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Original Article

Association between hyperglycemia at ICU admission and postoperative acute kidney injury in patients undergoing cardiac surgery: Analysis of the MIMIC-IV database

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ABSTRACT

Background: This study aimed to explore the correlation between hyperglycemia at intensive care unit (ICU) admission and the incidence of acute kidney injury (AKI) in patients after cardiac surgery.

Methods: We conducted a retrospective cohort study, in which clinical data were extracted from the Medical Information Mart for Intensive Care (MIMIC)-IV database. Adults (≥18 years) in the database who were admitted to the cardiovascular intensive care unit after cardiac surgery were enrolled. The primary outcome was the incidence of AKI within 7 days following ICU admission. Secondary outcomes included ICU mortality, hospital mortality, ICU length of stay, and the 28-day and 90-day mortality. Multivariable Cox regression analysis was used to assess the association between ICU-admission hyperglycemia and AKI incidence within 7 days of ICU admission. Different adjustment strategies were used to adjust for potential confounders. Patients were divided into three groups according to their highest blood glucose levels recorded within 24 h of ICU admission: no hyperglycemia (<140 mg/dL), mild hyperglycemia (140–200 mg/dL), and severe hyperglycemia (≥200 mg/dL).

Results: Of the 6905 included patients, 2201 (31.9%) were female, and the median (IQR) age was 68.2 (60.1–75.9) years. In all, 1836 (26.6%) patients had severe hyperglycemia. The incidence of AKI within 7 days of ICU admission, ICU mortality, and hospital mortality was significantly higher in patients with severe admission hyperglycemia than those with mild hyperglycemia or no hyperglycemia (80.3% *vs.* 73.6% and 61.2%, respectively; 2.8% *vs.* 0.9% and 1.9%, respectively; and 3.4% *vs.* 1.2% and 2.5%, respectively; all P <0.001). Severe hyperglycemia was a risk factor for 7-day AKI (Model 1: hazard ratio [HR]=1.4809, 95% confidence interval [CI]: 1.3126 to 1.6707; Model 2: HR=1.1639, 95% CI: 1.0176 to 1.3313; Model 3: HR=1.2014, 95% CI: 1.0490 to 1.3760; all P <0.050). Patients with normal glucose levels (glucose levels <140 mg/dL) had a higher 28-day mortality rate than those with severe hyperglycemia (glucose levels ≥200 mg/dL) (4.0% *vs.* 3.8%, P <0.001).

Conclusions: In post-cardiac surgery patients, severe hyperglycemia within 24 h of ICU admission increases the risk of 7-day AKI, ICU mortality, and hospital mortality. Clinicians should be extra cautious regarding AKI among patients with hyperglycemia at ICU admission after cardiac surgery.

Introduction

Acute kidney injury (AKI) is a frequently observed complication in patients after cardiac surgeries.[1,2] AKI after cardiac surgery is independently related to an increased risk of mortality in patients.[3] While recently reported to be 8% in patients after cardiac surgery, the mortality can be ≥60% in patients who develop AKI after surgery.[4] In the intensive care unit (ICU), the second-most common cause of AKI is cardiac surgery.[5] Therefore, early recognition and prevention of AKI

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after cardiac surgery is essential for improving patient care and prognosis.

Blood glucose is a simple and accessible ICU indicator, and dysglycemia is common in critically ill patients.[6] Stress-induced hyperglycemia is common in critically ill patients, such as those with sepsis, burns, acute myocardial infarction, major surgery, polytrauma, and stroke, which are believed to be caused by increased counter-regulatory hormones (growth hormone, glucagon, and catecholamines) and impaired responses.[7] This leads to increased gluconeogenesis and decreased glycogenolysis. Animal studies have shown that hyperglycemia can lead to the development of renal tubular damage and even AKI.[8,9] Hyperglycemia is correlated with higher mortality in critically ill patients.[10] In non-diabetic patients, hyperglycemia is associated with AKI.[11] After cardiac surgery, postoperative hyperglycemia was also found to be linked to adverse outcomes.[12,13] Previous studies have shown that blood glucose is a risk factor for poor outcomes after cardiac surgery.[14,15] Some studies have shown a correlation between hyperglycemia and AKI after cardiac surgery, but the relationship has not been further explored.[16,17] Moreover, glycemic control after cardiac surgery is still debatable.

Therefore, we conducted a retrospective cohort study, utilizing a vast and openly available Medical Information Mart for Intensive Care IV (MIMIC-IV) database. We aimed to examine the correlation between severity of hyperglycemia at ICU admission and the incidence of AKI within 7 days following ICU admission in patients after cardiac surgery. We also investigated the optimal glycemic range in post-cardiac surgery patients admitted to the ICU.

Methods

Data source

Data from MIMIC-IV (version 2.2) were used in this study. MIMIC-IV is a database created by Massachusetts Institute of Technology, containing health-related data of 431,231 patients at the Beth Israel Deaconess Medical Center (Boston, MA, USA) ICUs between 2008 and 2019. With the unique code given at admission, users can view a patient's demographics, vital signs, laboratory findings, organ failure scores, and comorbidities. The author (Juan Ruan) has completed the courses and certificates required to access the data (ID: 52932869). As the MIMIC-IV database is publicly available and anonymous, there was no need for approval from the ethics committee regarding its use.

Patient selection

Adult patients after cardiac surgery admitted to the cardiovascular intensive care unit (CVICU) were enrolled in the study. Patients were excluded if they met any of the following criteria: (1) length of ICU stay <24 h, (2) missing blood glucose measurement data, and (3) patients with pre-existing chronic renal disease. If the patient had been admitted to the hospital or ICU more than once, only data of the first admission were included in this analysis.

The diagnostic criteria for AKI were based on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[18] Serum creatinine and urine output within 48 h were used to define AKI stages. An increase in serum creatinine of ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h or an increase in serum creatinine of 1.5–1.9 times the baseline serum creatinine or a urine output of <0.5 mL/(kg·h) for 6–12 h is considered stage 1. An increase in serum creatinine of 2.0–2.9 times the baseline serum creatinine or a urine output of <0.5 mL/(kg·h) for ≥12 h is considered stage 2. An increase in serum creatinine of ≥4.0 mg/dL (≥353.6 μmol/L) within 48 h, or an increase in serum creatinine of 3.0 times the baseline serum creatinine, or a urine output of <0.3 mL/(kg·h) for ≥24 h or anuria for ≥12 h is considered stage 3. The baseline serum creatinine value was determined based on the lowest value within 7 days of admission. The first serum creatinine measured on admission was used as the baseline serum creatinine when serum creatinine was not present prior to admission.

Data extraction

Data from the MIMIC-IV database were obtained and extracted using Structured Query Language. The following data were obtained: patient demographics (age, sex, and body mass index [BMI]); vital signs (mean arterial pressure [MAP], heart rate, respiratory rate, blood oxygen saturation [SpO_2], and temperature); comorbidities (diabetes, chronic pulmonary obstructive disease [COPD], myocardial infarct, peripheral vascular disease, congestive heart failure, and cerebrovascular disease); laboratory data (white blood cell [WBC] count, platelets, serum glucose, serum creatinine, and lactate); Charlson Comorbidity Index within the first 24 h after ICU admission, Acute Physiology Score III (APS III); Simplified Acute Physiology Score II (SAPS II); Sequential Organ Failure Assessment (SOFA) score; and Oxford Acute Severity of Illness Score (OASIS).

For each included patient, we collected the first blood glucose values after admission, and the minimum and maximum blood glucose values within 24 h after admission measured in each patient. Hypoglycemia is defined as blood glucose <70 mg/dL on at least one occasion within the first day of admission to the ICU. We chose the maximum blood glucose recorded within 24 h of admission to the ICU as the highest blood glucose (HBG) value on the first day of ICU admission. HBG was divided into three groups: no hyperglycemia (<140 mg/dL), mild hyperglycemia (140–200 mg/dL), and severe hyperglycemia (≥200 mg/dL).[19]

Outcome variables

The primary outcome was the incidence of AKI within 7 days of ICU admission. Secondary outcomes included ICU mortality, hospital mortality, and the length of ICU stay. ICU mortality was defined from the time a patient was admitted to the ICU until death due to any cause.

Statistical analysis

The normality of the variables was evaluated using the Kolmogorov–Smirnov test. Continuous data with non-normal distribution were expressed as median (interquartile range [IQR]), whereas continuous data with normal distribution were expressed as mean±standard deviation. Categorical data were expressed as numbers and percentages. The *t*-test or one-way analysis of variance (ANOVA)was used to compare continuous

data, and the chi-squared test and Fisher's test were used to compare categorical data when examining baseline characteristics. Potential risk factors were identified using Cox regression analysis. A multivariable Cox regression analysis was conducted using variables with a *P*-value <0.001 to identify independent risk factors for AKI incidence. We also performed subgroup analyses to examine whether blood glucose levels had any effect on distinct subgroups, including age, sex, and diabetes mellitus. All analyses were conducted with the statistical software package R (version 4.3.0, https://cran.r-project.org/, The R Foundation) and the Free Statistics analysis platform (version 1.6, http://www.clinicalscientists.cn/freestatistics/, Beijing, China). A two-tailed test with a *P*-value <0.05 indicated statistically significant differences.

Results

Baseline characteristics of the study population

Of the 11,582 adult patients after cardiac surgery, admitted to the CVICU in the MIMIC-IV database, 6905 patients were included in the final analysis after excluding patients with multiple hospitalizations (*n*=2591), missing blood glucose data (*n*=49), incorrect data (value is negative) (*n*=2), ICU admissions of less than 24 h (*n*=629), and pre-existing chronic renal disease (*n*=1406) (Figure 1). Of these 6905 patients, 2201 (31.9%) were female, and the median age was 68.2 (60.1–75.9) years. Hyperglycemia at ICU admission was present in 6261 of the 6905 patients (90.7%), of whom 4425 (64.0%) had mild and 1836 (26.6%) had severe hyperglycemia (Table 1). The incidence of 7-day AKI after ICU admission in the total population was 74.3%.

Table 1 summarizes the baseline characteristics of the patients and surgery type. Patients in the severe hyperglycemia group typically showed worse status, as indicated by higher lactate levels, APS III score, OASIS score, SOFA score, and more comorbidities. Furthermore, 29.6% of the total population were diabetics. In the severe hyperglycemia group, 54.6% of the patients had diabetes. The number of people who experienced hypoglycemia was 39 (6.1%), 393 (8.9%), and 216 (11.8%) in the no hyperglycemia, mild hyperglycemia, and severe hyperglycemia groups, respectively. In the MIMIC-IV database, when postoperative AKI was defined by the KDIGO guidelines based on the serum creatinine and urine output criteria, the incidence of AKI within 7 days of admission in the no hyperglycemia group, mild hyperglycemia group, and severe hyperglycemia group was 61.2% (*n*=394), 73.6% (*n*=3259), and 80.3% (*n*=1475), respectively (*P* <0.001) (Table 2). In analyses where AKI was diagnosed using only serum creatinine or urine output criteria, the incidence was significantly lower than when AKI was diagnosed using only serum creatinine and urine output criteria. Using serum creatinine criteria only, the incidence of AKI within 7 days of admission in the no hyperglycemia group, mild hyperglycemia group, and severe hyperglycemia group was 20.0% (*n*=129), 25.5% (*n*=1128), and 35.9% (*n*=659), respectively (*P* <0.001). Using urine output criteria only, the incidence of AKI within 7 days of admission in the no hyperglycemia group, mild hyperglycemia group, and severe hyperglycemia group was 57.1% (*n*=368), 69.7% (*n*=3086), and 76.3% (*n*=1400), respectively (*P* <0.001) (Supplementary Table S1).

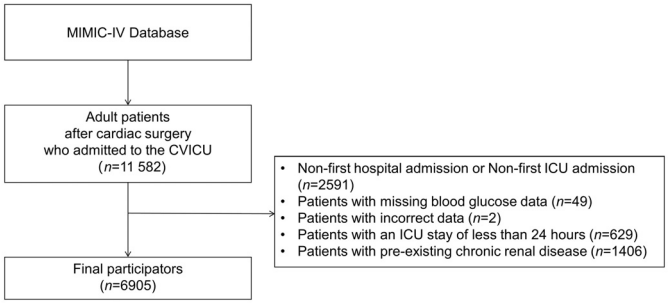

Figure 1. Flow chart of the population included in the study.
CVICU: Cardiovascular intensive care unit; ICU: Intensive care unit; MIMIC-IV: Medical Information Mart for Intensive Care IV database.

At the different AKI stages, the number of patients with severe hyperglycemia in each group was significantly higher than those with no hyperglycemia and mild hyperglycemia (*P* <0.05) (Table 2). In addition, significantly higher ICU and hospital mortality were observed in the severe hyperglycemia group (2.8% and 3.4%) than both the no hyperglycemia group (1.9% and 2.5%) and mild hyperglycemia group (0.9% and 1.2%) (all *P* <0.001) (Table 2). Nevertheless, the no hyperglycemia group had the highest 28-day mortality (4.0%), 90-day mortality (7.0%), and 1-year mortality rates (12.1%) (both *P* <0.001) (Table 2). Notably, the mild hyperglycemia group had the least ICU length of stay of 1.5 days (*P* <0.001) (Table 2).

Association of blood glucose levels with clinical outcomes

The results of univariate Cox regression analysis are shown in Figure 2. The maximum blood glucose level within 24 h of ICU admission was an independent risk factor for the incidence of 7-day AKI in patients after cardiac surgery (hazard ratio [HR]=1.0027, 95% confidence interval [CI]: 1.0021 to 1.0033, *P* <0.001). Compared to the no hyperglycemia group, the mild hyperglycemia group had a 1.28-fold increased risk of 7-day AKI (HR=1.2787, 95% CI: 1.1517 to 1.4197, *P* <0.001), while the severe hyperglycemia group had a 1.55-fold increased risk of 7-day AKI (HR=1.5462, 95% CI: 1.3834 to 1.7282, *P* <0.001). In addition, the univariate analysis revealed that age, BMI, MAP, respiratory rate, SpO_2, platelet count, WBC count, serum creatinine, myocardial infarction, congestive heart failure, cerebrovascular disease, peripheral vascular disease, COPD, and diabetes mellitus were significantly correlated with the incidence of 7-day AKI (all *P* <0.05). Moreover, the first blood glucose on admission was also identified as an independent risk factor for the incidence of 7-day AKI (HR=1.0017, 95% CI: 1.0011 to 1.0023, *P* <0.001), while the minimum blood glucose within 24 h of admission was not associated with the occurrence of 7-day AKI (*P*=0.511) (Figure 2).

When adjusted for other factors separately, it was found that the severe hyperglycemia group was a risk factor for the development of 7-day AKI on admission to the ICU (Model 1: HR=1.4809, 95% CI: 1.3126 to 1.6707, *P* <0.001; Model 2: HR=1.1639, 95% CI: 1.0176 to 1.331, *P* <0.05; Model 3: HR=1.2014, 95% CI: 1.0490 to 1.3760, *P* <0.05) (Figure 3). In

Table 1
Baseline characteristics of the study population.

Variables	No hyperglycemia group (*n*=644)	Mild hyperglycemia group (*n*=4425)	Severe hyperglycemia group (*n*=1836)	*P*-value
Demographic				
Sex				0.001
Female	245 (38.0)	1363 (30.8)	593 (32.3)	
Male	399 (62.0)	3062 (69.2)	1243 (67.7)	
Race				0.011
White	475 (73.8)	3298 (74.5)	1289 (70.2)	
Asian	20 (3.1)	94 (2.1)	44 (2.4)	
Black	29 (4.5)	169 (3.8)	76 (4.1)	
Others	120 (18.6)	864 (19.5)	427 (23.3)	
Age (years)	67.8 (57.0, 78.2)	68.3 (60.4, 75.7)	67.8 (60.4, 75.8)	0.688
BMI (kg/m^2)	27.0 (23.7, 30.5)	28.8 (25.7, 32.7)	29.7 (26.2, 34.0)	<0.001
Heart rate (beats/min)	78.5 (69.9, 87.4)	80.8 (75.5, 87.0)	82.6 (76.9, 90.0)	<0.001
MAP (mmHg)	76.9 (71.9, 83.4)	74.6 (71.0, 78.4)	73.8 (70.1, 77.9)	<0.001
Respiratory rate (breaths/min)	17.8 (15.9, 20.1)	17.3 (15.8, 19.0)	18.0 (16.3, 19.8)	<0.001
Temperature (°C)	37.1 (36.9, 37.6)	37.2 (36.9, 37.6)	37.2 (36.9, 37.6)	0.007
SpO_2 (%)	93.0 (91.0, 94.0)	93.0 (92.0, 95.0)	93.0 (92.0, 95.0)	<0.001
Laboratory data				
Hypoglycemia	39 (6.1)	393 (8.9)	216 (11.8)	0.001
Platelet (×10^6)	173.0 (133.0, 229.5)	132.0 (106.0, 163.8)	132.0 (102.0, 169.0)	<0.001
WBC count (×10^6)	11.0 (8.3, 14.0)	15.0 (12.1, 18.8)	16.3 (12.7, 21.0)	<0.001
Serum creatinine (mg/dL)	0.9 (0.7, 1.1)	0.9 (0.7, 1.0)	0.9 (0.8, 1.2)	<0.001
Lactate (mmol/L)	1.9 (1.3, 2.5)	2.4 (1.9, 3.1)	3.0 (2.3, 4.3)	<0.001
Medical history				
Myocardial infarct	147 (22.8)	1006 (22.7)	534 (29.1)	<0.001
Congestive heart failure	163 (25.3)	903 (20.4)	498 (27.1)	<0.001
Peripheral vascular disease	212 (32.9)	789 (17.8)	398 (21.7)	<0.001
Cerebrovascular disease	62 (9.6)	375 (8.5)	211 (11.5)	<0.001
COPD	171 (26.6)	924 (20.9)	388 (21.1)	0.004
Diabetes	45 (7)	996 (22.5)	1002 (54.6)	<0.001
Surgery type				<0.001
CABG	126 (19.6)	2010 (45.4)	858 (46.7)	
Valve surgery	72 (11.2)	1743 (39.4)	574 (31.3)	
Aortic surgery	34 (5.3)	103 (2.3)	67 (3.6)	
Others	412 (64)	569 (12.9)	337 (18.4)	
Severity scores				
Charlson comorbidity index	5.0 (3.0, 6.0)	4.0 (3.0, 5.0)	5.0 (4.0, 6.0)	<0.001
APS III score	33.0 (25.8, 42.0)	32.0 (25.0, 42.0)	38.0 (31.0, 51.0)	<0.001
SAPS II score	31.0 (25.0, 37.0)	34.0 (28.0, 40.0)	36.0 (29.0, 43.0)	<0.001
OASIS score	29.0 (23.0, 34.0)	30.0 (25.0, 35.0)	32.0 (27.0, 38.0)	<0.001
SOFA score	3.0 (1.0, 5.0)	5.0 (4.0, 7.0)	6.0 (4.0, 8.0)	<0.001

Data are presented as median (interquartile range), *n* (%), or mean ± standard deviations.
Blood sugar levels were classified as follows: no hyperglycemia group (<140 mg/dL), mild hyperglycemia group (140–200 mg/dL), and severe hyperglycemia group (≥200 mg/dL). *P*-value was calculated using *t*-test, one-way ANOVA, Pearson's chi-squared test, or Fisher's test, as appropriate. P <0.05 was considered significant.
AKI: Acute kidney injury; ANOVA: Analysis of variance; APS III: Acute physiology score III; BMI: Body mass index; CABG: Coronary artery bypass graft surgery; COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit; MAP: Mean arterial pressure; OASIS: Oxford acute severity of illness score; SAPS II: Simplified acute physiology score II; SOFA: Sequential organ failure assessment; SpO_2: Blood oxygen saturation; WBC: White blood cell.

Table 2
Prognosis of the study cohort.

Outcomes	No hyperglycemia group (*n*=644)	Mild hyperglycemia group (*n*=4425)	Severe hyperglycemia group (*n*=1836)	*P*-value
7-day AKI	394 (61.2)	3259 (73.6)	1475 (80.3)	<0.001
7-day AKI stage				<0.001
Stage 1	123 (19.1)	1185 (26.8)	504 (27.5)	
Stage 2	223 (34.6)	1872 (42.3)	808 (44)	
Stage 3	48 (7.5)	202 (4.6)	163 (8.9)	
ICU mortality	12 (1.9)	41 (0.9)	51 (2.8)	<0.001
Hospital mortality	16 (2.5)	51 (1.2)	62 (3.4)	<0.001
28-day mortality	26 (4.0)	57 (1.3)	70 (3.8)	<0.001
90-day mortality	45 (7.0)	112 (2.5)	94 (5.1)	<0.001
1-year mortality	78 (12.1)	185 (4.2)	143 (7.8)	<0.001
ICU length of stay	2.1 (1.3, 3.3)	1.5 (1.2, 2.7)	2.2 (1.3, 3.7)	<0.001

Data are presented as median (interquartile range) or *n* (%).
AKI: Acute kidney injury; ICU: Intensive care unit.

addition, we analyzed the relationship between AKI and blood glucose for different diagnostic criteria. Regardless of whether AKI was diagnosed by serum creatinine or urine volume criteria, severe hyperglycemia was a risk factor for AKI within 7 days of admission to the ICU (Supplementary Table S2).

Subgroup analyses were carried out to examine the robustness of the correlation between blood glucose levels and the incidence of AKI within 7 days among patients admitted to the ICU after cardiac surgery across different patient groups. The differential effect of blood glucose on AKI incidence within

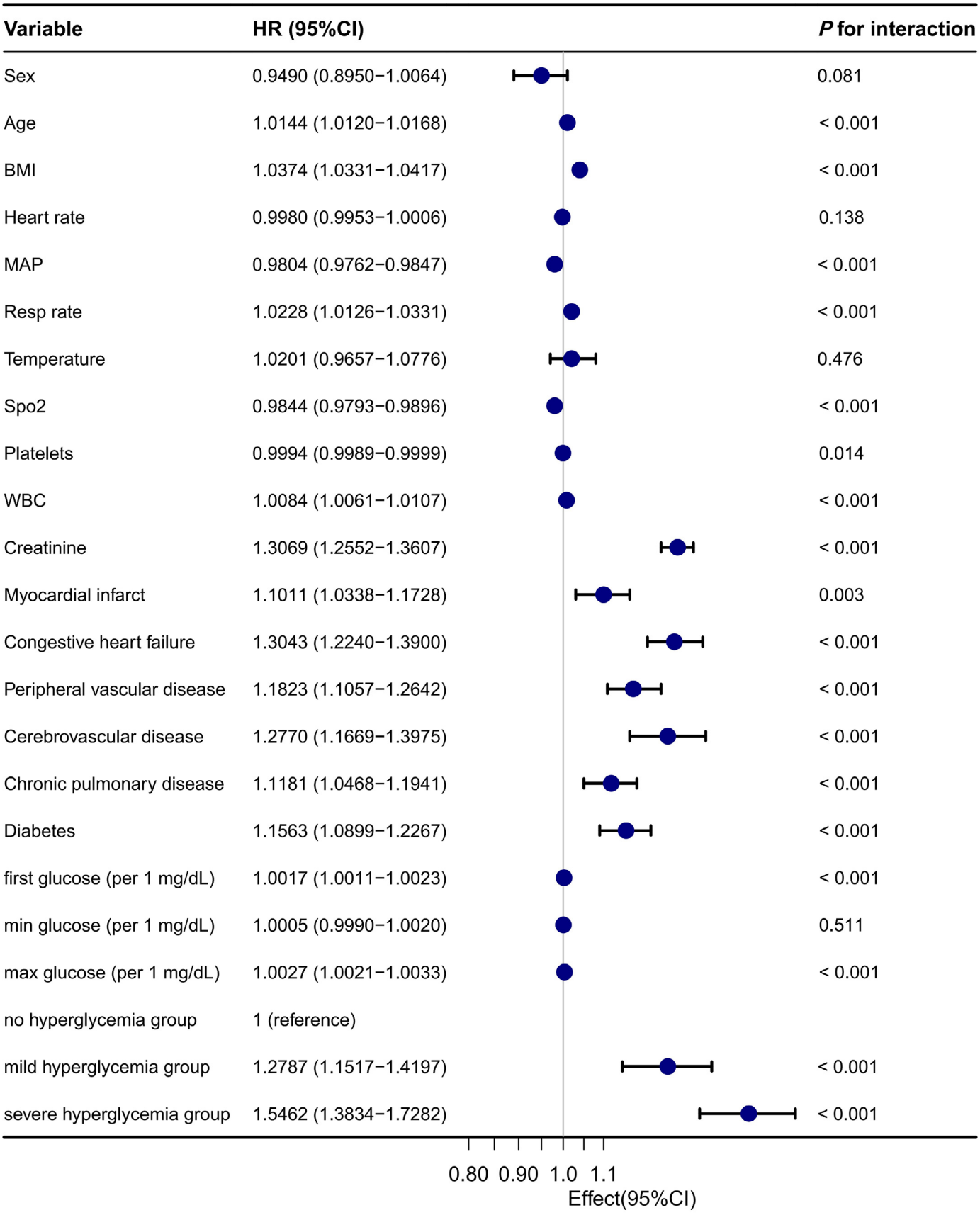

Figure 2. Univariate Cox regression analyses for 7-day AKI in cardiac surgery patients.
AKI: Acute kidney injury; BMI: Body mass index; CI: Confidence interval; HR: Hazard ratio; MAP: Mean arterial pressure; SpO_2: Blood oxygen saturation; WBC: White blood cell.

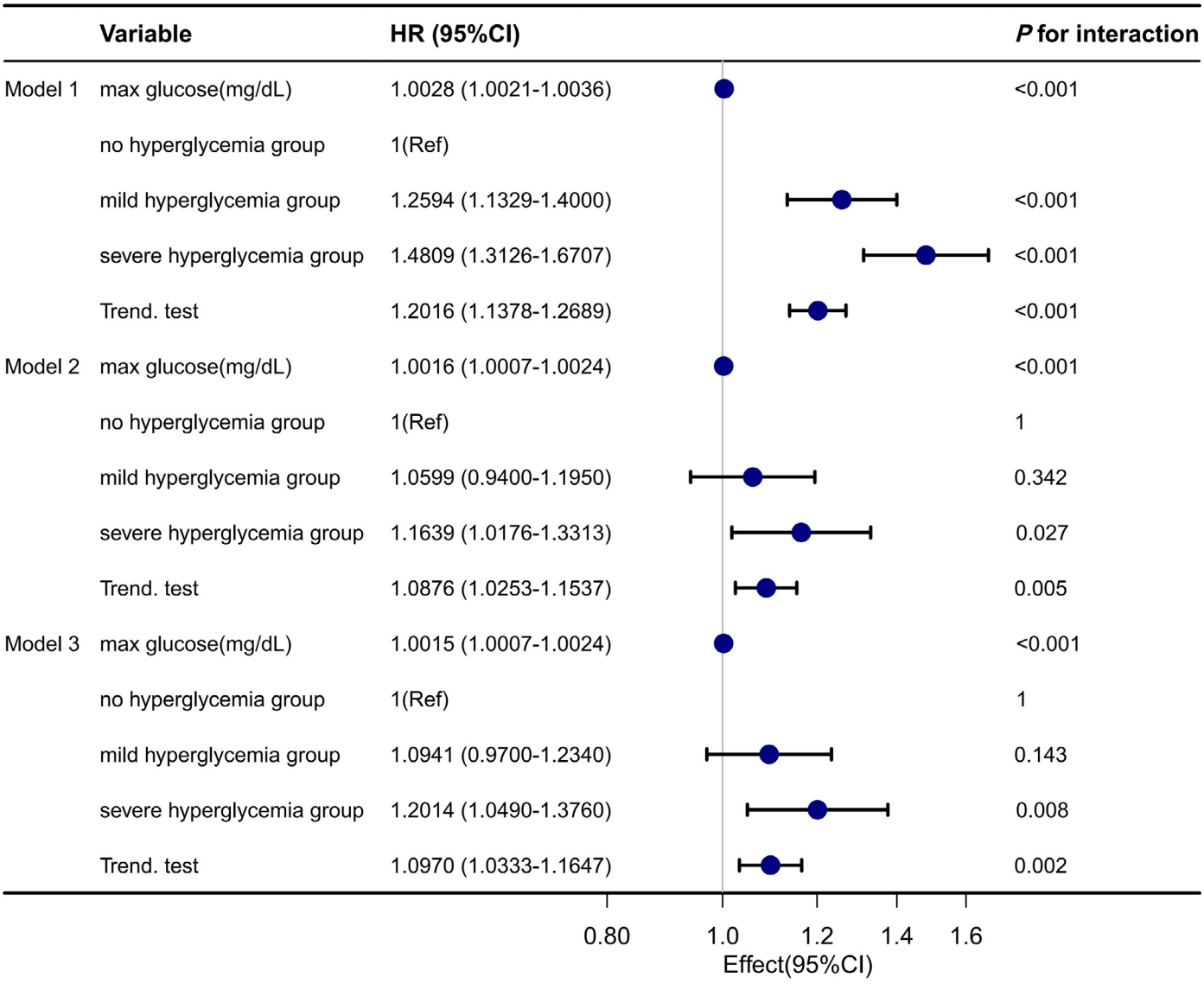

Figure 3. Multivariate Cox regression analyses for 7-day AKI in cardiac surgery patients. MODEL 1: First glucose; MODEL 2: MODEL 1 + age + BMI + MAP + resp rate + SpO_2 + WBC + creatinine; MODEL 3: MODEL 2 + congestive heart failure + peripheral vascular disease + cerebrovascular disease + chronic obstructive pulmonary disease + diabetes. AKI: Acute kidney injury; BMI: Body mass index; CI: Confidence interval; HR: Hazard ratio; MAP: Mean arterial pressure;SpO_2: Blood oxygen saturation; WBC: White blood cell.

7 days varied by sex (P <0.05). In female patients, patients in the severe (HR=1.4789, 95% CI: 1.1657 to 1.8764) and mild (HR=1.3246, 95% CI: 1.0717 to 1.6373) hyperglycemia groups had a higher incidence of 7-day AKI than those in the mild and no hyperglycemia groups. There were no similar increased risks of 7-day AKI among male patients. In patients <65 years old, hyperglycemia at ICU admission was not associated with the incidence of AKI during ICU stay. However, significantly higher risks of developing AKI were observed in patients aged ≥65 years with ICU admission for hyperglycemia, with an HR of 1.2856 (95% CI: 1.0779 to 1.5334) in the severe hyperglycemia group, and an HR of 1.1748 (95% CI: 1.0027 to 1.3765) in the mild hyperglycemia group. In the subgroup of patients with diabetes, multifactorial Cox proportional regression showed no difference in the incidence of AKI among patients with or without hyperglycemia. However, in patients without a previous history of diabetes, admission to the CVICU with severe hyperglycemia after their cardiac surgeries was an indicator of a higher risk of 7-day AKI during the ICU stay (HR=1.1829, 95% CI: 1.0158 to 1.3776) (Figure 4).

We also performed a subgroup analysis of the correlation between blood glucose levels and ICU mortality. Among patients with comorbid AKI, those in the severe hyperglycemia group (HR=1.3296) had a higher ICU mortality than those in the mild and no hyperglycemia groups. However, patients in the mild hyperglycemia group (HR=0.4863, 95% CI: 0.2436 to 0.9708) had lower ICU mortality than those in the severe and no hyperglycemia groups. Among patients without AKI, there were too few deaths to allow quantitative comparisons. But it could be observed that ICU mortality was lower in patients with mild hyperglycemia than in the severe and no hyperglycemia groups (Figure 5).

Subgroup	Variable	Total	Event (%)	HR (95%CI)	*P* for interaction
Sex	Female				0.021
	no hyperglycemia group	245	144 (58.8)	1(Ref)	
	mild hyperglycemia group	1363	1014 (74.4)	1.3246 (1.0717-1.6373)	
	severe hyperglycemia group	593	485 (81.8)	1.4789 (1.1657-1.8764)	
	Trend.test	2201	1643 (74.6)	1.1743 (1.0583-1.3029)	
	Male				
	no hyperglycemia group	399	250 (62.7)	1(Ref)	
	mild hyperglycemia group	3062	2245 (73.3)	0.9663 (0.8339-1.1197)	
	severe hyperglycemia group	1243	990 (79.6)	1.0453 (0.8850-1.2347)	
	Trend.test	4704	3485 (74.1)	1.0497 (0.9750-1.1301)	
Age(years)	Age<65				0.711
	no hyperglycemia group	284	154 (54.2)	1(Ref)	
	mild hyperglycemia group	1703	1146 (67.3)	1.0141 (0.8385-1.2266)	
	severe hyperglycemia group	725	555 (76.6)	1.1073 (0.8896-1.3781)	
	Trend.test	2712	1855 (68.4)	1.0678 (0.9659-1.1805)	
	Age>=65				
	no hyperglycemia group	360	240 (66.7)	1(Ref)	
	mild hyperglycemia group	2722	2113 (77.6)	1.1748 (1.0027-1.3765)	
	severe hyperglycemia group	1111	920 (82.8)	1.2856 (1.0779-1.5334)	
	Trend.test	4193	3273 (78.1)	1.1149 (1.0342-1.2019)	
Diabetes	Non−diabetes				0.868
	no hyperglycemia group	599	356 (59.4)	1(Ref)	
	mild hyperglycemia group	3429	2502 (73)	1.0961 (0.9638-1.2465)	
	severe hyperglycemia group	834	669 (80.2)	1.1829 (1.0158-1.3776)	
	Trend.test	4862	3527 (72.5)	1.0853 (1.0095-1.1668)	
	Diabetes				
	no hyperglycemia group	45	38 (84.4)	1(Ref)	
	mild hyperglycemia group	996	757 (76)	0.9335 (0.6308-1.3813)	
	severe hyperglycemia group	1002	806 (80.4)	1.0515 (0.7051-1.5680)	
	Trend.test	2043	1601 (78.4)	1.1076 (0.9941-1.2340)	

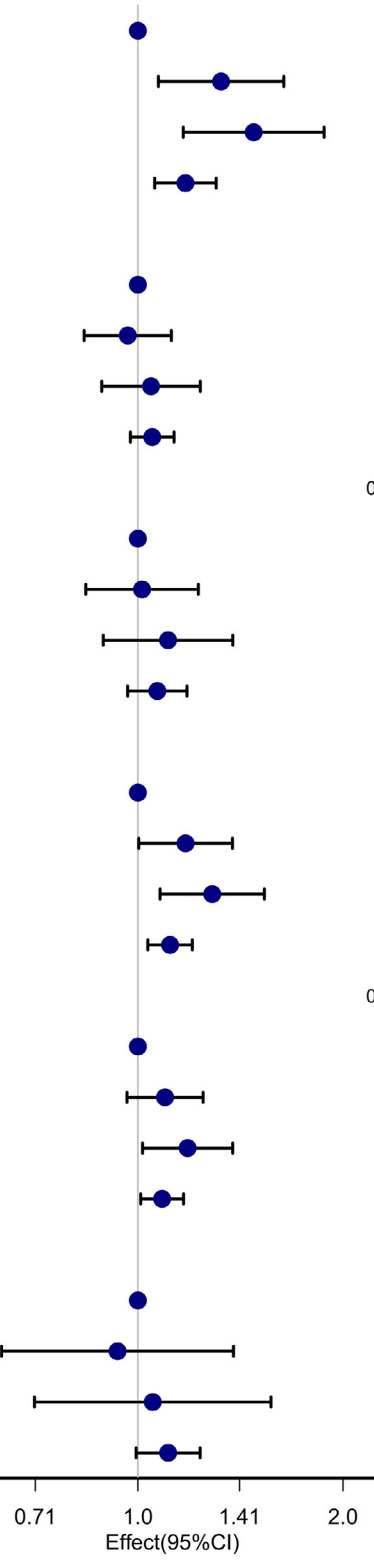

Figure 4. The association between glucose level and 7-day AKI in subgroups. Hazard ratios were adjusted for first glucose, age, BMI, MAP, resp rate, SpO_2, WBC, creatinine, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, and diabetes.
AKI: Acute kidney injury; BMI: Body mass index; CI: Confidence interval; HR: Hazard ratio; MAP: Mean arterial pressure; SpO_2: Blood oxygen saturation; WBC: White blood cell.

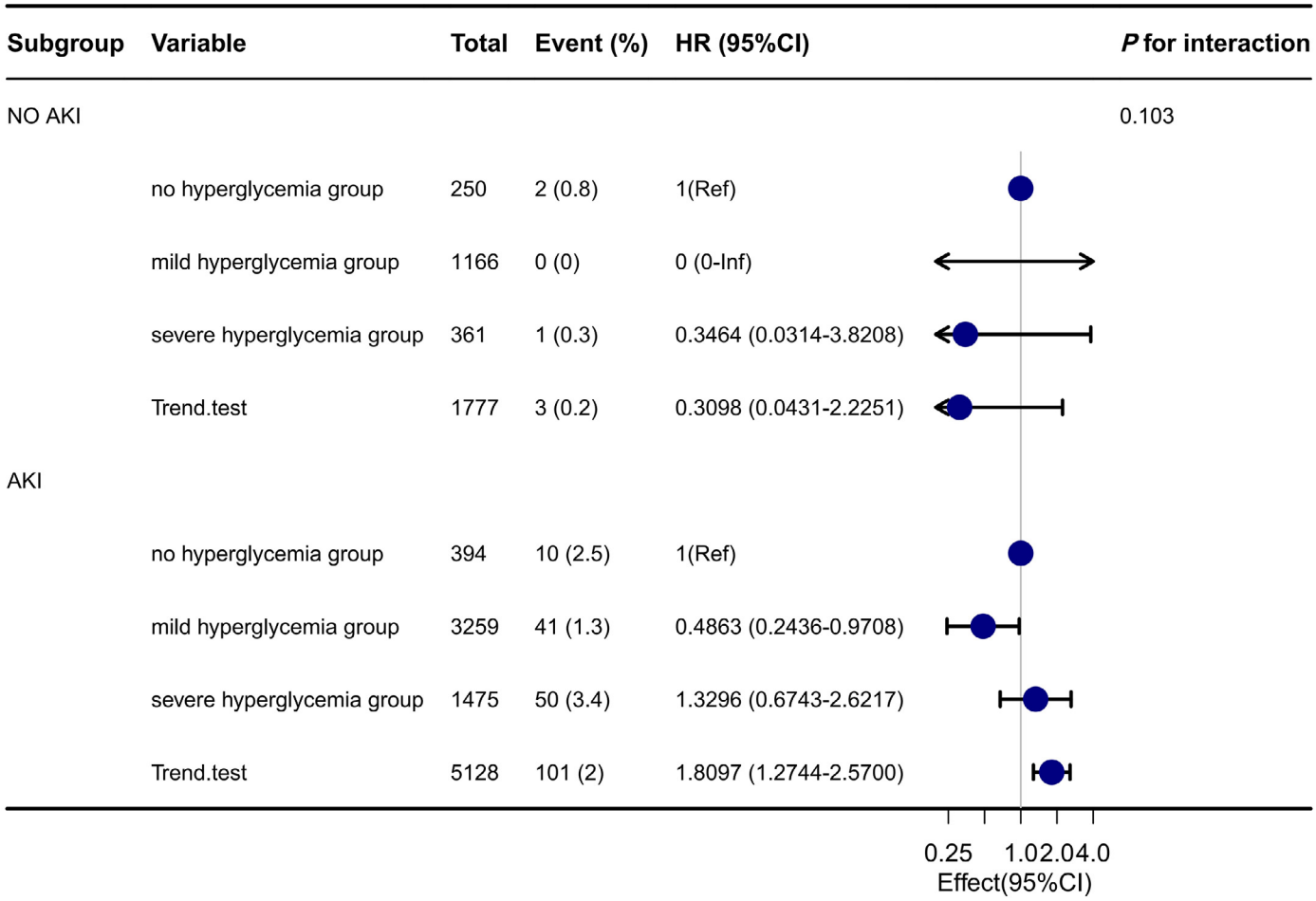

Figure 5. The association between glucose level and in-ICU mortality in subgroups.
CI: Confidence interval; HR: Hazard ratio; ICU: Intensive care unit.

Optimal blood glucose range for patients after cardiac surgery

To explore the optimal blood glucose range among patients undergoing cardiac surgery, potential non-linear associations between the levels of maximum blood glucose values within 24 h after admission and the incidence of AKI in all patients were examined using restricted cubic splines (Figure 6). Our analysis showed that patients should ideally have a blood glucose concentration <177 mg/dL for better prognosis, which was categorized as mild hyperglycemia in our study.

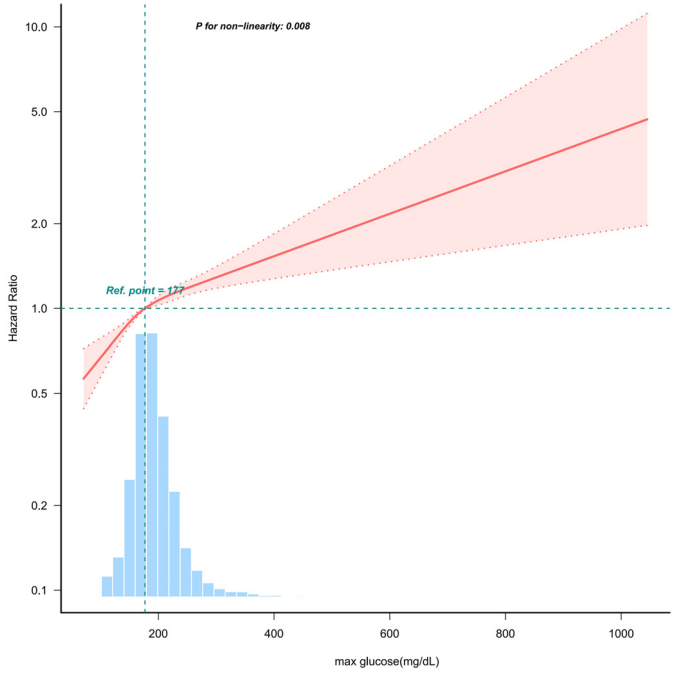

Figure 6. Smooth curve fitting of the relationship between the HBG recorded within 24 h of admission to the ICU and 7-day AKI. AKI: Acute kidney injury; HBG: Highest blood glucose; ICU: Intensive care unit.

Discussion

This study investigated the relationship between the HBG level 24 h within CVICU admission and clinical prognosis in patients after cardiac surgery. The overall incidence of 7-day AKI after ICU admission was 74.3%, including 61.2% in the no hyperglycemia group, 73.6% in the mild hyperglycemia group, and 80.3% in the severe hyperglycemia group. The severe hyperglycemia group had a significantly higher risk of 7-day AKI and ICU mortality. Our results indicated that blood glucose level should ideally be <177 mg/dL for patients after cardiac surgery.

In this study, patients had a much higher rate of AKI within 7 days of cardiac surgery than previously reported.[17,20] One possible explanation is that when both serum creatinine and urine volume criteria were used to diagnose AKI, it is possible that

more patients with AKI were enrolled, whereas less than one-third of the previous studies used this criterion.[21] Some studies reported that the incidence of AKI will increase from 23.8% to about 72.8% when the KDIGO urine volume criteria are used in addition to the KDIGO serum creatinine criteria.[22] We still chose to define postoperative AKI based on the KDIGO criteria of urine output combined with serum creatinine. This is because, if the urine volume diagnostic criteria are discarded, there is a risk of missed diagnosis of early AKI, which could affect patient prognosis and outcome.[23] Analyses of AKI diagnosis using only serum creatinine criteria (Supplementary Table 1) showed a substantial reduction in the calculated incidence of AKI in the cohort, consistent with previous results in the literature. The association between hyperglycemia and AKI persisted among patients screened for AKI with different diagnostic criteria.

Hyperglycemia was present in 90.7% patients in this study, which is consistent with previous studies.[24,25] Hyperglycemia upon ICU admission is common in post-cardiac surgery patients and has been previously reported as a significant predictor of poor outcome in post-cardiac surgery patients.[26–28] A retrospective study of 1826 mixed general medical, surgical, and coronary patients showed significantly higher maximum admission glucose levels (258 mg/dL *vs.* 177 mg/dL) in deceased patients compared to surviving patients.[29] Consistent with other reports, our study found higher ICU mortality rate and longer length of ICU stay in the severe hyperglycemia group than in the mild hyperglycemia group. Stress-induced hyperglycemia involves multiple mechanisms, such as increased gluconeogenesis, insulin resistance, massive catecholamine release, and cytokine activation.[30] Our study found that abnormal postoperative blood glucose values exacerbate renal impairment and ultimately increase patient mortality risk. The incidence of postoperative AKI increases progressively as the concentration of blood glucose rises, leading to a higher risk of 1-year mortality. There are various possibilities for the link between hyperglycemia and renal function decline. Hyperglycemia may further exacerbate myocardial injury by inducing the release of inflammatory cytokines, increasing oxidative stress, and exacerbating endothelial damage, thereby exacerbating ischemia-reperfusion injury for both the heart and kidney.[31] In our cohort, patients in the severe hyperglycemia group had higher lactate levels, presumably reflecting the presence of a hypoxic and hypoperfusion environment in the organism. This early hemodynamic deterioration can lead to a decrease in reduced renal perfusion, resulting in renal injury. Hyperglycemia can also cause increased generation of oxygen-free radicals and oxidative stress, as well as obstruction of blood flow-mediated vasodilation in microcirculation, resulting in intra-renal hypoxia and ischemia, causing renal damage.[32,33]

Surprisingly, patients with no hyperglycemia (blood glucose levels <140 mg/dL) had a higher 28-day mortality rate than those with severe hyperglycemia (blood glucose levels ≥200 mg/dL). In addition, the ICU mortality rate was higher in the no hyperglycemia group than in the mild hyperglycemia group (1.9% *vs.* 0.9%, P <0.05). This finding contradicts the results of a previous study, where it was found that adjusting postoperative blood glucose to normoglycemic levels (80–110 mg/dL) had a significant beneficial effect.[10] However, the Normoglycaemia in Intensive Care Evaluation – Survival Using Glucose Algorithm Regulation (NICE-SUGAR) multicenter, randomized controlled trial on intensive insulin therapy found that patients with a glycemic target of 140–180 mg/dL have a lower 90-day mortality rate than patients with a glycemic target of 80–110 mg/dL, suggesting no recommendation for application of the lower target in critically ill adults.[34] We think that parallels can be drawn with this recent study, suggesting that cardiac surgery patients can tolerate mild postoperative hyperglycemia (141–170 mg/dL) well, which may be related to the improvement of short-term patient outcomes after surgery.

However, there is still controversy over the strategy of glycemic control in patients after cardiac surgery. Van den Berghe et al.[10] conducted a study in a surgical ICU setting and found that patients receiving tight glycemic control had a significant reduction in mortality and the incidence of AKI. However, recent trials have shown an increased risk of death in the tight glycemic control group compared to the normal blood glucose level group during cardiac surgery, making it challenging to recommend tight glycemic control in patients after cardiac surgery.[35] We then attempted to identify the optimal range of glycemic control for patients after cardiac surgery through curve fitting, which suggested that the patient's blood glucose level should ideally be <177 mg/dL. Apart from this, according to our study, the 28-day mortality rates were higher in the no hyperglycemic group than in the mild and severe hyperglycemic groups. Subgroup analysis showed that in patients with combined AKI, the ICU mortality rate was lower in the mild hyperglycemia group than in the no and severe hyperglycemia groups. This suggests that mild hyperglycemia is prognostically beneficial in the AKI patient population. Considering the long-term prognosis, our analysis indicates that it is better to maintain the patients' perioperative blood glucose levels above normal levels. However, we acknowledge that this needs further investigation. Furthermore, the occurrence of clinical hypoglycemia should be avoided. Our study showed that although the incidence of AKI within 7 days in postcardiac surgery patients who developed hypoglycemia was not significantly different from that in patients without hypoglycemia (P >0.05), the 28-day mortality rate in patients who developed hypoglycemia was higher than that in patients who did not develop hypoglycemia (3.5% *vs.* 2.1%, P <0.05) (Supplementary Table S3).

Subgroup analysis showed that the effect of patient glucose on AKI in the postoperative 7 days differed by sex. Female patients were more likely to develop AKI within 7 days of ICU admission at severely high blood glucose levels than male patients. It has been documented that female diabetic patients are more likely to develop macrovascular complications than male patients.[36] This may be because of an imbalance of sex hormones due to hyperglycemia, potentially increasing the levels of oxidative stress and endothelial dysfunction, promoting an inflammatory milieu in response to estrogen receptors, affecting vascular response to nitric oxide, and impairing vasorelaxant properties.[37] Subsequently, kidney function is compromised. Therefore, in female postcardiac surgery patients, elevated blood glucose further increases the risk of AKI within 7 days of ICU admission. This has implications for patient care in the ICU to further implement precision therapy. In addition, the results of the subgroup analysis suggested that patients admitted to the CVICU with severe hyperglycemia after cardiac surgery had a higher risk of developing 7-day AKI during their ICU stay than patients without a history of diabetes mellitus.

This may be due to differences in the pathophysiologic basis of hyperglycemia in diabetic and non-diabetic patients.[38]

Postoperative AKI has been reported to be one of the most common complications in cardiac surgery, as well as a risk factor for poor prognosis.[39–41] The mortality rate of patients after cardiac surgery increases from 0.4%–4.4% to 1.3%–22.3% when the AKI stage is aggravated. Severe AKI following cardiac surgery is an independent risk factor for death, resulting in an eight-fold mortality risk.[42] This is in line with the results of our current study. According to our analysis, the ICU mortality rate of patients after cardiac surgery, who developed AKI, increased from 0.2% to 2.0% (Supplementary Table S4). In addition, the median length of hospitalization of patients after cardiac surgery who developed AKI increased from 1.3 days to 2.1 days. Therefore, identifying and mitigating the risk factors associated with postoperative AKI are crucial to improve patient's prognosis.

Limitations

There are some limitations in our study. First, the study is a single-center, retrospective, clinical analysis. The results may not be generalizable. Second, the study was conducted retrospectively and could only show a correlation – not a causal relationship, between admission hyperglycemia and the incidence of AKI after cardiac surgery. However, after correcting for numerous factors, blood glucose values remain an independent risk factor for the development of AKI. Third, we were unable to obtain data regarding patients' preoperative laboratory tests and intraoperative situation because relevant information was not currently available in the MIMIC-IV database; it is likely that this was among the main factors that contributed to the occurrence of AKI in patients after cardiac surgery. However, patients' SOFA score was obtained upon admission to the ICU, which serves partially as the proxy for their pre-operative condition. After adjustment for the first blood glucose on admission and SOFA score, severe hyperglycemia remained an independent risk factor for AKI within 7 days (HR=1.1698, 95% CI: 1.0322 to 1.3257, P <0.05) (Supplementary Table S5).

Conclusion

Maximum blood glucose level within 24 h of ICU admission is associated with an increased risk of 7-day AKI incidence, ICU mortality, and hospital mortality in patients admitted in the ICU after cardiac surgery.

Author Contributions

Juan Ruan: Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Weipeng Huang:** Writing – review & editing, Formal analysis. **Jun Jiang:** Writing – review & editing, Formal analysis. **Chang Hu:** Writing – review & editing, Methodology. **Zhiyong Peng:** Writing – review & editing, Project administration. **Shuhan Cai:** Writing – review & editing, Project administration.

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Ethics Statement

The Institutional Review Boards at MIT and the Beth Israel Deaconess Medical Center have reviewed and approved this research involving human participants. Informed consent is not required, as all data have been de-identified.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2024.04.004.

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