery bypass graft; HbA1c: Glycosylated hemoglobin; NOS: Newcastle-Ottawa Scale; CVBG: Coefficient of variation of blood glucose.

included studies when the association between GV and in-hospital outcomes was estimated. The NOS of the included studies were 8 to 9 stars, suggesting good quality (▶ **Table 2**).

Meta-analysis results

Pooled results of nine studies [16–24] showed that a high acute GV was associated with an increased risk of MAE during hospitalization for patients after cardiac surgery (OR: 1.29, 95 % CI: 1.15 to 1.45, p < 0.001; ▶ **Fig. 2a**) with mild heterogeneity (p for Cochrane Q-test = 0.12, I^2 = 38 %). Sensitivity analysis limited to studies of on-pump surgery only (OR: 1.37, 95 % CI: 1.18 to 1.60, p < 0.001; I^2 = 45 %) or studies with GV evaluated by CVBG only (OR: 1.27, 95 % CI: 1.13 to 1.42, p < 0.001; I^2 = 36 %) also showed consistent results (▶ **Table 3**). Interestingly, subgroup analysis suggested that a high acute GV was related to an increased incidence of MAE in patients after CABG (OR: 1.24, 95 % CI: 1.12 to 1.38, p < 0.001; I^2 = 11 %) or mixed types of cardiac surgery (OR: 1.49, 95 % CI: 1.25 to 1.78, p < 0.001; I^2 = 3 %), but not for those after isolated valvular surgery (OR: 1.05, 95 % CI: 0.85 to 1.30, p = 0.65; p for subgroup difference = 0.04; ▶ **Table 3**). Moreover, the association was weakened in studies after adjustment of HbA1c (OR: 1.20, 95 % CI: 1.10 to 1.30, p < 0.001; I^2 = 0 %) as compared to those without adjustment of HbA1c (OR: 1.54, 95 % CI: 1.28 to 1.85, p < 0.001; I^2 = 11 %; p for subgroup difference = 0.01; ▶ **Table 3**). Subgroup analysis according to study location, design, prevalence of diabetes, duration of GV measurements, and study quality scores showed similar results (p for subgroup difference all > 0.05; ▶ **Table 3**). Finally, meta-analysis of three studies [16, 22, 23] showed that a high acute GV was also related to an increased risk of in-hospital mortality in patients



▶ **Fig. 3** Funnel plots for the publication bias underlying the meta-analysis of the association between acute GV and the risk of MAE in patients after cardiac surgery.

after cardiac surgery (OR: 1.55, 95 % CI: 1.15 to 2.09, p = 0.004; I^2 = 0 %; ▶ **Fig. 2b**).

Publication bias

▶ **Fig. 3** shows the funnel plots regarding the association between acute GV and the incidence of in-hospital MAE in patients after cardiac surgery. Visual inspection found symmetry of the plots, which suggested a low risk of publication bias. Egger's regression test also suggested a low risk of publication bias (p = 0.80). For the meta-analysis of the relationship between acute GV and the risk of in-hospital mortality, the publication bias could be evaluated since only three studies were included.

Discussion

In this meta-analysis, we pooled the results of nine eligible cohort studies and the results showed that a high GV during the perioperative period was associated with an increased risk of in-hospital MAE in patients after cardiac surgery. The results were mainly based on patients receiving on-pump cardiac surgeries and studies with GV measured using CVBG. Subsequent subgroup analyses according to the location of study country, study design, prevalence of diabetes, duration of GV measurements, and study quality scores showed consistent results. In addition, the subgroup analysis suggested that the association between a high acute GV and an increased risk of MAE after cardiac surgery was weakened but still significant after the adjustment of HbA1c. Finally, a high GV during the perioperative period was also associated with an increased risk of in-hospital mortality in these patients. Taken together, results of the meta-analysis suggest that a high acute GV in perioperative period may be a risk factor of poor in-hospital outcome in patients after cardiac surgery, even after considering the mean glucose status.

To the best of our knowledge, this study is the first systematic review and meta-analysis which investigated the association between acute GV in perioperative period and the in-hospital outcomes of patients after cardiac surgery. The methodological advantages of the study may include the followings. First, we conducted the extensive literature search in four commonly used electronic databases and retrieved the up-to-date literatures concerning the potential prognostic role of acute GV in patients after cardiac surgery. In addition, only cohort studies were included, and the results of the meta-analysis supported a longitudinal association between a high GV and poor in-hospital outcome in these patients. Moreover, multivariate regression analyses were performed among all of the included studies when the association between acute GV and in-hospital MAE was evaluated. Accordingly, results of the meta-analysis suggest that the relationship between a high acute GV and an increased risk of MAE may be independent of the potential confounding factors such as the age, sex, and comorbidities of the patients. Finally, we performed multiple sensitivity and subgroup analyses for the outcome of MAE. The consistent results in these studies further confirmed the stability and robustness of the findings. Overall, the above results indicate that a high acute GV during the perioperative period may be a risk factor of poor in-hospital outcome of patients after cardiac surgery, and measuring acute GV may be important for prognostic prediction in these patients.

Several parameters have been used to assess glycemic variability currently. There is a new vital glycemic control index called time in target range (TIR) that was recently proposed to describe the percentage of time when glucose levels are within the target range during one day [32]. According to the American Diabetes Association (ADA) guidelines, the TIR is highly recommended for assessing blood glucose fluctuations and determining glycemic target levels [33]. However, none of the included studies used TIR to indicate acute GV because this parameter is recently proposed. In this meta-analysis, most of the included studies used CVBG as the parameter for reflecting cute GV, which is convenient and easy to calculate but may be affected by the different protocols of glucose monitoring [34]. Efforts are still needed to determine the optimal parameter and cutoff for GV in patients with acute clinical conditions.

Results of the subgroup analysis showed that difference of surgery type may affect the association between acute GV and the incidence of MAE in patients after cardiac surgery. We observed a significant association in patients who received CABG or mixed type of cardiac surgery, but not in patients after isolated valvular surgery. These results should be interpreted with caution because only one study was available for the subgroup of isolated valvular surgery. In addition, results of the meta-analysis according also showed that the association between a high acute GV and the risk of in-hospital MAE was weakened but still significant in studies after adjustment of HbA1c, as compared to that of studies without adjustment of HbA1c. These findings may suggest that the relationship between a high acute GV and an increased risk of MAE in patients after cardiac surgery may be independent of the mean glycemic levels, as indicated by HbA1c. The mechanisms underlying the association between a high acute GV and poor in-hospital outcome of patients after cardiac surgery remain poorly understood at current stage. Previous studies have shown that a high acute GV may be a risk factor for acute kidney injury [35], arrhythmia (including postoperative AF) [36, 37], and postoperative delirium [23, 38] after cardiac surgery, all of these events have been related to an increased risk of in-hospital mortality in these patients. Pathophysio-

logically, a high glycemic fluctuation is associated with enhanced oxidative stress and an increased level of systemic reactive oxygen species (ROS) [39], which may mediate multiple organ injury and functional disorder in vulnerable patients, such as those who are in recovery from cardiac surgeries [40]. Studies are warranted to determine the key molecular mechanisms underlying the association between a high acute GV and poor in-hospital outcome in patients after cardiac surgery.

This study also has limitations. First, the number of studies available for the meta-analysis is small, and more prospective cohort studies are needed to validate the finding. Moreover, the parameters, cutoffs, and evaluating durations for acute GV varied among the included studies, which may lead to heterogeneity. However, since no consensus has been reached regarding the optimized parameter and protocol for evaluating GV in patients with acute clinical conditions, studies are needed in this regard. In addition, it is important to determine if the results were similar in patients with and without preexisting diabetes. However, this is not possible based on the currently included studies because stratified analyses according to diabetic status of the patients were rarely reported. Further studies are needed. Furthermore, although multivariate regression analysis was used in all of the included studies, we could not exclude the possibility that there may be residual factors confounding the association, such as the potential influences of different antidiabetic medications and glycemic control strategies. A recent study showed that dapagliflozin (one of the sodium-glucose cotransporter-2 inhibitors) may ameliorate glycemic variability in patients with type 2 diabetes [41], while dapagliflozin has also been shown to benefit cardiac function [42]. Since poor cardiac function has been recognized as an independent risk factor of poor in-hospital outcome of patients after cardiac surgery [43], use of antidiabetic such as dapagliflozin may therefore confound the relationship between acute GV and in-hospital outcome of these patients. Finally, this meta-analysis was on the basis of observational studies. Accordingly, a causative relationship between a high GV and an increased risk of in-hospital MAE and mortality after cardiac surgery could not be derived based on this meta-analysis. Clinical studies should be considered to investigate if reduced acute glycemic fluctuation could improve the prognosis of these patients.

Conclusion

To sum up, results of the meta-analysis indicate that a high acute GV in perioperative period may be a risk factor of poor in-hospital outcome in patients after cardiac surgery. The association between a high acute GV and an increased risk of MAE after cardiac surgery is weakened but still significant even after the adjustment of HbA1c. Measuring acute GV may be important for prognostic prediction in patients after cardiac surgery. Further studies are needed to determine the optimal parameters and cutoff values for defining a high GV in these patients. In addition, studies are needed to determine whether reducing acute GV is associated with improved early outcome of patients after cardiac surgery.

Conflict of Interest

The authors declare that they have no conflict of interest.

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