Is there a Predictive Value of Hemoglobin A1C for Complications of Cardiac Surgery?

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ABSTRACT

Objective: To investigate the effect of preoperative hemoglobin A1c levels for the complications of cardiac surgery.
Study Design: Meta-analysis.
Place of Study: Siyami Ersek Chest and Cardiovascular Surgery Education and Research Hospital, Istanbul, Turkey.
Methodology: PubMed, Scopus, Web of Science and Ovid electronic databases were used. The studies were included the recorded preoperative levels of hemoglobin A1C and postoperative complications developed after cardiac surgery. Results of the studies were evaluated, based on either random or fixed effect model, according to presence of heterogeneity (I^2>25%).
Results: In total, 2,312 articles were obtained. After reviewing the articles, 33 articles covering 3500 patients meeting the inclusion criteria were included. The results pointed out that there was a relationship between preoperative hemoglobin A1c levels and mediastinitis, stroke, pneumonia, sepsis, renal failure and mortality. Heterogeneity was observed for myocardial infarction, atrial fibrillation and multiorgan failure (I^2 >25%).
Conclusion: Preoperative hemoglobin A1C levels were associated with development of mediastinitis, stroke, pneumonia, sepsis, renal failure and mortality after cardiac surgery.

Key Words: *Hemoglobin A1C, Cardiac surgery, Complication, Meta-analysis.*

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INTRODUCTION

Diabetes mellitus (DM) is one of the most observed systemic diseases in surgical patients. In current guideline of American Diabetes Association (ADA), four criteria have been determined for diagnosis of DM.[1] Fasting plasma glucose ≥126 mg/dL; two hour plasma glucose during oral glucose tolerance test ≥200 mg/dL; a random plasma glucose ≥ 200 mg/dL; hemoglobin A1c (HbA1c) ≥6.5%. One of these criteria is adequate for diagnosis of DM. HbA1c is an indirect measure of average glucose levels. It must be taken into consideration that many factors may affect hemoglobin glycation (hemodialysis, pregnancy, age, race, anemia *etc*.) as well as glycemia.[1]

In a recent meta-analysis, Zheng *et al.* demonstrated that HbA1c levels were associated with non-fatal myocardial infarction after percutaneous coronary intervention.[2] On the other hand, Qi *et al*. found a relationship between elevated HbA1c and atrial fibrillation.[3]

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In literature, there is only one meta-analysis, which evaluated the importance of preoperative HbA1c for outcomes (complications) in cardiac surgical patient population.[4] The main issue of the studies including HbA1c is the various cut-off points that becloud the results. Moreover, various causes of increase in HbA1c make interpretation difficult. Therefore, the authors aimed to investigate the relationship between HbA1c and outcomes in cardiac surgery.

METHODOLOGY

Databases were screened in accordance with the guidelines published by Moher *et al*.[5] The authors performed database screening to investigate the importance of preoperative HbA1c levels for determining the postoperative complications following cardiac surgery procedures in adult patients. The researchers investigated the database up to 11th June 2020. There was no limitation determined for the publication date of the articles. PubMed, Scopus, Ovid and Web of Science were used as electronic databases. There was no screening performed apart from the electronic database. However, articles that may be relevant were investigated in the reference sections of the articles. Keywords used were (cardiac surgery, heart surgery, valve surgery, complication, hemoglobin A1c, glycated hemoglobin, glycosylated hemoglobin). The articles published in other languages were not included.

Table I: Summary of studies.

Author	Year	Country	No of patients	DM (%)	CABG (%)	Outcomes	Cut-off point (%)	Type of surgery	Study design
Almogati *et al.*	2019	Saudi	305	81.6	100	Mediastinitis, POAF, RF, Mortality	7	CABG	R
Bardia *et al.*	2017	USA	763	19	0	Mediastinitis, POAF, RF, MI, Re-op, stroke, CT, Mortality	6.5	valve	P
Biskupski *et al.*	2014	Poland	350	100	40.5	RF, MI, Re-op, stroke, LCOS, Mortality	7	combined	R
Engoren *et al.*	2014	USA	880	47.15	100	Mediastinitis, POAF, RF, MI, stroke, sepsis, Mortality	7 and 6	CABG	R
Faritous *et al.*	2014	Iran	216	35.2	100	RF, MI, CT, sepsis, MOF, Mortality	7	CABG	P
Finger *et al.*	2016	USA	511	34.2	50.6	Mediastinitis, RF, Re-op, sepsis, mortality	7	combined	R
Gumuş *et al.*	2013	Turkey	510	40.2	92.4	Mediastinitis, POAF, RF, Re-op, CT, LCOS, GIS, mortality.	6	combined	R
Halkos *et al.***	2008	USA	3089	40.1	100	Mediastinitis, POAF, RF, MI, mortality	7	CABG	P
Kim *et al.*	2019	South Korea	503	100	100	Mediastinitis, RF, Re-op, stroke, mortality	7	CABG	R
Knapik *et al.*	2011	Poland	735	100	100	RF, MI, stroke, sepsis, MOF, mortality	7	CABG	R
Matsuura *et al.*	2009	Japan	101	100	100	Mediastinitis, POAF, RF, Re-op, mortality	6.5	CABG	R
Narayan *et al.*	2017	India	4678	65	100	Mediastinitis, POAF, RF, GIS	6.5	CABG	R
Nicolini *et al.*	2018	Multicenter	2606	36.1	100	Mediastinitis, RF, stroke, mortality	7	CABG	P
Oezkur *et al.*	2015	Germany	307	34.5	100	RF, mortality	6	combined	P
Ramadan *et al.*	2018	Egypt	80	100	100	Mediastinitis, POAF, RF, MI, stroke, LCOS, mortality	7	CABG	P
Robich *et al.*	2019	USA	6415	34.2	100	POAF, RF, Re-op, stroke, LCOS, mortality	6.5	CABG	R
Santos *et al.*	2015	Argentina	96	100	100	Mediastinitis, RF, MI, stroke, sepsis, mortality	7	CABG	P
Sato *et al.*	2010	Japan	130	100	60	Mediastinitis, RF, stroke, sepsis, mortality	6.5	combined	P
Strahan *et al.*	2013	Australia	712	100	100	RF, MI, Re-op, stroke, MOF, mortality	7	CABG	R
Subramaniam *et al.*	2014	USA	1461	38.6	74.1	Mediastinitis, POAF, RF, MI, Re-op, stroke, CT, mortality	6.5	combined	P
Tsuruta *et al.*	2011	Japan	306	100	100	Mediastinitis, POAF, RF, MI, Re-op, stroke, LCOS, GIS	6.5	CABG	P
Alserius *et al.*	2008	Sweden	605	27	100	Mediastinitis, Mortality	6 and 7	CABG	P
Fohl *et al.*	2013	USA	626	100	59	Mediastinitis,	7	Combined	R
Gatti *et al.*	2017	Italy	2130	35.1	100	Mediastinitis,	7	CABG	P
Göksedef *et al.*	2010	Turkey	148	35.3	70.8	Mediastinitis, mortality	7	Combined	P
Halkos *et al.**	2008	USA	5199	25.8	100	Mediastinitis,	7	CABG	P
Arslan *et al.*	2015	Turkey	180	66.6	100	Re-op, Pneumonia, POAF, Mediastinitis, mortality	7	CABG	R
Elsayed *et al.*	2019	Egypt	80	100	100	RF, MI, LCOS, mortality	8.6	CABG	P
Elghoneimy *et al.*	2020	Saudi	104	100	100	Re-op, mortality	8.5	CABG	R
Joshi *et al.*	2020	India	350	48	66.28	Re-op, RF, Mediastinitis, mortality	7	Combined	R
Islam *et al.*	2019	Bangladesh	60	100	100	POAF, RF, Mediastinitis, LCOS, mortality	7	CABG	P
Khan *et al.*	2019	USA	1133	48.3	100	Sepsis, Pneumonia, mortality	7	CABG	R
Gür *et al.*	2020	Turkey	118	100	100	Pneumonia, POAF, mortality	7	CABG	R

RF: renal failure; CT: cardiac tamponade; LCOS: low cardiac output syndrome, R: retrospective; P: prospective. CABG: coronary artery bypass grafting: POAF: postoperative atrial fibrillation; RF: renal failure; MI: myocardial infarction; Re-op: reoperation.

Selection of studies was planned according to the PRISMA guidelines (Participants, Intervention, Comparison, Outcomes and Study design).[6]

All studies (retrospective or prospective) were included. Inclusion criteria were clinical human study, published in English language regarding with control subjects on any open cardiac surgery. Exclusion criteria were: experimental studies, case reports or case series, non-surgical interventions, studies without control groups, editorials and reviews, non-cardiac surgery. Studies that were related to the investigation topic but did not provide information about cut-off point of preoperative HbA1c were not included in the analysis. The intervention group was designed as HbA1c> cut-off point; and control group was designed as HbA1c < cut-off point; for our analysis. Additionally, articles presenting the relevant data as figures or graphs were excluded from the analysis.

The researchers recorded data from the articles (first author name, year of publication, event and sample number in each group, research design) independently. The authors included the articles which recorded the levels of HbA1c as percentage and classified the groups according to cut-off point of HbA1c. Grouping in studies with more than one threshold value was resolved by consensus. Disagreements related to data and articles were resolved by compromise. Data were entered into the meta-analysis programme as those with the relevant events in each group and the total number of patients in groups.

Table II: PRISMA checklist.

Section/topic	No.	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-7
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	no

Statistical analysis used the Jamovi® and Open MetaAnalyst® programmes. The Odds ratio (OR) and 95% confidence interval (CI) were applied. Heterogeneity was assessed with the I^2 statistic. While heterogeneity was accepted as significant, if I^2 ≥25%. Determination of the cause of heterogeneity was evaluated with analysis of moderators. Meta-analysis used fixed or random models. In the presence of heterogeneity (I^2 >25%), the random effects model was used; and in the absence of heterogeneity (I^2 <25%), the fixed effects model was used. Publication bias was assessed, according to the Begg test with $p<0.05$ indicating statistical significance.

RESULTS

A total of 2,312 records were obtained at electronic databases. Eighteen hundred and fifty records were removed because of duplication. Review of titles and abstracts of 462 articles excluded, another 369 records were irrelevant. A total of 93 full-text articles assessed for eligibility. Eventually, 33 research articles comprising 35,487 patients were included in quantitative synthesis.[7-39] The flowchart for database screening is shown (Figure 1). The demographic data and features of the articles were reviewed (Table I). Thirteen recorded complications included atrial fibrillation (AF), myocardial infarction (MI), low cardiac output syndrome (LCOS), gastrointestinal complications, cardiac tamponade, multiorgan failure (MOF), mediastinitis, stroke, pneumonia, sepsis, renal failure, re-operation and mortality.

There was a relationship between preoperative HbA1c levels and mediastinitis (OR: 1.08, 95% CI: 0.88-1.28 and $p<0.001$), stroke (OR: 0.42, 95% CI: 0.14-0.71 and $p=0.004$), pneumonia

(OR: 0.45, 95% CI: 0.14-0.75 and p=0.004), sepsis (OR: 0.57, 95% CI: 0.02-1.11 and p=0.04), renal failure (OR: 0.49, 95% CI: 0.40-0.58 and p<0.001) and mortality (OR: 0.289, 95% CI: 0.088-0.490 and p=0.005). The other complications such as atrial fibrillation (OR: -0.01, 95% CI: -0.10-0.07 and p=0.77), myocardial infarction (OR: 0.57, 95% CI: -0.07-1.20 and p=0.079), cardiac tamponade (OR: 0.03, 95% CI: -0.75-0.81 and p=0.93), re-operation (OR: -0.20, 95% CI: -0.46-0.05 and p=0.12), low cardiac output syndrome (OR: 0.09, 95% CI: -0.12-0.30 and p=0.41), gastrointestinal system complications (OR: -0.004, 95% CI: -0.38-0.38 and p=0.08), and multi-organ failure (OR: 0.77, 95% CI: -1.40-2.94 and p=0.49) were not related with HbA1c levels. The forest plots of analyses represented in Figures 2a-b, 3a-b and 4a-b.

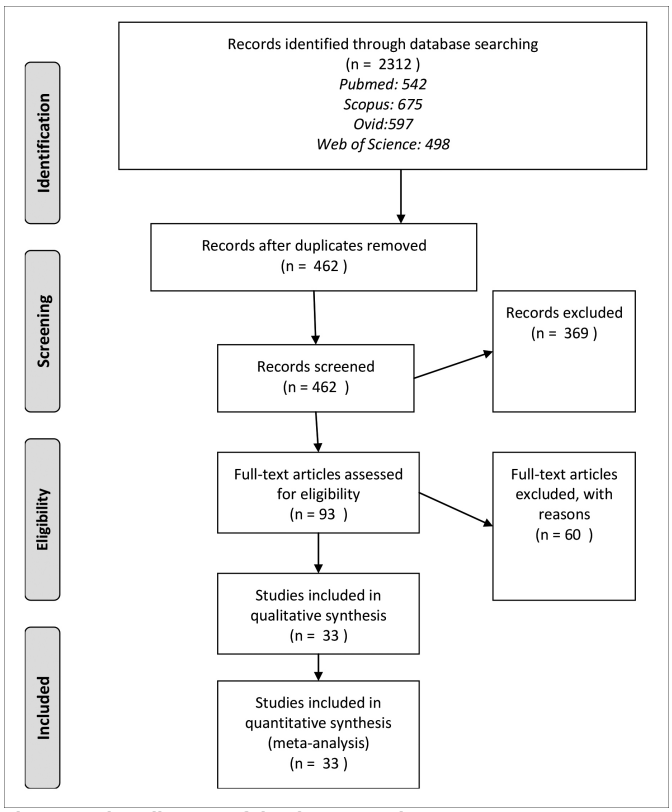

Figure 1: Flow diagram of database search.

When the heterogeneity between the studies were analysed, heterogeneity was observed in articles including atrial fibrillation (Q: 18.65, df: 13, I^2= 30.3%, P=0.13), myocardial infarction (Q: 17.99, df: 11, I^2= 41.18, P=0.08), and multi-organ failure (Q: 5.10, df: 2, I^2= 64.34%, P=0.08). I^2 was greater than 25% in those trials. The cause of heterogeneity was investigated, it appeared as preoperative levels of HbA1c for MI (I^2 for level 6.5%= 0 and for level 7%=72.3 in MI). We analysed HbA1c cut-off point, design of trials (prospective/retrospective) and types of surgery (coronary artery bypass grafting/valve /combined) as moderators. However, the cause of heterogeneity in trials, including AF, could not be determined. Analysis for MOF could not be done because of small number of trials about this outcome.

Assessment results of possible publication bias, according to the Begg test, were not significant for MI and MOF (tau ^{2} >0.05). The checklist of the review is presented in Table II.

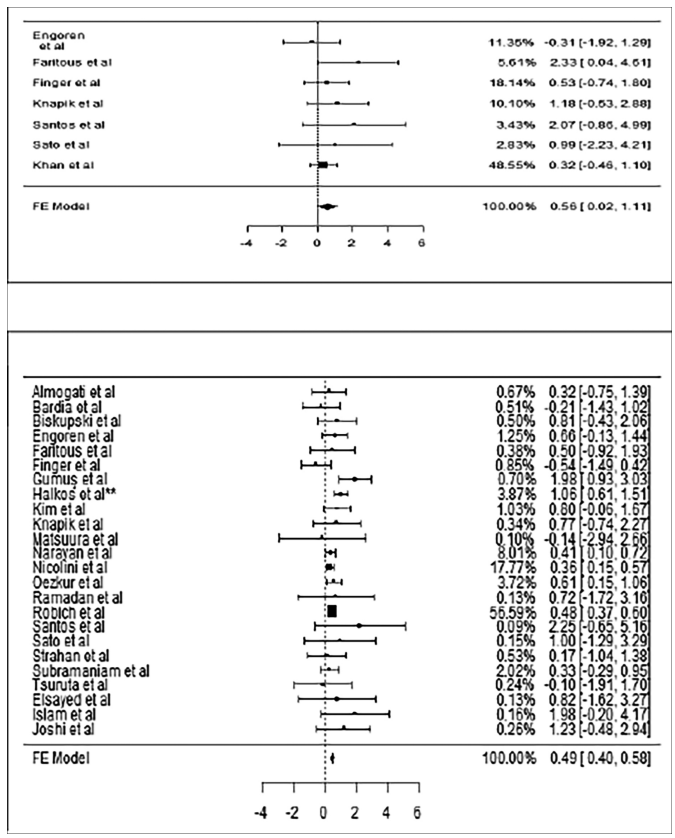

Figure 2 (a,b): Forest plots of sepsis (a) and renal failure (b) analyses.

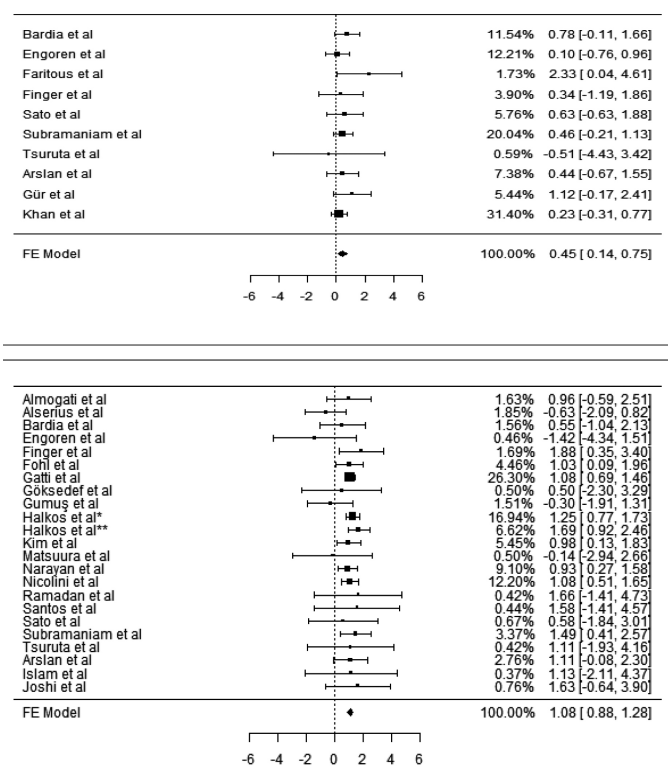

Figure 3 (a,b): Forest plots of pneumonia (a) and mediastinitis (b) analyses.

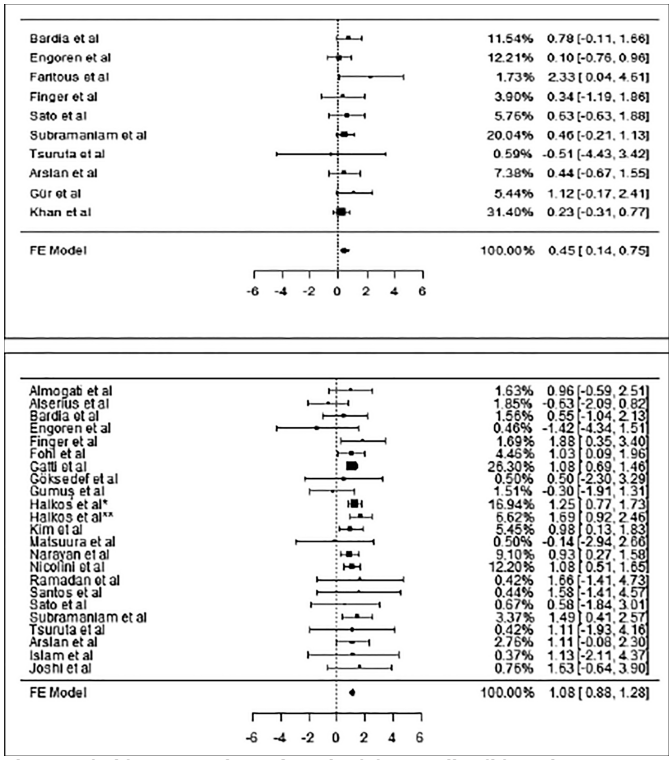

Figure 4 (a,b): Forest plots of stroke (a) mortality (b) analyses.

DISCUSSION

Data was obtained from the articles recorded 13 outcomes. It is found that preoperative high HbA1c levels were related with only seven complications (mediastinitis, stroke, pneumonia, sepsis, renal failure and mortality). There was no relationship between HbA1c levels and AF, MI, cardiac tamponade, LCOS, gastrointestinal complication and MOF. Heterogeneity was observed for trials about MI, AF and MOF. The main reason was HbA1c levels for MI. However, the authors could not apply subgroup analysis for MOF, because of small number of studies (only three trials were included) and could not determine a reason as a cause of heterogeneity for studies including AF.

The cut-off value of HbA1c is recommended as 6.5% (48 mmol/mol) by ADA in recent guideline.[1] However for different countries, there are many different results. Mousavi *et al*. found 80% sensitivity and 76% specifity for 5.05% for gestational DM at Iranian population.[40] In Chinese adult patients, three authors found three different values in different trials. Wang *et al.* obtaind 6.5% as a result, while Liu *et al.* and Liang *et al.* found as 6.3% and 5.9%, respectively.[41-43] On the other hand, Do Vale Moreira *et al*. observed the cut-off point as ≥6.8% for Brazilian adult patients in 714 patients. [44]

In this analysis, most of the preoperative HbA1c cut-off points were 7% in included articles. The others were 6%, 6.5%, 8.5% or 8.6%. At this point, it is important for standardisation of trials, the cut-off value must be 6.5%, recommended by ADA.

Two points draw the attention. First, the direct cardiovascular complications such as AF and MI were not related with HbA1c levels. Moreover, a second point all of the infectious complications (sepsis, pneumonia and mediastinitis) were related.

The most agreed risk factors of AF are known as age, obesity, smoking, gender, sedentary lifestyle, DM and obstructive sleep apnea.[45] In a large population based study, Kim *et al*. analysed 9,797,418 patients.[46] They observed that both DM and concomitant increase in body mass index have rised the risk of new onset AF. Especially, duration of DM (≥5 years) and obesity showed synergistic effect and provided the possible risk of new onset AF the highest. In contrast to previous classical knowledge, there was no correlation between DM and MI. This data is compatible with a meta-analysis performed by Zhang *et al*.[47]

The second point of this analysis about infectious complications, was a predictable result. Zhang *et al*. meta-analysis demonstrated that sternal infections were associated with DM after cardiac surgery procedures.[47] That result is correlated with a more recent meta-analysis applied by Martin *et al*.,[48] who found that DM was associated with increased risk of surgical site infection after surgery. However, DM was not a risk factor for ventilator associated pneumonia after cardiac surgery.[49]

Biancari *et al*., in a more recent meta-analysis, evaluated the association of HbA1c and sternal wound infection after cardiac surgery.[4] They included 17,609 patients from 14 trials and showed the increased risk of sternal wound infection because of preoperative HbA1c levels over 6-7%.

In a retrospective study, Hudson *et al*. found higher blood glucose levels among the patients with high HbA1c.[50] High HbA1c level was associated with 30-day mortality, acute kidney injury. However, they found no relation between HbA1c and infections. They used 6% as the cut-off point for HbA1c. On the other hand, the result for mortality was similar with Hudson *et al.*[50]

There are some controversial points about reliability of HbA1c against plasma glucose levels. Some authors prefer HbA1c compared with plasma glucose, because microangiopathic complications are strongly associated with HbA1c, it is better related with cardiovascular disease, fasting is not needed for assessment, acute situations such as stress, diet or smoking does not affect, it has a greater pre-analytical stability, and biological variability is lower.[51] The other authors argue against HbA1c. According to them, HbA1c is a poor sensitivity for DM diagnosis, it is poor marker for important pathophysiological abnormalities, standardisation of HbA1c assay is poor, in many subjects HbA1c assay is unreliable, percentage of Hba1c is not effective for prediction of DM, the trials about prevention of DM are not based on HbA1c, and diagnosis of DM in ~60% by HbA1c can resulted with a delay.[51]

This meta-analysis is different from the others in literature[2-4] with the classification of groups. The authors investigated the outcomes by the cut-off points as percentage not by the mean ± standard deviation values between the groups.

The main limitation of this analysis is the absence of standardisation of HbA1c levels in individual trials. It has ranged from 6% to 8.6%. The other limitations are inclusion of only the English language articles using different types of study designs instead of randomised controlled trials only; surgical procedures were not standardised as isolated CABG or valve surgery.

CONCLUSION

There was a relationship between preoperative HbA1c high levels and mediastinitis, stroke, pneumonia, sepsis, renal failure and mortality after cardiac surgery. It is thought by the authors that the studies must be standardised due to HbA1c cut-off point as 6.5% according to ADA recommendations and also they must be larger randomised controlled trials. On the other hand, different HbA1c threshold values for different complications should be investigated and evaluated separately for each outcome.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

SO, IK, YS, SO, YA, IO: Concept, design, data collection, analysis, literature search, writing.

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