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The Effect of Preoperative and Postoperative Glycemic Control on Acute Kidney Injury After Off-Pump Coronary Artery Bypass Grafting: A Case-Control Study

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ABSTRACT

Background: Acute kidney injury (AKI) is a common complication after cardiac surgery. It is closely related to poor perioperative glycemic control. We aimed to explore the relationship between preoperative hemoglobin A1c (HbA1c) levels and cumulative postoperative insulin usage and AKI after off-pump coronary artery bypass grafting (OPCABG).

Method: The included a total of 284 patients undergoing isolated OPCABG from 2018 to 2020. According to KDIGO's diagnostic criteria, patients were divided into the AKI group and the non-AKI group. Methods included ① increase in SCr by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours; ② increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; ③ urine volume <0.5 ml/kg/hour for 6 hours.

Results: Fifty-one patients (17.9%) had postoperative AKI. HbA1c levels (non-AKI group 6.1 (5.8, 7.1) vs. the AKI group 7.1 (5.9, 8.6) (P = 0.014, cut-off=7.2, AUC=0.61, sensitivity 49%, specificity 76.4%) and postoperative insulin usage (non-AKI group 16.0 (4.0, 36.0) vs. the AKI group 56.0 (11.0, 132.0), P < 0.001, cut-off=39.5, AUC=0.673, sensitivity 60.8%, specificity 76.8%) were different between the two groups. Multivariate logistic regression analysis showed that HbA1c > 7.2% (OR=2.869, P = 0.04) and postoperative insulin usage > 39.5 U (OR=7.548, P < 0.001) were independently associated with AKI.

Conclusions: HbA1c levels and cumulative postoperative insulin usage could be used as independent predictors for AKI after OPCABG. Postoperative insulin usage is more predictive than preoperative HbA1c levels.

INTRODUCTION

AKI is a common complication after cardiac surgery, with an incidence of 5-40%; early AKI usually occurs within one week [Wang 2017; O'Neal 2016; Gumbert 2020]. Impaired renal function may increase the risk of death, and increase the risk of dialysis, increases the cost of hospitalization and prolongs length of ICU stay. In addition, a meta-analysis has shown that postoperative AKI is an independent risk factor for end-stage renal disease or CKD after discharge [Coca 2012]. Therefore, the prediction and early intervention of AKI have important clinical significance.

Poor perioperative glycemic control increases the risk of AKI. High-glucose levels promote oxidative stress and increase reactive oxygen species (ROS), which cause stronger vessel constriction and insufficient oxygen supply in the kidney. Signaling pathways related to both AKI and DM are closely associated with apoptosis, inflammation, and ROS production [Li 2020; Mendez 2016]. HbA1c is an important biomarker that can reflect the patient's blood glucose control status within three months. Previous studies demonstrated that chronic hyperglycemia is independently related to the postoperative AKI, and higher HbA1c levels could predict the AKI [Marenzi 2018; Oezkur 2015; Oh 2018; Xu 2020; Kocogulları 2017; Khalili 2021; Izkhakov 2019; Randhawa 2021; Gumus 2013; Nicolini 2018]. Moreover, AKI may promote hyperglycemia or hypoglycemia [Fiaccadori 2016]. Insulin is an important drug for glycemic control, and it often is used in patients whose oral medications are not effective or who do not eat or drink after surgery. This study explores the relationship between glycemic control and AKI from the aspects of preoperative and postoperative.

PATIENTS AND METHODS

This research was launched in the Affiliated Hospital of Qingdao University, Huangdao Branch. This cardiac center is a tertiary hospital and performs more than 600 cardiac operations annually. This study is a single-center retrospective case-control study, and the study protocol was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Qingdao University. The requirement of informed consent from participants was waived.

Inclusion criteria: ① All patients who underwent isolated coronary artery bypass grafting from 2018 to 2020; ② > 18 years old. Exclusion criteria: ① Emergency surgery (patients undergoing surgery within 24 hours of admission); ② Preoperative serum creatinine > 133 μmol/L; ③ Preoperative LVEF < 35%; ④ Re-exploration; ⑤ Cardiopulmonary bypass (CPB); ⑥ Intra-aortic balloon pump (IABP).

Perioperative management: All patients underwent intravenous blood glucose testing on admission. According to

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diabetics condition, previous hypoglycemic therapy may be adjusted. Patients who had not been diagnosed with diabetes and had elevated fasting blood glucose before admission were rechecked and given diabetic diet education. When there were no contraindications, we first used metformin and/or acarbose to control blood glucose. Whether or not to use insulin before surgery is determined by the endocrinologist consultation.

After patients entered the operating room, an internal jugular vein cannula routinely was placed, and physicians used it to estimate the pressure of right atrium. All patients had a median sternotomy. Heparin sodium (1mg/Kg) was used for anticoagulation after dissection of the pericardium. During the operation, the anesthesiologist re-checked the blood gas analysis to decide whether to pump insulin to control blood glucose. The chief surgeon and anesthesiologist adjusted the fluid management, according to the patient's intraoperative status, atrial pressure, and urine output. All patients were scheduled to receive off-pump CABG. The left internal mammary artery (LITA) was chosen to bypass the left anterior descending branch (LAD), the diagonal artery (DA), and other coronary vessel anastomoses sequentially based on the condition. The LAD of the saphenous vein (SV) was anastomosed if the LITA was occluded, or the blood flow was poor.

After the operation, patients went to the cardiac surgery intensive care unit and were managed by a professional team. Doctors would give patients subcutaneous injections or intravenous pumps of insulin to control blood glucose, based on blood glucose levels. Patients who received intravenous insulin pumping after the operation would have a fasting blood glucose check once an hour, and the drug pumping speed would be adjusted, based on the checking results.

Data collection: Follow-up blood creatinine results were taken within seven days after the operation. AKI was diagnosed, according to KDIGO's criteria [Kellum 2013]. ① increase in SCr by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours; ② increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; ③ urine volume <0.5 ml/kg/hour for 6 hours. CAG/PCI is defined as receiving coronary angiography or percutaneous coronary intervention within three days before surgery. Postoperative insulin usage is the cumulative amount of insulin usage within five days after surgery.

Statistical analysis: All continuous variables that meet the normal distribution were described by the mean ± standard deviation, and the difference between the two groups was compared by the student's t-test. Non-normal distribution data were represented by the median [IQR], and the difference between the two groups is compared using the Wilcoxon ranks test. Categorical variables are expressed in absolute numbers (percentages), and chi-square analysis is used to compare differences between groups. Univariable logistic regression analysis was performed. Variables with P < 0.2 were put into the multivariate logistic regression model. We chose a backward stepwise logistic regression analysis method to establish the model. The ROC curve was used to calculate the cut-off, sensitivity, specificity, and Youden index. The statistical analysis software is SPSS 26.0 and R 4.1.0.

RESULTS

A total of 284 patients were enrolled in this study, including 201 males (70.7%), with an average age of 63.2 years, and 100 (35.2%) diabetic patients. Postoperative AKI occurred in 51 patients (17.9%), of which 45 were 1 stage AKI, 6 were 2 stage AKI, there were no patients with 3 stage AKI, and no patients received renal replacement therapy. The process of patient screening is shown in Figure 1. All clinical information is in Table 1.

Univariable logistic analysis showed that diabetes ($P = 0.024$), ACEI ($P = 0.026$), oral diuretics ($P = 0.038$), oral hypoglycemic drugs ($P = 0.021$), preoperative insulin ($P = 0.004$), cystatin-C ($P = 0.019$), HbA1c ($P = 0.004$), and postoperative insulin doses ($P < 0.001$) were independently different between the two groups. The analysis results of all variables are shown in Table 2. Multivariate logistic regression analysis showed that ACEI (OR=2.718, $P = 0.024$), diuretics (OR=2.036, $P = 0.046$), cystatin-C (OR=7.204, $P = 0.009$), HbA1c > 7.2% (OR=2.869), $P = 0.04$), postoperative insulin dose > 39.5U (OR=7.548, $P < 0.001$). The result is shown in Table 3.

The ROC curve showed that the cut-off value of HbA1c was 7.2% (AUC=0.61, sensitivity 49%, specificity 76.4%, Youden index 0.254), and the cut-off value of postoperative insulin dose was 39.5 U (AUC=0.673, sensitivity 60.8%, specificity 76.8%, Youden index 0.376). (Figure 2) (Figure 3) The data distribution of HbA1c and postoperative insulin doses are represented by a scatter plot. (Figure 4) (Figure 5)

DISCUSSION

The incidence of AKI in this study is 17.6%. This incidence is similar to previous studies. The off-pump coronary artery bypass technique doesn't use CPB, so it has less impact on the patient's intracellular environment. During the OPCABG, the patient's blood pressure is higher than during on-pump surgery. Therefore, the off-pump surgical technique could decrease the effect of insufficient perfusion. In addition, on-pump surgery needs more heparin sodium for anticoagulation (3mg/Kg vs 1mg/Kg), which may lead to more blood loss. Therefore, the surgery of OPCABG is not to increase the rates of AKI [Garg 2014; Seabra 2010].

HbA1c, as a biomarker of chronic hyperglycemia, has shown predictive value for AKI in previous studies [Marenzi 2018; Oezkur 2015; Oh 2018; Xu 2020; Kocogulları 2017; Khalili 2021; Izkhakov 2019; Randhawa 2021; Gumus 2013; Nicolini 2018]. This conclusion is applicable to diabetic patients, non-diabetic patients, and unselected patients. This study found there is a significant difference in the distribution of HbA1c levels between the non-AKI group and the AKI group. After adjusting the confounding variables by the multivariate logistic regression model, which demonstrated the relationship between preoperative blood glucose level and postoperative AKI. Poor blood glucose control will promote the occurrence of postoperative AKI.

The classification standard used in previous study was between 5.6% to 7% [Oezkur 2015; Kocogulları 2017;

Table 1. Baseline of patients

Variables	non-AKI (*N* = 233)	AKI (*N* = 51)	*P*
Age (year)	63.0 (8.2)	64.5 (8.6)	0.231
Sex (male)	170 (73.0%)	31 (60.8%)	0.118
BMI (kg/m²)	26.4 (12.1)	25.2 (3.1)	0.460
Smoking	99 (42.5%)	19 (37.3%)	0.596
Diagnosis	-	-	0.757
Acute myocardial infarction	59 (25.3%)	11 (21.6%)	
Stable angina	27 (11.6%)	5 (9.8%)	
Unstable angina	147 (63.1%)	35 (68.6%)	
Heart failure	16 (6.9%)	3 (5.9%)	1.000
Old myocardial infarction	22 (9.4%)	7 (13.7%)	0.509
Hypertension	138 (59.2%)	32 (62.7%)	0.759
Diabetes	75 (32.2%)	25 (49.0%)	0.034
Peripheral vascular disease	5 (2.1%)	3 (5.9%)	0.320
Stroke	28 (12.0%)	5 (9.8%)	0.837
COPD	5 (2.1%)	1 (2.0%)	1.000
ACEI	30 (12.9%)	13 (25.5%)	0.039
ARB	66 (28.3%)	14 (27.5%)	1.000
CCB	85 (36.5%)	21 (41.2%)	0.640
β-RB	177 (76.0%)	43 (84.3%)	0.268
Statin	230 (98.7%)	50 (98.0%)	1.000
Oral diuretics	113 (48.5%)	33 (64.7%)	0.052
Oral hypoglycemic drugs	70 (30.0%)	24 (47.1%)	0.030
Preoperative insulin	15 (6.4%)	10 (19.6%)	0.006
Creatinine (umol/L)	88.8 (13.3)	88.8 (19.0)	0.998
Cystatin C (mg/L)	0.9 (0.2)	1.0 (0.2)	0.017
Admission blood glucose (mmol/L)	5.3 (4.7, 6.6)	5.8 (5.0, 8.4)	0.074
HbA1c(%)	6.1 (5.8, 7.1)	7.1 (5.9, 8.6)	0.014
HbA1c > 7.2%	55 (23.6%)	25 (49.0%)	<0.001
TG (mmol/L)	1.4 (1.0, 1.9)	1.4 (0.9, 2.0)	0.823
LDLC (mmol/L)	2.3 (1.8, 3.0)	2.3 (2.0, 2.8)	0.900
Hemoglobin (g/L)	132.5 (15.4)	130.2 (14.0)	0.341
LVEF (%)	61.0 (58.0, 63.0)	60.0 (57.0, 63.0)	0.370
Coronary stent	40 (17.2%)	8 (15.7%)	0.961
Preoperative CAG/PCI	20 (8.6%)	3 (5.9%)	0.721
Surgical time (min)	210.0 (180.0, 270.0)	210.0 (185.0, 232.5)	0.434
Postoperative insulin dosage (U)	16.0 (4.0, 36.0)	56.0 (11.0, 132.0)	<0.001
Postoperative insulin dosage > 39.5 U	54 (23.2%)	31 (60.8%)	<0.001

Izkhakov 2019; Gumus 2013; Nicolini 2018]. This study found that the best diagnostic cut-off value is 7.2%. These are the following differences between this study and previous studies: ① Patients in this study had not been screened for specific diseases. Moreover, in a tertiary referral hospital, patients always have more complicated conditions. The median HbA1c level of the two groups was higher than normal, which means most of the patients enrolled had poor blood glucose control. ② Previous studies did not report the blood glucose-related indicators of patients, such as

Table 2. Univariate regression analysis of risk factors for AKI

Variables	OR	95% CI	*P*
Age	1.02	0.985-1.063	0.231
Sex (male)	0.57	0.305-1.081	0.086
BMI	0.95	0.868-1.048	0.327
Smoking	0.8	0.43-1.5	0.493
Diagnosis			
Stable angina (refer)	-	-	0.757
Unstable angina	1.29	0.462-3.576	0.63
Acute myocardial infarction	1.01	0.318-3.183	0.991
Heart failure	0.85	0.238-3.025	0.799
Old myocardial infarction	1.53	0.614-3.792	0.363
Hypertension	1.16	0.621-2.166	0.643
Diabetes	2.03	1.096-3.743	0.024
Peripheral vascular disease	2.85	0.659-12.331	0.161
Stroke	0.8	0.292-2.172	0.656
COPD	0.91	0.104-7.978	0.934
ACEI	2.31	1.107-4.839	0.026
ARB	0.96	0.486-1.886	0.9
CCB	1.22	0.657-2.262	0.53
BRB	1.7	0.755-3.832	0.2
Statin	0.65	0.066-6.4	0.714
Oral diuretics	1.95	1.038-3.652	0.038
Oral hypoglycemic drugs	2.07	1.117-3.836	0.021
Preoperative insulin	3.54	1.49-8.435	0.004
Creatinine	1	0.979-1.021	0.998
Cystatin C	4.68	1.288-16.998	0.019
Admission blood glucose	1.08	0.969-1.208	0.161
HbA1c	1.32	1.093-1.605	0.004
HbA1c > 7.2%	3.11	1.663-5.824	<0.001
TG	1.05	0.863-1.289	0.603
LDLC	0.91	0.646-1.285	0.596
Hb	0.99	0.971-1.01	0.34
LVEF	0.98	0.937-1.03	0.456
Coronary stent	0.9	0.392-2.054	0.798
CAG/PCI	0.67	0.19-2.331	0.524
Surgical time	1	0.992-1.001	0.169
Postoperative insulin dosage	1.01	1.004-1.012	<0.001
Postoperative insulin dosage > 39.5U	5.14	2.711-9.736	<0.001

glycated albumin GA, time in range TIR, glucose variability GV, Triglyceride-Glucose Index TyG, and other indicators. In addition, intraoperative and postoperative blood glucose levels also play an important role in the occurrence of AKI. Lacking the patient's preoperative insulin usage and postoperative insulin usage fails to accurately reflect the patient's condition. In our study, the use of insulin before and after surgery showed a significant difference in the univariate analysis. Hence, previous studies may be unadjusted to some confounding variables. ③ Difference in follow up. In this

Table 3. Univariate and multivariate regression analysis of risk factors for AKI

Variables	Unadjusted			Adjusted		
	OR	CI	*P*	OR	CI	*P*
Male	0.57	0.305-1.081	0.086			
DM	2.03	1.096-3.743	0.024			
PVD	2.85	0.659-12.331	0.161			
ACEI	2.31	1.107-4.839	0.026	2.718	1.143-6.461	0.024
Diuretics	1.95	1.038-3.652	0.038	2.036	1.014-4.089	0.046
Oral hypoglycemic drugs	2.07	1.117-3.836	0.021			
Preoperative insulin	3.54	1.49-8.435	0.004			
Cystatin C	4.68	1.288-16.998	0.019	7.204	1.626-31.911	0.009
Admission blood glucose	1.08	0.969-1.208	0.161			
HbA1c > 7.2%	3.11	1.663-5.824	<0.001	2.869	1.051-7.835	0.04
Surgical time	1	0.992-1.001	0.169			
Postoperative insulin dosage > 39.5 U	5.14	2.711-9.736	<0.001	7.548	2.985-19.084	<0.001

research, postoperative AKI is defined as early AKI, and the follow-up time was seven days. Previous studies only observed three days after surgery, therefore the follow up ended when some patients develop AKI. ④ The exclusion and inclusion criteria of each study are different. This study excluded patients with emergency surgery, preoperatively diagnosed with CKD, preoperative creatinine> 133 (mmol/L), preoperative LVEF <35%, re-exploration, and use of IABP. All patients' hemoglobin was greater than 80 g/L. Differences in each cohort may also lead to different cut-offs.

HbA1c is not a perfect indicator. HbA1c is a non-enzymatic combination of serum glucose and hemoglobin and is an important indicator of the patient's glycemic control [Klein 2020]. The patient's glycemic control is related to postoperative AKI, so previous studies tend to use HbA1c to predict the occurrence of postoperative AKI. The accuracy of HbA1c is affected by the patient's anemia, hemoglobin variants, and so on [Ang 2015; Nitin 2010; Weykamp 2013]. Recently, some studies reported that other indicators, such as TIR, GV, GA, TyG, and others show good predictive value for renal complications [Yoo 2017; Saik 2020; Ding 2013; Clement 2019; Nam 2019; Varghese 2021; Qin 2020]. The preoperative HbA1c level only represents the patient's preoperative blood glucose. Autologous blood recovery and red blood cell transfusion are often performed during cardiac surgery, but the impact of these events on HbA1c has not been evaluated.

Insulin therapy is an important therapy for diabetes, and it is widely used in situations where oral hypoglycemic drugs have poor efficacy. Therefore, increased insulin usage means higher blood glucose levels. This is consistent with the conclusion of previous research [Kogan 2018; Li 2015; Munnee 2016; Wang 2020; Ram 2020]. This is similar to the worse prognosis of patients with the high-dose inotropic drug. Compared with preoperative HbA1c levels, increased insulin usage was more sensitive (60.8% vs. 49%). Therefore,

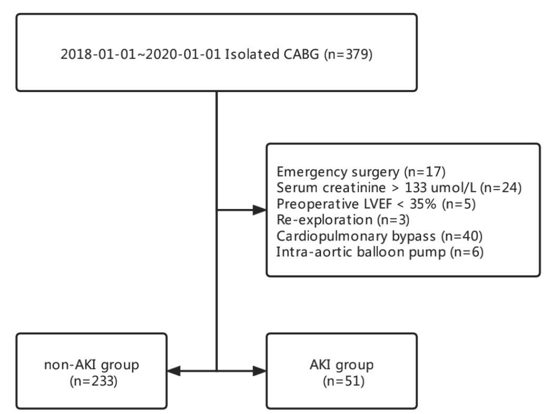

Figure 1. Flow diagram of the study population

patients who need high-dose insulin after surgery should pay more attention to creatinine levels and urine output.

Renal function should closely be monitored when insulin use increases after cardiac surgery. Increased insulin use means that patients have insulin resistance, which requires active intervention and improvement of insulin sensitivity through various treatment measures. Combined with the current research, we suggest four ideas: ① Optimize the blood sugar treatment plan and strengthen the preoperative blood sugar control of patients. Caddell et al. [Caddell 2010] proposed an effective method to treat patients, according to their preoperative insulin resistance (patient-specific insulin-resistance-guided protocol); ② Preoperative carbohydrate loading before surgery to improve insulin resistance. The benefits of preoperative carbohydrate use have been confirmed by a meta-analysis [Ricci 2022]. ③ Early insulin intervention [Blixt 2021; Blixt 2012]. The timing of high-dose insulin intervention can be advanced

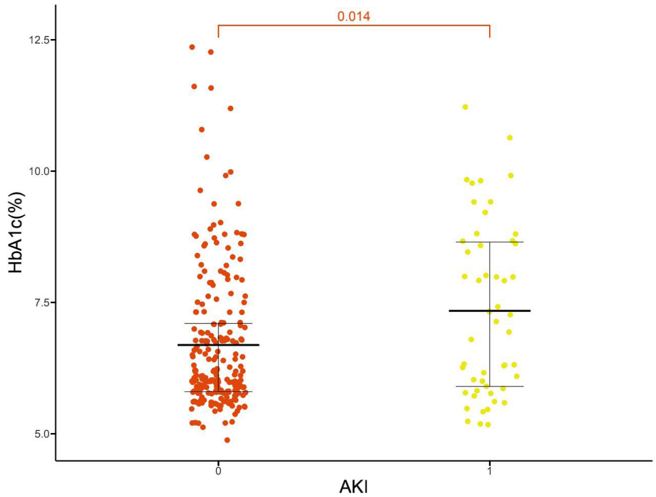

Figure 2. Distribution of preoperative HbA1c level (0: non-AKI group; 1: AKI group)

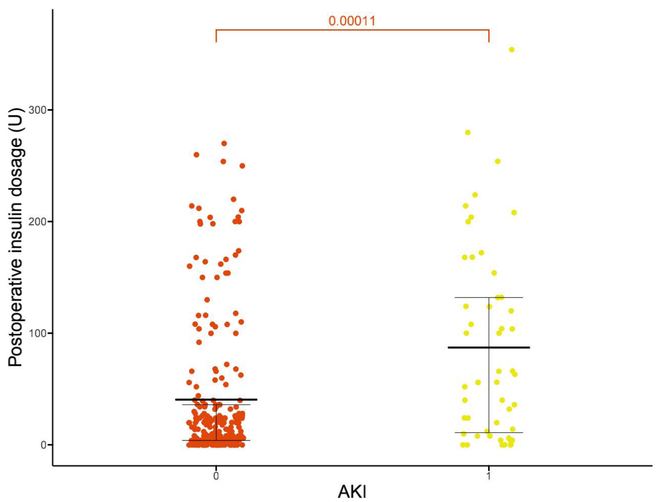

Figure 3. Distribution of insulin cumulative dose (0: non-AKI group; 1: AKI group)

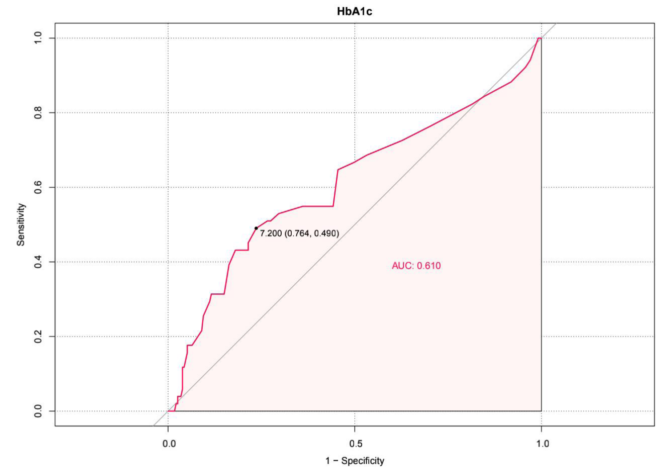

Figure 4. ROC analysis of preoperative HbA1c level (cut-off=7.2, AUC=0.61)

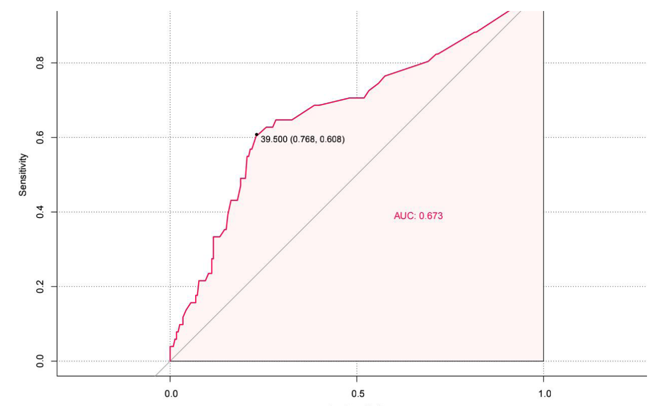

Figure 5. ROC analysis of insulin cumulative dose (cut-off=39.5, AUC=0.673)

to intraoperative time. ④ Optimize the use of insulin after surgery. Hui et al.'s [Hui 2012] study supports the adoption of a protocol-directed insulin infusion sliding scale as a standard of care for patients.

CONCLUSION

The level of HbA1c before surgery and the cumulative dose of insulin after surgery may be used as independent predictors of AKI after off-pump coronary artery bypass grafting. But the postoperative insulin usage is more predictive than preoperative HbA1c levels.

Limitation: This study is a single-center retrospective case-control study. Postoperative insulin doses were used to describe postoperative blood glucose levels. The effect of postoperative blood glucose levels on AKI should be more precisely evaluated. Limited by the conditions of medical records, the accurate preoperative insulin doses were not available. A prospective cohort study with a large sample of multiple centers is needed.

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