Turkish Online Journal of Qualitative Inquiry (TOJQI)
Volume 12, Issue 10, October 2021: 4952-4966

Evaluate the Complicated Clinical Outcomes of Glycometabolic Status after Cardiac Surgery: A Systematic Review and Meta-Analysis

Sina Danesh[1], Abnoos Mokhtari Ardekani[2*], Saeed Torabi[3], Sevda Ghader[4]
[1]Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran.
[2]Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Science, & Physiology Research Center, Kerman University of Medical Sciences, Kerman, Iran.
[3]Department of Anesthesiology and Intensive Care Medicine, University Hospital of Cologne, Cologne, Germany.
[4]Department of Pediatrics, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran.
***Corresponding Author:**Abnoos Mokhtari Ardekani

Abstract
Background and aim:hyperglycemia can be a strong predictor of postoperative complications and mortality in people without a history of diabetes mellitus undergoing cardiac surgery. The aim of current Systematic Review and Meta-Analysis study was evaluate the complicated clinical outcomes of Glycometabolic Status after cardiac surgery.
Method: From the electronic databases, PubMed, Scopus, Web of Science, EBSCO, and Embase have been used to perform a systematic literature over the last ten years between 2011 and September 2021. Risk ratio with 95% confidence interval, fixed effect model and Inverse-variance or Mantel-Haenszel method were calculated. The Meta analysis have been evaluated with the statistical software Stata/MP v.16 (The fastest version of Stata).
Result:1384 studies were selected to review the abstracts, the full text of 232 studies was reviewed. Finally, twelve studies were selected. Risk ratio of Early mortality and Late mortality between Lower HbA1c level and Higher HbA1c level was 0.01 (RR, 0.01 95 % CI 0.00, 0.01) and (RR, 0.08 95 % CI 0.02, 0.14), respectively. Risk ratio of Sternal wound infection between Lower HbA1c level and Higher HbA1c level was 1.04 (RR, 1.04 95 % CI 1.24, 0.83)with low heterogeneity(I^2 = 37.01%; p=0.09).
Conclusion: Current systematic review and meta-analysis study showed that preoperative examination of HbA1c levels could play an important role in patients undergoing heart surgery. HbA1c levels indicate a persistent risk.
Keywords: HbA1c, Glycometabolic Status, Cardiac Surgery

Introduction
Diabetes mellitus (DM) is a disorder in which the body does not produce enough or respond normally to insulin, causing blood sugar (glucose) levels to be abnormally high(1). About 422 million adults have DM, according to the World Health Organization(2).In these patients, the risk of cardiovascular disease(CVDs) is 2 to 4 times higher than other people, and the risk of death from CVDs in these patients is about 2 to 5 times higher.According to reports, 25% of patients with DM have undergoing coronary revascularization(3). Evidence suggests that postoperative increase in blood glucose levels is associated with increased postoperative complications and decreased survival following coronary artery bypass grafting(4). In random serum samples, hyperglycemia does not necessarily indicate a long-term status of glycometabolic control,

but factors such as underlying disease and related therapies can also lead to hospitalization (5, 6).Studies have shown that hyperglycemia can be a strong predictor of postoperative complications and mortality in people without a history of DM undergoing cardiac surgery (7-9).Glycosylated hemoglobin (HbA1c) is a marker of evaluation of long-term glycemic control in diabetic patients and predicts risks for the development and/or progression of diabetic complications. Glycosylation process depends on the exposure to glucose, so on the half-life of erythrocyte(10).Measurement of HbA1c before surgery can be a good choice for defining glycometabolic status, as it reflects blood glucose 2-3 months before evaluation(11).According to the latest report from the American Diabetes Association, people with diabetes should reach a target HbA1c level of less than 7% to reduce the risk of diabetes-related complications(11). Numerous studies have examined the potential clinical implications of HbA1c levels in diabetic patients undergoing heart surgery versus controls; it is important to reach a comprehensive conclusion and provide sufficient evidence in this regard; because most studies are retrospective, and because the number of patients in each study is small, studies with a larger community are needed. Therefore the aim of current Systematic Review and Meta-Analysis study was evaluate the complicated clinical outcomes of Glycometabolic Status after cardiac surgery.

Methods

Search strategy

From the electronic databases, PubMed, Scopus, Web of Science, EBSCO, and Embase have been used to perform a systematic literature over the last ten years between 2011 and September 2021. The reason for choosing studies in the last ten years is to be able to provide sufficient evidence in this area and use newer studies. Therefore, a software program (Endnote X8) has been utilized for managing the electronic titles.

Searches were performed with mesh terms:

("Diabetes Mellitus"[Mesh]) AND ("Hyperglycemia/analysis"[Mesh] OR "Hyperglycemia/blood"[Mesh] OR"Hyperglycemia/classification"[Mesh] OR "Hyperglycemia/complications"[Mesh] OR "Hyperglycemia/surgery"[Mesh])) OR "Glycated Hemoglobin A"[Mesh]) AND "Cardiac Surgical Procedures"[Mesh].

This systematic review has been conducted on the basis of the key consideration of the PRISMA Statement–Perfumed Reporting Items for the Systematic Review and Meta-analysis(12), and PICO strategy (Table1).

Selection criteria

Inclusion criteria: Prospective and retrospective cohort studies, Randomized controlled trials studies, controlled clinical trials; in human;cardiac surgery or open-heart surgery; age>18 years; in English. In vitro studies, case studies, case reports and reviews; Animal studies were excluded from the study.

Table 1. PICO strategy.

PICO strategy	Description
P	Population/ Patient: Patients undergoing cardiac surgery
I	Intervention: cardiac surgery
C	Comparison:HbA1c level
O	Outcome: Early and Late mortality, Sternal wound infection, Acute kidney injury, Myocardial infarction, Hospital length of stay

Data Extraction and analysis method

The quality of randomized studies included was assessed using Collaboration's tool(13). The scale scores for low risk was 1 and for High and unclear risk was 0. Scale scores range from 0 to 6. A higher score means higher quality. Newcastle-Ottawa Scale (NOS) (14) used to assessed quality of the cohort studies and case-control studies, This scale measures three dimensions (selection, comparability of cohorts and outcome) with a total of 9 items. In the analysis, any studies with NOS scores of 1- 3, 4- 6 and 7- 9 were defined as low, medium and high quality, respectively.

For Data extraction, two reviewers blind and independently extracted data from abstract and full text of studies that included. Prior to the screening, kappa statistics was carried out in order to verify the agreement level between the reviewers. The kappa values were higher than 0.80. Risk ratio and mean differences with 95% confidence interval (CI), fixed effect model andMantel-Haenszel or Inverse-variance method were calculated. Random effects were used to deal with potential heterogeneity and I^2 showed heterogeneity. I^2 values above 50% signified moderate-to-high heterogeneity. The Meta analysis have been evaluated with the statistical software Stata/MP v.16 (The fastest version of Stata).

Results

In the review of the existing literature using the studied keywords, 1384 studies were found. In the initial review, duplicate studies were eliminated and abstracts of 1051 studies were reviewed. At this stage, 819 studies did not meet the inclusion criteria, so they were excluded, and in the second stage, the full text of 232 studies was reviewed by two authors. At this stage, 220 studies were excluded from the study due to incomplete data, inconsistency of results in a study, poor studies, lack of access to full text, inconsistent data with the purpose of the study. Finally, twelvestudies were selected (Figure1).

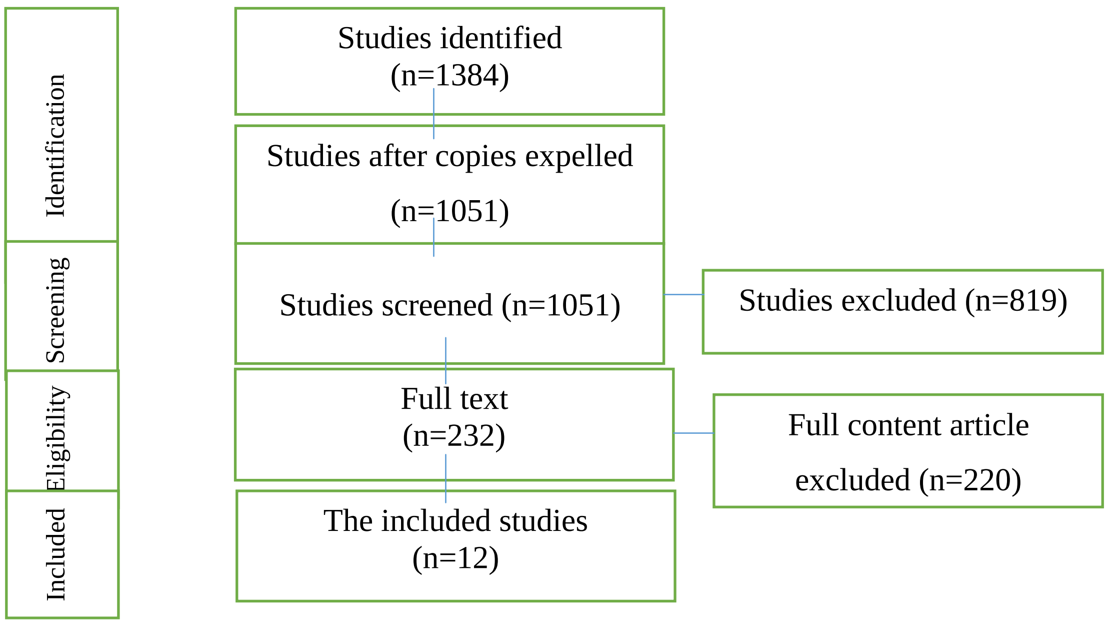

Figure 1. Study Attrition

Characteristics

Twelvestudies have been included in present article. The number of patientsin Lower HbA1c level and Higher HbA1c level groups was, 8437 with mean of age 61.42 years (male: 7098; female: 1339) and 5861 with mean of age 60.82 years (male: 4650; female: 1211), respectively. Other characteristics of the participants are reported in Table 2.

Table 2. Studies were selected for systematic review and meta-analysis.

Study. years	Number of patients				Mean of age		G1			G2			Pre.B.r		post.B.r	
	G1		G2		G1	G2	HTN (%)	HL (%)	Smoking (%)	HTN (%)	HL (%)	Smoking (%)	G1	G2	G1	G2
	M	F	M	F												
Kim et al.,2020 (15)	115	91	121	85	59.10	59.10	83.9	46.9	NR	59.10	46.9	NR	NR	NR	NR	NR
Khan et al., 2019 (16)	583	235	195	122	65	66.2	93.5	NR	NR	92.3		NR	NR	NR	NR	NR
Almogati et al.,2019 (17)	125	27	125	28	59.10	59.10	83.9	46.9	NR	59.10	46.9	NR	NR	NR	NR	NR
Robich et al.,2019 (18)	1429	284	1087	3615	62	61	61.2	42.6	41.4	51.7	50	38.7	NR	NR	NR	NR
Aydınlı et al.,2018 (19)	113	47	110	84	62.1	59.8	49.4	19.6	20.6	39.3	14.3	12.9	NR	NR	NR	NR
Ramadan et al.,2018 (20)	29	11	32	8	58.52	56.27	60	40	47.5	70	41	45	NR	NR	NR	NR
Nicolini et al.,2018 (21)	1705	249	554	116	67.2	68.4	46.5	71.9	50.11	81.2	89.4	57.89	Hb: 14.1	Hb: 13.6	Hb: 12.1	Hb: 12.6
Narayan et al.,2017 (22)	2299	177	1955	247	58.8	58.9	60.02	NR	25.12	70.84	NR	26.29	NR	NR	NR	NR

Kocogulları et al.,2017 (23)	88	24	74	16	63	60	65.2	44.6	45.4	56.7	50	36.7	Hb: 13.6 C:0.90 BUN: 16 CrCL: 109 FBG: 94	Hb:13.8 C:0.90 BUN: 17 CrCL: 111 FBG: 95	$Hb_{1th\ day}$: 9.1 $C_{1th\ day}$: 0.85 $C_{3th\ day}$: 0.75 $C_{7th\ day}$: 0.80	$Hb_{1th\ day}$: 9.0 $C_{1th\ day}$: 1 $C_{3th\ day}$: 0.87 $C_{7th\ day}$: .88
Finger et al.,2017 (24)	343	131	42	15	62.9	60	46.5	71.9	50.11	81.2	89.4	57.89	NR	NR	NR	NR
Gumus et al.,2013 (25)	177	40	205	88	60.9	60.2	43.8	51.6	57.6	62.1	50.3	45.4	Hb: 9.9	Hb: 12	Hb: 9.1	Hb: 9.8
Tsuruta et al.,2011 (26)	92	23	150	41	58.5	60.9	75.9	54.3	52.6	70.8	62.2	63.5	Hb: 5.8 C:1.1 CrCL: 109 FBG: 127.3	Hb: 6.9 C:1 CrCL: 109 FBG: 153.5	NR	NR

M: male; F: female; G1: Lower HbA1c level; G2: Higher HbA1c level; HTN: Hypertension; HL: Hyperlipidemia; Pre.B.r Preoperative blood results; post.B.r: postoperative blood results; Hb: Haemoglobin ((mg/dl)); c: Creatinine (mg/dl) ; BUN: blood urea nitrogen (mg/dl); CrCL: Creatinine Clearance (ml/min); FBG: fasting blood glucose((mg/dl); Haemoglobin (Hb); LHbA1cL: Lower HbA1c level; H HbA1cL: Higher HbA1c level

Early mortality

Risk ratio of Early mortality between Lower HbA1c level and Higher HbA1c level was 0.01 (RR, 0.01 95 % CI 0.00, 0.01)with high heterogeneity(I^2 = 62.75%; p=0.00) (Figure2). Subgroup meta-analysis showed in comparingHbA1c level <5.5% vs >5.5% was 0.01 (RR, 0.01 95 % CI 0.00, 0.02)with low heterogeneity(I^2 = 51.88%; p=0.18); comparingHbA1c level <6% vs >6% was 0.01 (RR, 0.01 95 % CI 0.00, 0.01)with low heterogeneity(I^2<0%; p=0.86); comparingHbA1c level <6.5% vs >6.5% was 0.01 (RR, 0.01 95 % CI 0.00, 0.01)with low heterogeneity(I^2=5.72%; p=0.30); comparingHbA1c level <7% vs >7% was 0.01 (RR, 0.01 95 % CI 0.00, 0.01)with high heterogeneity(I^2=79.77%; p=0.00); comparingHbA1c level <7.5% vs >7.5% was 0.00 (RR, 0.00 95 % CI 0.00, 0.01)with low heterogeneity(I^2=1.38%; p=0.36) and comparingHbA1c level <8% vs >8% was 0.00 (RR, 0.00 95 % CI -0.01, 0.01)with low heterogeneity(I^2=10.84%; p=0.29). The direction of the estimates in each glycemic level comparison subgroup favored lower HbA1c level. Overall early mortality was 1.7%.

Late mortality

Risk ratio of Late mortality between Lower HbA1c level and Higher HbA1c level was 0.08 (RR, 0.08 95 % CI 0.02, 0.14)with low heterogeneity(I^2 = 0%; p=0.99) (Figure3). Subgroup meta-analysis showed in comparingHbA1c level <5.5% vs >5.5% was 0.08(RR, 0.08 95 % CI -0.08, 0.24); comparingHbA1c level <6% vs >6% was 0.08(RR, 0.08 95 % CI -0.08, 0.24); comparingHbA1c level <6.5% vs >6.5% was 0.06(RR, 0.06 95 % CI -0.06, 0.18); comparingHbA1c level <7% vs >7% was 0.09(RR, 0.09 95 % CI -0.07, 0.24)with lowheterogeneity(I^2=0%; p=0.36); comparingHbA1c level <7.5% vs >7.5% was 0.08(RR, 0.08 95 % CI -0.08, 0.24)and comparingHbA1c level <8% vs >8% was 0.08(RR, 0.08 95 % CI -0.08, 0.24).Lower HbA1c level resulted in reduced late mortality in every glycometabolic level comparison subgroup.

Sternal wound infection

Risk ratio of Sternal wound infection betweenLower HbA1c level and Higher HbA1c level was 1.04(RR, 1.04 95 % CI 1.24, 0.83)with low heterogeneity(I^2 = 37.01%; p=0.09) (Figure4). Subgroup meta-analysis showed in comparingHbA1c level <6% vs >6% was 0.30(RR, 0.30 95 % CI 1.29, 1.89); comparingHbA1c level <6.5% vs >6.5% was 0.74(RR, 0.74 95 % CI 1.22, 0.25)with low heterogeneity(I^2<0%; p=0.81); comparingHbA1c level <7% vs >7% was 1.03(RR, 1,03 95 % CI 1.32, 0.75)with lowheterogeneity(I^2=11.07%; p=0.34); comparingHbA1c level <7.5% vs >7.5% was 1.60(RR, 1.60 95 % CI 2.13, 1.07)with low heterogeneity(I^2<0%; p=0.57) and comparingHbA1c level <8% vs >8% was 1.53(RR, 1.5395 % CI 2.06, 1.01). The highest HbA1c subgroup comparisons were associated with the highest benefit of lower glycometabolic level comparator.

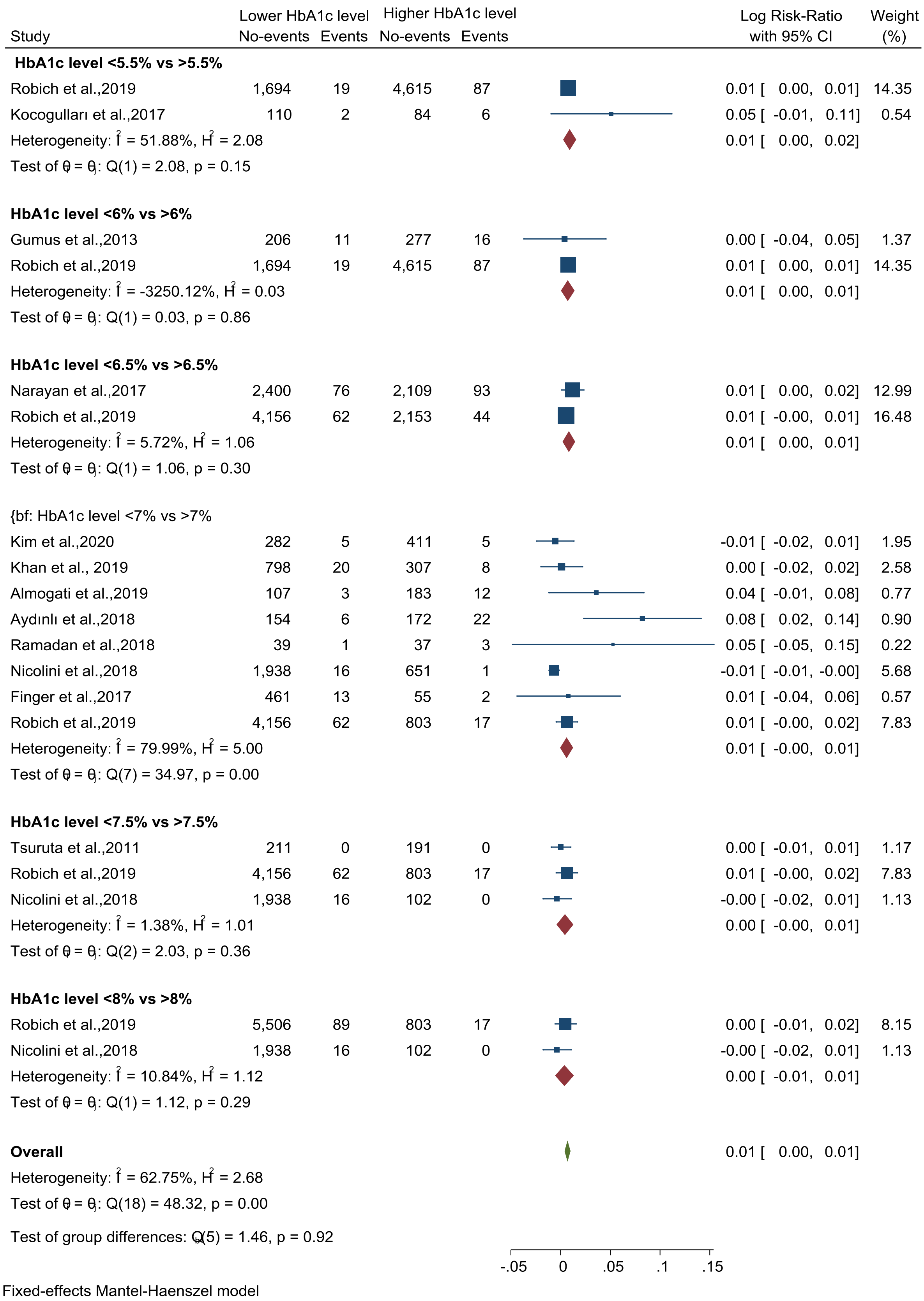

Figure 2. The Forest plot showed early mortalitybetween Lower and Higher HbA1c level

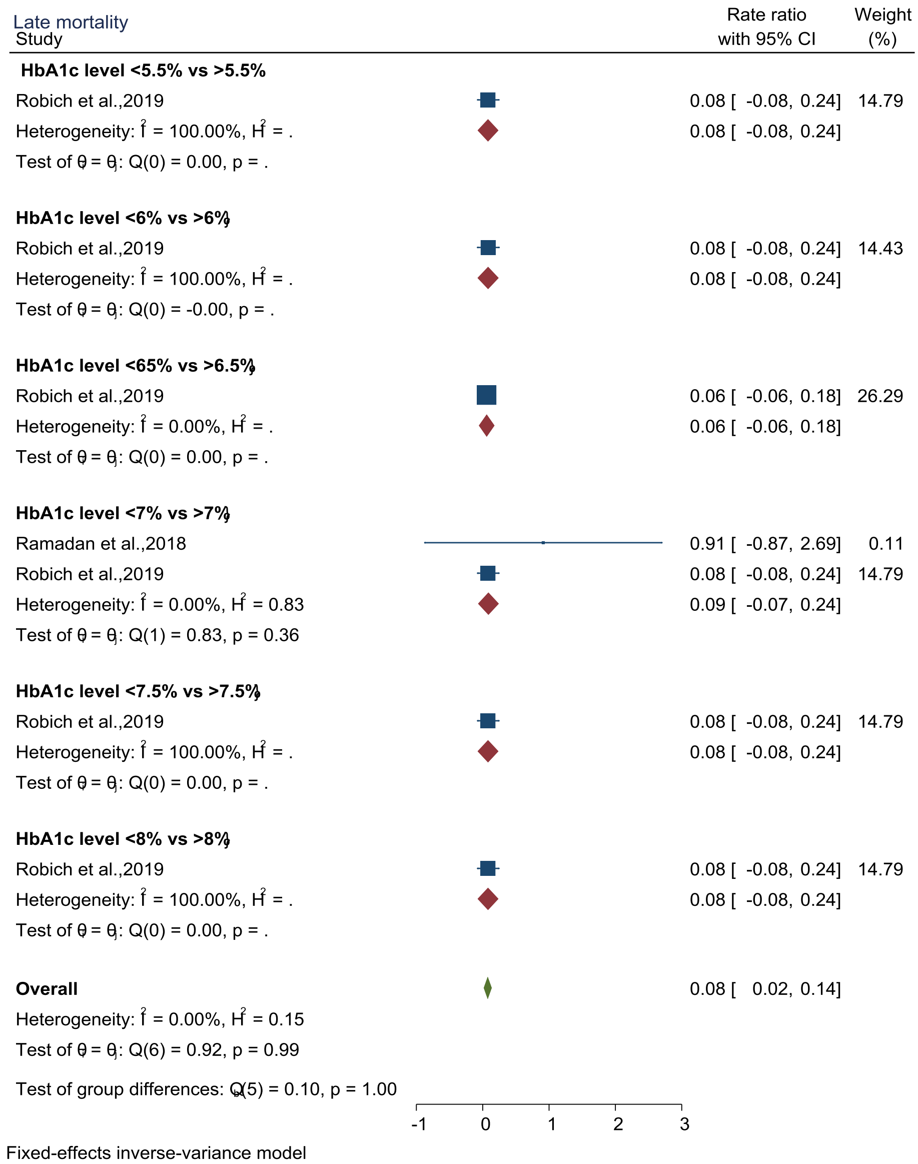

Figure 3. The Forest plot showed late mortalitybetween Lower and Higher HbA1c level

Stroke or Transient ischemic attack

Risk ratio of Stroke or Transient ischemic attackbetween Lower HbA1c level and Higher HbA1c level was 0.49(RR, 0.49 95 % CI 0.67, 0.32)with low heterogeneity(I^2<0%; p=0.84) (Figure5). Subgroup meta-analysis showed in comparingHbA1c level <5.5% vs >5.5% was 0.30(RR, 0.30 95 % CI -0.82, 0.21); comparingHbA1c level <6% vs >6% was 0.30(RR, 0.30 95 % CI -0.82, 0.21); comparingHbA1c level <6.5% vs >6.5% was 0.49(RR, 0.49 95 % CI -0.77, -0.21)with low heterogeneity(I^2<0%; p=0.40); comparingHbA1c level <7% vs >7% was 0.65(RR, 0.65 95 % CI -1.07, -0,23)with lowheterogeneity(I^2<0%; p=0.91); comparingHbA1c level <7.5% vs >7.5% was 0.66(RR, 0.66 95 % CI -1.16, -0.15)with low heterogeneity(I^2<0%; p=0.81) and comparingHbA1c level <8% vs >8% was 0.58(RR, 0.58 95 % CI -1.07, -0.08)with low heterogeneity(I^2<0%; p=0.55). The statistically significant stroke/TIA reduction in lower HbA1c group was also present in all remaining comparisons.

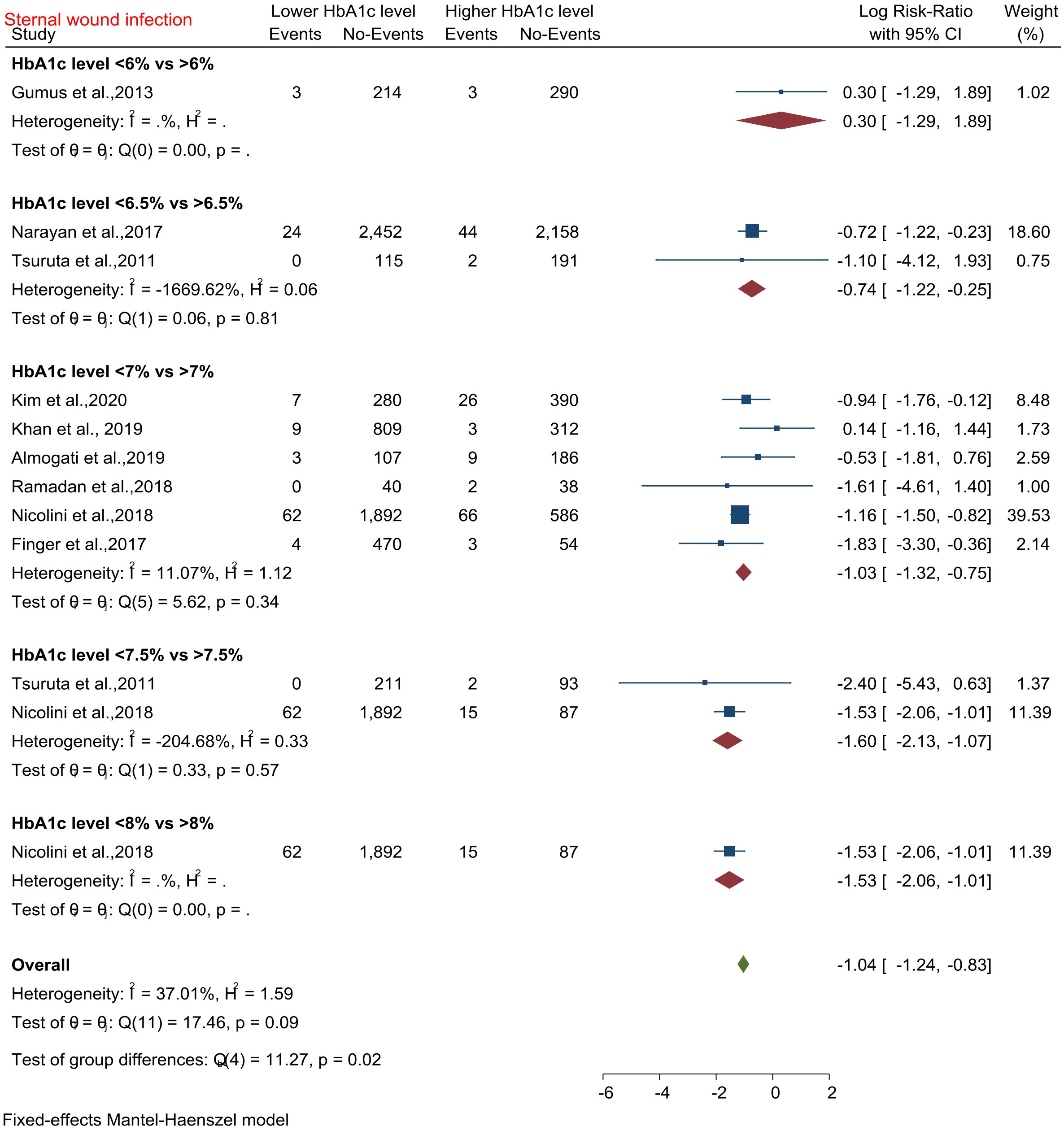

Figure 4. The Forest plot showed Sternal wound infectionbetween Lower and Higher HbA1c level

Acute kidney injury

Risk ratio of Acute kidney injury betweenLower HbA1c level and Higher HbA1c level was 0.27(RR, 0.27 95 % CI -0.31, -0.22)with low heterogeneity(I^2 = 27.69%; p=0.13) (Figure6). Subgroup meta-analysis showed in comparingHbA1c level <5.5% vs >5.5% was 0.23(RR, 0.23 95 % CI -0.33, -0.12)with high heterogeneity(I^2 = 79.98%; p=0.03); comparingHbA1c

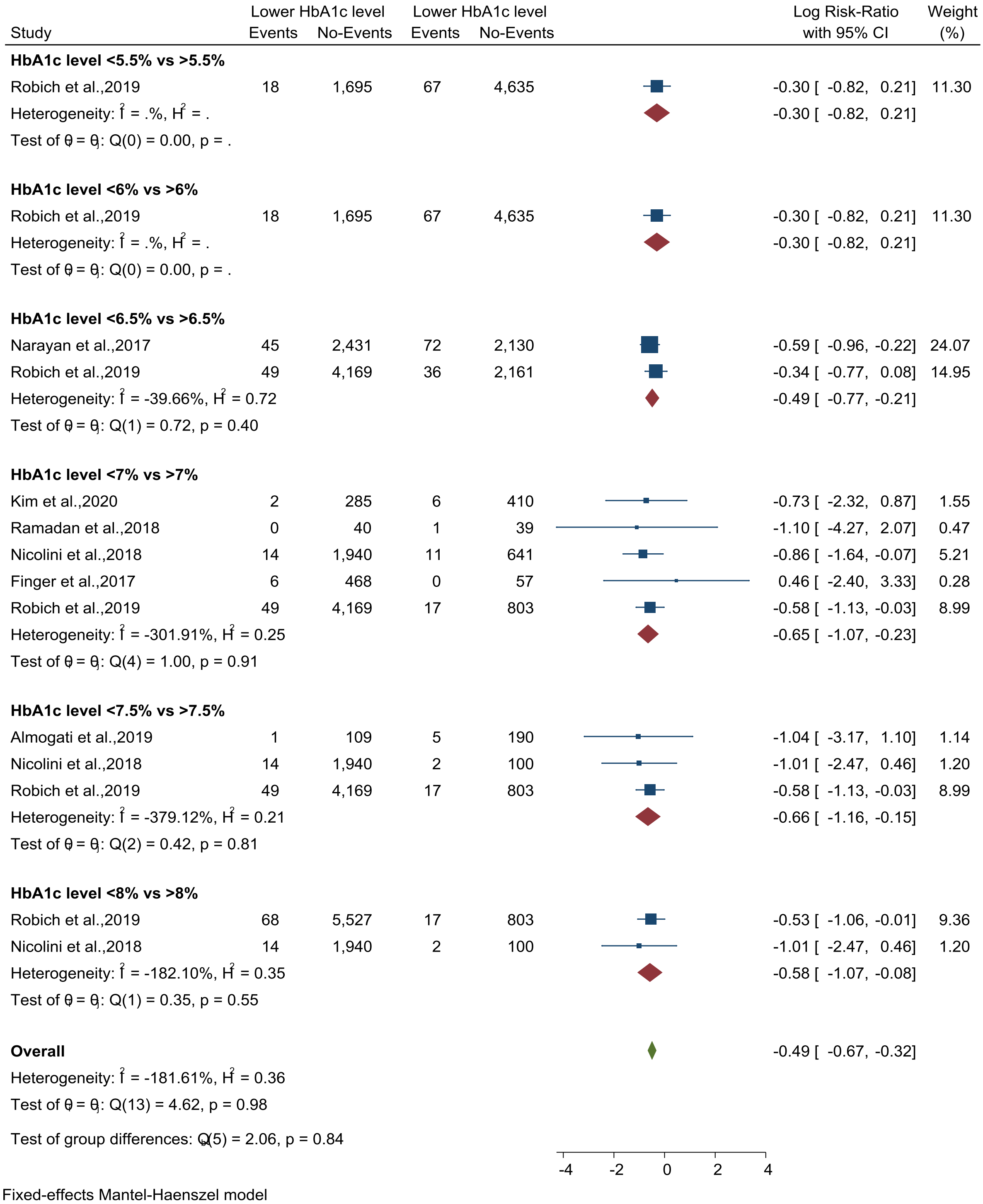

Figure 5. The Forest plot showed stroke/TIA between Lower and Higher HbA1c level

level <6% vs >6% was 0.25 (RR, 0.25 95 % CI -0.35, -0.14)with high heterogeneity(I^2=90.18%; p=0.00); comparingHbA1c level <6.5% vs >6.5% was 0.26 (RR, 0.26 95 % CI 0.34, 0.17)with low heterogeneity(I^2<0%; p=0.3059); comparingHbA1c level <7% vs >7% was 0.30 (RR, 0.30 95 % CI -0.39, -0.20)with low heterogeneity(I^2=1.78%; p=0.40); comparingHbA1c level <7.5% vs >7.5% was 0.31 (RR, 0.31 95 % CI 0.42, 0.20)with low heterogeneity(I^2<0%; p=0.96) and comparingHbA1c level <8% vs >8% was 0.26 (RR, 0.26 95 % CI -0.37, 0.15)with low heterogeneity(I^2<0%; p=0.98). The direction of the estimates in each glycemic level comparison subgroup favored lower HbA1c level, which reached a trend of reduction in the subgroup comparing.

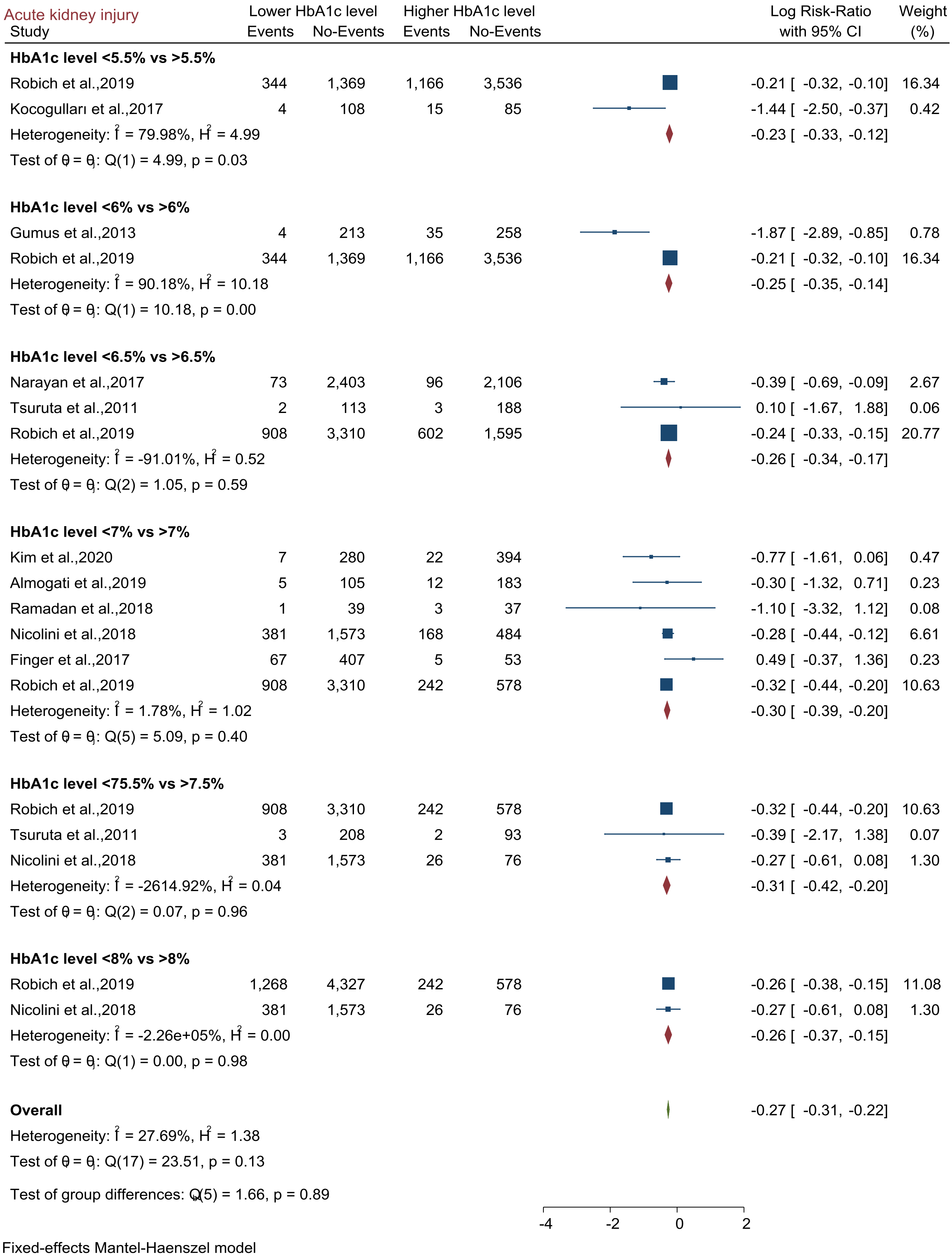

Figure 6. The Forest plot showed acute kidney injurybetween Lower and Higher HbA1c level

Discussion

Diabetes and insulin resistance are on the rise at the moment and are considered one of the most serious threats to public health(27).However, evidence suggests that elevated blood glucose levels are not unique to people with diabetes.Studies have shown that hyperglycemia is observed in surgery, even in non-diabetic patients(28). Multiple daily glucose measurements or even continuous blood glucose monitoring can provide more reliable information about glycometabolic status, but are not available to the general population(29).Various proposed methods have been proposed over time to assess and monitor glycometabolic status(5). HbA1c values indicate the average endogenous glucose exposure for 2 to 3 months(30). HbA1c indicates a long-term glyco-metabolic status in patients(31). the aim of current Systematic Review and Meta-Analysis study was evaluate the complicated clinical outcomes of Glycometabolic Status after cardiac surgery. The highest reduction in initial mortality was observed at the level of 5.0% HbA1c.Late mortality had the lowest prevalence compared to the lowest HbA1c level. Elevated postoperative blood glucose levels are associated with increased morbidity and mortality and long-term hospitalization after surgery(8, 32).Studies show that the risk of cardiovascular accidents and mortality can be significantly reduced by strict glucose control(33).Relatively long-term changes in glyco-metabolic status, regardless of previous diagnosis of diabetes, are associated with an increased risk of postoperative mortality, AKI, neurological complications, wound infection, and length of hospital stay in patients undergoing heart surgery.The results of the present meta-analysis are in line with the recommendations of the American Diabetes Association.In the present study, preoperative HbA1c levels had a statistically significant effect on the incidence of mortality in diabetic patients after cardiac surgery.One study found that the results differed from the present study. The difference in results could be attributed to the difference in follow-up time for postoperative mortality. The exact mechanisms of the association between higher HbA1c concentrations and worse clinical outcomes are not yet sufficiently elucidated.Higher HbA1c levels are commonly associated with metabolic syndrome, the components of which (obesity, dyslipidemia, hypertension, insulin resistance) increase the risk of worse surgery outcome(34). Adequate glucose control to improve surgical outcomes in diabetic and non-diabetic adults undergoing valve surgery should be demonstrated in specific prospective trials(5).In contrast to the glyco-metabolic status of preoperative disorder, the effect of abnormal or appropriate postoperative glycemic control is relatively unknown. Indeed, very few studies have addressed such issues, although persistent metabolic hyperglycemic syndrome is expected to have a significant impact on several aspects of postoperative surgical outcome, from recurrent vascular recurrence or tissue valve degeneration, endocarditis, or other side effects.The results of the present study showed that the optimal preoperative glyco-metabolic status may be beneficial for people undergoing heart surgery, however, the present study had some limitations that should be carefully interpreted in interpreting the results.Most studies were retrospective, and in some cases high heterogeneity was observed. Critical information, such as DM type, ejection fraction, coronary artery disease, surgery time, and comorbidities, which are potentially distorting, has not been reported in several studies. Is to limit the size of the effect of our findings. Also, differences in methodology can have a significant impact on the results.

Conclusion

Current systematic review and meta-analysis study showed that preoperative examination of HbA1c levels could play an important role in patients undergoing heart surgery. HbA1c levels indicate a persistent risk. Lower levels of preoperative HbA1c are associated with a lower risk of premature and late mortality compared with higher levels of HbA1c, as well as lower neurological complications and wound infection. It is recommended that all patients undergo HbA1c testing prior to Cardiac Surgery.

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