The prognostic value of postoperative blood glucose in non-diabetic patients with rheumatic heart disease

Wanzi Hong
Guangdong General Hospital
Yu Wang
Guangdong General Hospital
Xuebiao Wei
Guangdong General Hospital
Danqing Yu
Guangdong General Hospital
Chunxiang Zhang
University of Alabama at Birmingham
Ning Tan
Guangdong General Hospital
Lei Jiang (jianglei@smu.edu.cn)
Guangdong General Hospital https://orcid.org/0000-0002-3505-4020

Research article

Keywords: rheumatic heart disease; valve replacement surgery; blood glucose; in-hospital death

Posted Date: September 10th, 2019

DOI: https://doi.org/10.21203/rs.2.14257/v1

Version of Record: A version of this preprint was published at BMC Cardiovascular Disorders on December 1st, 2019. See the published version at https://doi.org/10.1186/s12872-019-01278-2.

Abstract

Background: Blood glucose (BG) is a risk factor of adverse prognosis in non-diabetic patients in several conditions. However, a limited number of studies were performed to explore the relationship between postoperative BG and adverse outcomes in non-diabetic patients with rheumatic heart disease (RHD) undergoing valve replacement surgery (VRS). Methods: We identified 1395 non-diabetic patients who diagnosed with having RHD, and underwent preoperative coronary angiography and at least one valve replacement. BG was measured at admission to the intensive care unit (ICU) after surgery. The association of postoperative BG level with in-hospital and one-year mortality was accordingly analyzed. Results: Included patients were stratified into four groups according to postoperative BG level's (mmol/L) quartiles: Q1 (< 9.3 mmol/L, n=348), Q2 (9.3-10.9 mmol/L, n=354), Q3 (10.9-13.2 mmol/L, n=341), and Q4 (≥ 13.2 mmol/L, n=352). The in-hospital death (1.1% vs. 2.3% vs. 1.8% vs. 8.2%, P<0.001) and MACEs (2.0% vs. 3.1% vs. 2.6% vs. 9.7%, P<0.001) were significantly higher in the upper quartiles. Postoperative BG > 13.0 mmol/L was the best threshold for predicting in-hospital death (area under the curve (AUC) = 0.707, 95% confidence interval (CI): 0.634-0.780, P<0.001). Multivariate logistic regression analysis indicated that postoperative BG > 13.0 mmol/L was an independent predictor of in-hospital mortality (adjusted odds ratio (OR) = 3.418, 95% CI: 1.713–6.821, P<0.001). In addition, Kaplan–Meier curve analysis showed that the risk of one-year death was increased for a postoperative BG > 13.2 (log-rank = 32.762, P<0.001). Conclusion: Postoperative BG, as a routine test, could be served as a risk-stratified measure for non-diabetic patients with RHD.

Novelty Statement

Blood glucose is critical for patients undergoing surgery. However, as a postoperative routine examination, a small number of studies have focused on postoperative blood glucose. This study aimed to investigate the effects of postoperative blood glucose and determine whether it could be a valuable factor for non-diabetes patients of rheumatic heart disease undergoing valve replacement surgery, at last, 1395 non-diabetic patients were included in this study, and postoperative BG was shown to be served as a risk-stratified measure for non-diabetic patients with RHD.

Background

Rheumatic heart disease (RHD) is an abnormal autoimmune response caused by group A Streptococcus bacterium. As a major burden in developing countries, RHD affects > 34 million people, causing > 345 000 deaths, and 10 million disability-adjusted life years lost per year [1]. Valve replacement surgery can effectively improve the patients' quality of life. However, that surgical method wouldn't be beneficial for all RHD patients, especially for aged patients [2] . Therefore, it is imperative to find effective predictors for these patients and pay more attention to improve postoperative survival.

As an important part of the body's energy supply, blood glucose is maintained at a constant level, which is the primary source of energy for the needs of various organs and tissues in the body.However, it has

been recognized that diabetes is a lifelong chronic disease with a high prevalence rate, which seriously affects the life health and quality of life of patients, and may be accompanied by a variety of complications with the progress of the disease[3].Further, research has been noted that hyperglycemia, even if not defined as diabetes, can aggravate the patient's condition, affect the vital organs of the body, and significantly increase the mortality of the patient[4]. At the same time, a previous study showed that the probability of postoperative hyperglycemia was 40%-50%, and postoperative hyperglycemia was an important factor affecting the prognosis and recovery after surgery[5]. Therefore, blood glucose is critical for patients with RHD undergoing valve replacement. However, as a postoperative routine examination, a small number of studies have focused on postoperative blood glucose. Therefore, this study aimed to investigate the effects of postoperative blood glucose and determine whether it could be a valuable factor for RHD patients without diabetes undergoing valve replacement surgery.

Methods

Study design and population

A total of 1858 patients with RHD were consecutively screened in the Guangdong General Hospital (Guangzhou, China) between March 2009 and July 2013. All the patients with RHD received at least 1 valve replacement and preoperative coronary angiography. RHD was diagnosed according to previous acute rheumatic fever and/or symptom of precordial abnormalities and presence of heart murmur, and more importantly based on echocardiographic findings. Patients who committed suicide in hospital, or did not have a postoperative glucose data, or have diabetes were excluded from this study. Subjects with HbA1c ≥ 6.5% or fasting plasma glucose (FGB) ≥ 7.0 mmol/L were excluded as well. Finally, 1395 patients were eligible to be included in our analysis (Fig. 1). The primary endpoint was in-hospital all-cause mortality except for suicide during hospitalization, and the secondary endpoint was one-year mortality after operation and in-hospital major adverse clinical events (MACEs), which were defined as composite end points, such as death, renal failure with dialysis, and stroke.

This study was approved by the Ethics Committee of the Guangdong Provincial People's Hospital, accompanying with a waiver of informed consent due to the retrospective study design. Oral informed consent was obtained from the patients or their close relatives by telephone, and was recorded by trained nurses during the follow-up period.

Data collection and follow-up

Baseline clinical characteristics and laboratory data, in-hospital mortality, and the type of surgery were collected. Blood samples for evaluating glucose levels were collected at admission to the intensive care unit (ICU) after operation. The FBG was measured by using an autoanalyzer (Roche AG, Basel, Switzerland). Other venous blood samples for laboratory analysis were collected in the next morning after admission to the ICU before operation. Follow-up data were obtained from interviewing patients, family members, or primary care physicians by telephone or clinical records of hospital readmissions or outpatient interviews for a period of one year after operation.

Statistical analysis

SPSS software version 13.0 (SPSS, Inc., Chicago, Illinois) was used for the analyses. Continuous data was presented as mean ± SD or medians and interquartile ranges, then compared by the ANOVA or Wilcoxon rank-sum test accordingly. Categorical data was presented as percentage and compared by χ^2 or fisher test. Variables whose p value was less than 0.05 in univariate logistic regression analysis were included in the multivariable analysis. Kaplan–Meier curve analysis was performed to evaluated cumulative rate of one-year mortality and compared using the log-rank test. A value of $p < 0.05$ was considered significant.

Results

Patients' clinical characteristics

Here, 1395 patients (female, 67.1%; male, 32.9%; age, 57 ± 6 years) were participated in this study, including 348 in Q1 group (< 9.3 mmol/L), 354 in Q2 group (9.3-10.9 mmol/L), 341 in Q3 group (10.9-13.2 mmol/L), and 3528 in Q4 group (≥ 13.2 mmol/L) (Table 1). Patients with a high postoperative glucose level were significantly older (56.3 ± 5.7 vs. 57.2 ± 5.5 vs. 57.5 ± 5.7 vs. 58.0 ± 5.5, P = 0.001) and were more likely female (39.7% vs. 33.1% vs. 31.7% vs. 27.3%, P = 0.006). No significant differences were found among those 4 groups in the percentages of smoking, hypertension, mitral valve replacement, Tricuspid intervention, coronary artery bypass grafting (CABG), the level of serum creatinine, and Glycated hemoglobin. However, the percentages of NYHA > II, and Aortic valve replacement, the level of FBG, and lg C-eactive protein (lgCRP) were significantly higher in patients with a high postoperative glucose. In addition, the rate of left ventricular ejection fraction (LVEF) was lower in those patients. 47 (3.4%) patients died during the hospitalization, among which 4 (1.1%) were in Q1, 8 (2.3%) were in Q2, 6 (1.8%) were in Q3, and 29 (8.2%) were in Q4 (P□0.001). Furthermore, the incidence of in hospital MACEs (2.0% vs. 3.1% vs. 2.6% vs. 9.7%, p<0.001) was significantly different among the four groups. Receiver operating characteristic (ROC) curve showed that postoperative BG > 13.0 mmol/L was the best threshold for predicting in-hospital death, accompanying with a sensitivity of 61.7% and specificity of 76.9% (area under the curve (AUC) = 0.707, 95% confidence interval (CI): 0.634-0.780, P < 0.001, Figure 2).

In the univariable logistic regression analysis, the postoperative BG > 13.0 mmol/L was associated with in-hospital death (odds ratio (OR) = 4.666, 95% CI: 2.559-8.507, P < 0.001). The significant variables were age, NYHA III/IV, estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2, lgCRP, LVEF, TVR, and CABG. These variables were entered into a multiple logistic regression analysis, in which the results showed that postoperative BG > 13.0 mmol/L remained an in- dependent predictor of in-hospital mortality (adjusted OR = 3.418, 95% CI: 1.713–6.821; P < 0.001). In addition, it was revealed that the eGFR < 60 ml/min/1.73 m2 (OR = 2.952, 95%CI: 1.311-6.645, P = 0.009) and TVR (OR = 3.855, 95%CI: 1.127-3.52, P = 0.032) were independently associated with in-hospital death (Table 2).

A total of 1248 (89.5%) patients completed one-year follow-up after surgery. However, during this period, 58 patients died. Result of Kaplan–Meier curve analysis is displayed in Figure 3, illustrating the cumulative 1-year mortality among the four groups. The results suggested that the risk of death was increased for a postoperative BG > 13.2 (log-rank 32.762, P<0.001, Figure. 3).

Discussion

Our study revealed that high postoperative BG level was associated with increased morbidity and mortality in non-diabetic RHD patients undergoing VRS, while preoperative BG level was not associated with those factors.

Rheumatic heart disease (RHD), a major burden in developing countries, causes enormous losses every year. Valve replacement surgery is an important treatment to improve the quality of life of patients, especially in elderly patients. Therefore, it is necessary to find effective predictors for these patients and pay more attention to improving postoperative survival. Glucose is the main source of energy for the body. Therefore, blood glucose levels are closely related to physical health, especially in critically ill patients.

Previous studies mostly focused on diabetes, or preoperative glucose. In fact, non-diabetic patients and postoperative glucose are also important. The mechanism of how an elevated postoperative BG level was associated with mortality has not been still fully understood. Thus, the following aspects should be taken into account.

Firstly, body glucose levels are regulated by the endocrine system. Postoperative acute hyperglycemia is regarded as the body's stress response, and stress hyperglycemia complicated by cardiac surgery is clinically common, especially after cardiopulmonary bypass, the incidence rate reaches 95%-100% [6]. Gandhi et al. suggested that when the BG level was greater than 100 mg/dl, the risk of various complications could be increased by 30% for every 20 mg/dl increase. Thoracic surgery is a strong stimulus for the body, and when the variability of patient's BG level is considerable, it will aggravate the damage caused by such stress reaction, that is equivalent to a "second strike" effect [7].

On the one hand, hyperglycemia is always associated with hyperlactatemia [8, 9], increasing morbidity and mortality in acute critical illness [10, 11]. A previous confirmed that lactate levels might appropriately reflect the severity of disease and organ failure, and also were independently associated with short-term mortality in critically ill patients with liver cirrhosis [12]. Although anaerobic glycolysis increases the substrate, however, suppressing hyperglycemia generating 2,3-diphosphoglycerate, absolute insulin secretion, or relatively insufficient may lead to an increase in plasma free fatty acid concentration, and fatty acid can increase the myocardial oxygen consumption.

On the other hand, BG concentration can influence the function of immune system. The inflammatory response is closely associated with the prognosis of surgery and has been demonstrated in a large number of studies [13, 14]. Studies have shown that inflammation affects wound healing and leads to an

increase in postoperative mortality [15]. A variety of inflammatory mediators have also been shown as predictors of postoperative risk [16]. Researches have shown that plasma levels of interleukin 8 (IL-8) and C-reactive protein (CRP) are higher in patients with hyperglycemia than in patients with normal BG levels [17, 18], thereby reducing T cell expression and the body's immune response [19-21]. All the above-mentioned reasons may explain that the immune response may be the cause of acute hyperglycemia, leading to a poor prognosis in patients undergoing cardiac surgery.

This study had some limitations. First, as this was a retrospective analysis based on prospectively collected data, some confounding might have affected the results. Second, the primary endpoint was all-cause mortality except for suicide which reduced the ability to fully evaluate the causes of death and consequently accurately compare the “cause of death” outcomes from this study with those of other populations.

Conclusions

In conclusion, we demonstrated that with the increase of postoperative BG, the prognosis of patients is worse. BG is able to accurately predict in-hospital death and mortality in non-diabetic patients with RHD after valve replacement surgery. Furthermore, we found that BG > 13.0 mmol/L is the optimum threshold for predicting in-hospital mortality, which was associated with one-year death.

Abbreviations

BG blood glucose

RHD rheumatic heart disease

VRS valve replacement surgery

AUC area under the curve

CI confidence interval

OR odds ratio

FBG fasting blood glucose

MACEs major adverse clinical events

ICU intensive care unit

CABG coronary artery bypass grafting

LVEF left ventricular ejection fraction

ROC Receiver operating characteristic

AUC area under the curve

eGFR estimated glomerular filtration rate

CRP C-reactive protein

IL-8 interleukin 8

NYHA New York Heart Association

Declarations

Ethics approval and consent to participate: This study was approved by the Ethics Committee of the Guangdong Provincial People's Hospital, accompanying with a waiver of informed consent due to the retrospective study design. Oral informed consent was obtained from the patients or their close relatives by telephone, and was recorded by trained nurses during the follow-up period.

Consent for publication: Not applicable.

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: None

Funding: This study was supported by National Natural Science Foundation (Grant no. 81800262) and Science and Technology Planning Project of Guangdong (Grant no. 2018A030313029). The work was not funded by any industry sponsors.

Authors' contributions: Lei Jiang and Ning Tan contributed to the conception or design of the study. Wan-zi Hong, Yu Wang, Xue-biao Wei, Danqing Yu, Chun-xiang Zhang and Lei Jiang contributed to the acquisition, analysis, or interpretation of data. Wan-zi Hong and Yu Wang drafted the manuscript. Ning Tan critically revised the manuscript. All the authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Acknowledgements: None

References

1. Carapetis JR, Beaton A, Cunningham MW et al. Acute rheumatic fever and rheumatic heart disease. Nature reviews Disease primers 2016, 2:15084.
2. Carapetis JR, Steer AC, Mulholland EK, Weber MJLID: The global burden of group A streptococcal diseases. 2005, 5(11):685-694.

3. Atun R, Davies JI, Gale EAM et al: Diabetes in sub-Saharan Africa: from clinical care to health policy. The lancet Diabetes & endocrinology. 2017, 5(8):622-667.
4. Huang Y, Cai X, Mai W et al. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. Bmj. 2016, 355:i5953.
5. Ali Abdelhamid Y, Kar P, Finnis ME et al. Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. Critical care (London, England). 2016, 20(1):301.
6. Hiesmayr MJ. Hyperglycemia and Outcome After Myocardial Infarction and Cardiac Surgery: So What? Semin Cardiothorac Vasc Anesth. 2006, 10(3):220-223.
7. Capes SE, Hunt DK, Pathak P et al. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke. 2001, 32(10):2426.
8. Raper RF, Cameron G, Walker D et al. Type B lactic acidosis following cardiopulmonary bypass. Crit Care Med 1997, 25(1):46-51.
9. Maillet JM, Le Besnerais P, Cantoni M et al. Frequency, risk factors, and outcome of hyperlactatemia after cardiac surgery. Chest. 2003, 123(5):1361-1366.
10. Kaukonen KM, Bailey M, Egi M et al. Stress hyperlactatemia modifies the relationship between stress hyperglycemia and outcome: a retrospective observational study. Crit Care Med. 2014, 42(6):1379-1385.
11. Green JP, Berger T, Garg N et al. Hyperlactatemia affects the association of hyperglycemia with mortality in nondiabetic adults with sepsis. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2012, 19(11):1268-1275.
12. Drolz A, Horvatits T, Rutter K et al. Lactate improves prediction of short-term mortality in critically ill cirrhosis patients: a multinational study. Hepatology 2019 Jan;69(1):258-269.
13. Hu YF, Chen YJ, Lin YJ et al. Inflammation and the pathogenesis of atrial fibrillation. Nature reviews Cardiology. 2015, 12(4):230-243.
14. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. Journal of the American College of Cardiology. 2012, 60(22):2263-2270.
15. Agca R, Heslinga SC, van Halm VP et al. Atherosclerotic cardiovascular disease in patients with chronic inflammatory joint disorders. Heart. 2016, 102(10):790-795.
16. Gonzalez-Gay MA, Gonzalez-Juanatey C. Cardiovascular risk factor assessment: still an unmet need in chronic inflammatory diseases. Heart. 2016, 102(24):1937-1939.
17. Marfella R, Siniscalchi M, Esposito K et al. Effects of stress hyperglycemia on acute myocardial infarction: role of inflammatory immune process in functional cardiac outcome. Diabetes care. 2003, 26(11):3129-3135.
18. Gandhi GY, Nuttall GA, Abel MD et al. Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. Mayo Clinic proceedings. 2005, 80(7):862-866.

19. Macintyre AN, Gerriets VA, Nichols AG et al. The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. Cell Metab 2014, 20(1):61-72.
20. Kishton RJ, Sukumar M, Restifo NP. Metabolic Regulation of T Cell Longevity and Function in Tumor Immunotherapy. Cell Metab. 2017, 26(1):94-109.
21. Thaiss CA, Levy M, Grosheva I et al. Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection. Science. 2018, 359(6382):1376-1383.

Tables

Table 1. Patients' baseline characteristics

Clinical variables	Postoperative BG level (mmol/L)				
	Quartile 1 (n=348)	Quartile 2 (n=354)	Quartile 3 (n=341)	Quartile 4 (n=352)	P
Age (year)	56.3±5.7	57.2±5.5	57.5±5.7	58.0±5.5	0.001
Males, n (%)	138（39.7）	117（33.1）	108（31.7）	96（27.3）	0.006
Smoking, n (%)	37(10.6)	42(11.9)	30(8.8)	36(10.2)	0.618
Hypertension, n (%)	29（8.3%）	30（8.5）	39（11.4）	40（11.4）	0.319
NYHA III-IV, n (%)	148（42.5）	129（36.4）	162（47.5）	164（46.6）	0.012
FBG (mmol/L)	4.7±0.5	4.8±0.6	4.9±0.6	4.9±0.6	<0.001
Postoperative glucose (mmol/L)	8.1±1.0	10.1±0.5	12.0±0.7	15.8±2.0	<0.001
Serum creatinine (umol/L)	83.4±29.7	78.6±22.3	79.6±24.6	81.5±25.7	0.069
lgCRP (mg/L)	0.5±0.4	0.5±0.4	0.5±0.4	0.6±0.4	0.006
Glycated hemoglobin(%)	5.8±0.4	5.8±0.4	5.8±0.4	5.8±0.4	0.222
LVEF (%)	61.7±8.6	62.1±8.6	62.5±8.5	60.7±10.3	0.047
Type of surgery					
Aortic valve replacement	170（48.9）	163（46.0）	189（55.4）	198（56.3）	0.015
Mitral valve replacement	331（95.1）	318（95.5）	314（92.1）	326（92.6）	0.174
Tricuspid intervention	270（77.6）	275（77.7）	254（74.5）	271（77.0）	0.730
CABG	13（3.7）	12（3.4）	14（4.1）	20（5.7）	0.445
In-hospital death	4（1.1）	8（2.3）	6（1.8）	29(8.2)	<0.001
In-hospital MACEs	7(2.0)	11(3.1)	9(2.6)	34(9.7)	<0.001

NYHA, New York Heart Association; FBG, fasting blood glucose; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; MACEs, major adverse clinical events.

Table 2. Univariate and multivariate logistic analyses for in-hospital death

Clinical variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P	OR	95% CI	P
Age	1.1.06	1.054,1.160	<0.001	1.056	0.994,1.122	0.076
Female	0.714	0.394,1.293	0.266			
Smoking	0.796	0.282,2.251	0.668			
Hypertension	1.348	0.562,3.235	0.504			
NYHA III-IV	1.981	1.095,3.583	0.024	1.459	0.720,2.959	2.95
FBG	0.859	0.494,1.495	0.592			
Postoperative BG > 13.0 mmol/L	4.666	2.559,8.507	0.001	3.418	1.713,6.821	<0.001
eGFR < 60 ml/min/1.73 m^2	3.568	1.796,7.088	0.001	2.952	1.311,6.645	0.009
LgCRP	3.580	1.751,7.321	0.001	2.162	0.968,4.826	0.060
Glycated hemoglobin						
LVEF	0.956	0.930,0.983	0.001	0.973	0.942,1.004	0.089
AVR						
MVR						
TVR	2.615	1.026,6.665	0.044	3.855	1.127,13.188	0.032
CABG	3.576	1.454,8.792	0.006	2.821	0.869,9.156	0.084

NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; BG, blood glucose; CRP, C-reactive protein; CABG, coronary artery bypass grafting.

Figures

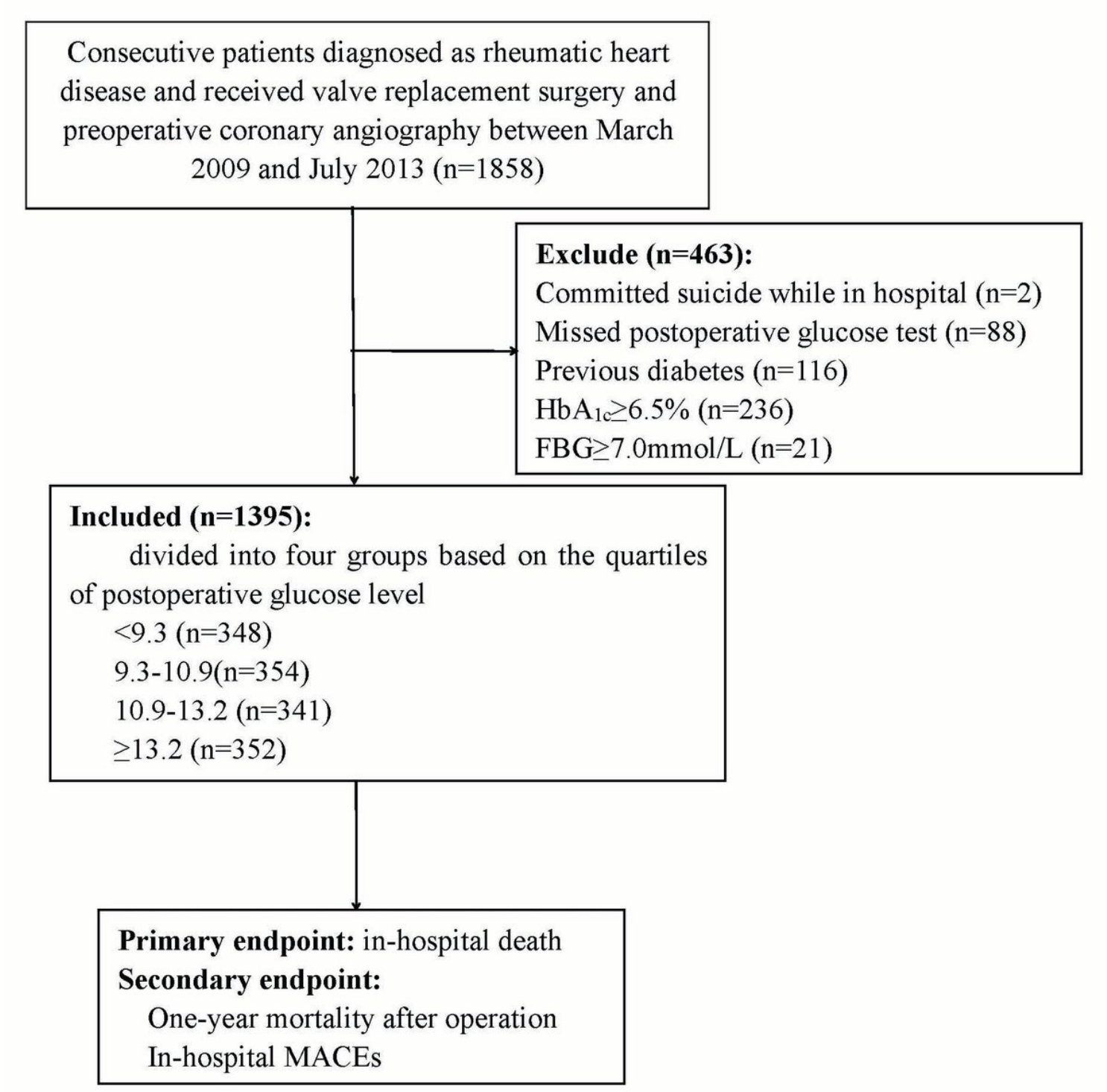

Figure 1

Flowchart of the population screened.

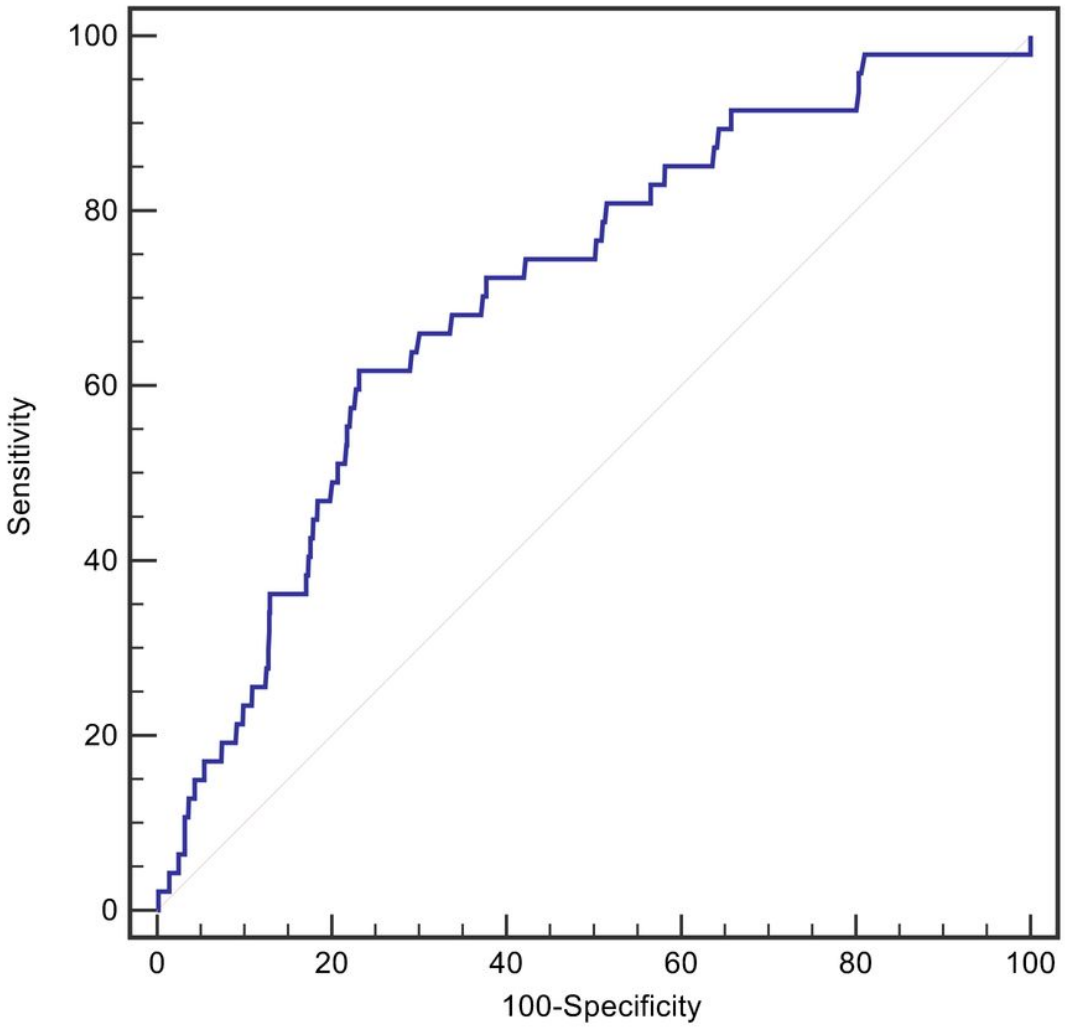

Figure 2

Receiver operating characteristic (ROC) curve of postoperative blood glucose for in-hospital death.

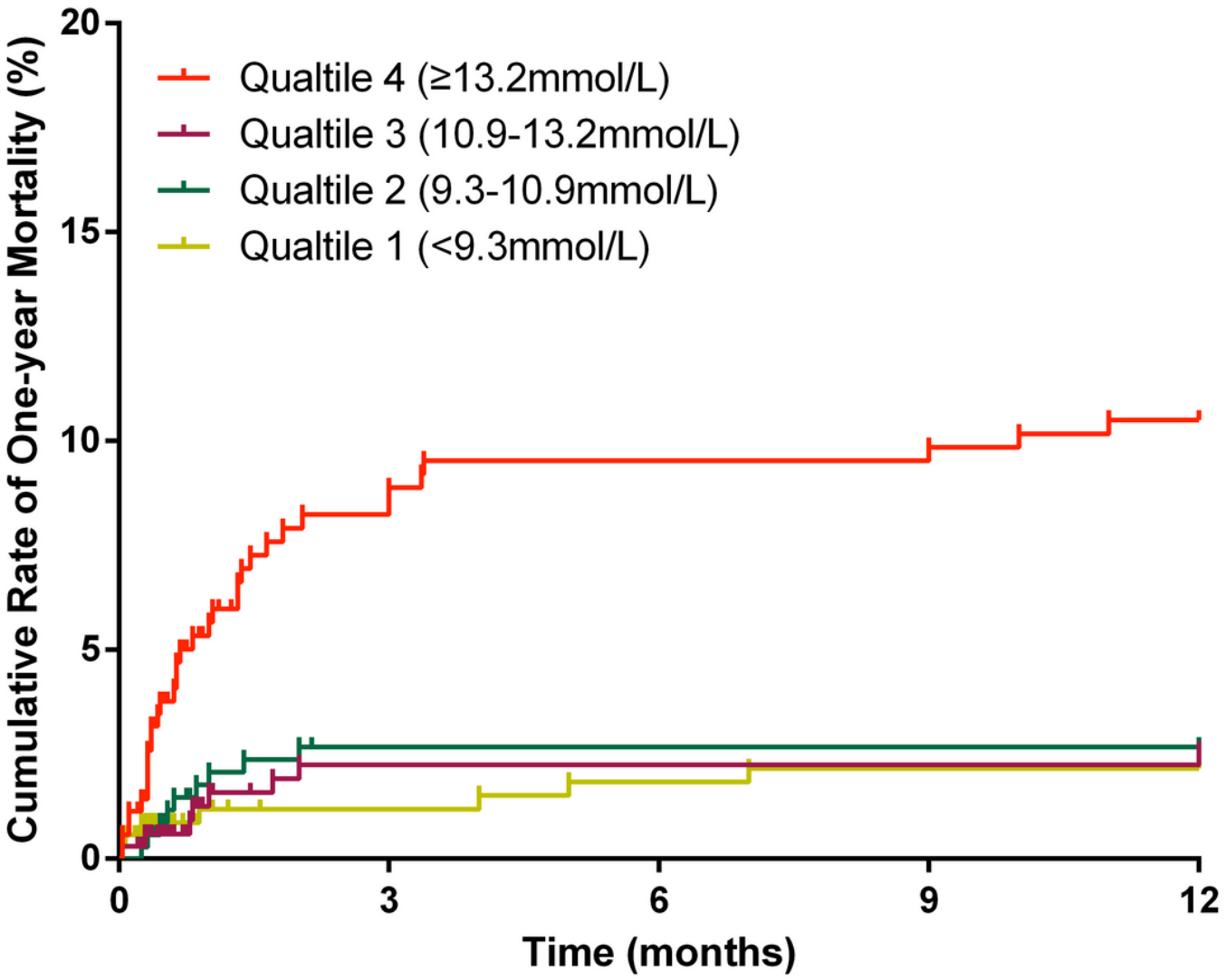

Figure 3

Cumulative rate of 1-year mortality for patients in 4 different groups of postoperative blood glucose.