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Article

Association between Admission Blood Glucose and In-Hospital MACE in Non-Diabetic STEMI (Killip I) Patients Undergoing Primary PCI

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Abstract

Background: The increase in major adverse cardiovascular events (MACE) in patients with diabetes after primary percutaneous coronary intervention (pPCI) is significantly correlated with the admission blood glucose (ABG). However, it is unclear whether ABG in non-diabetic patients is related to MACE after pPCI. We aimed to explore the relationship between ABG and in-hospital MACE in non-diabetic ST-segment elevation myocardial infarction (STEMI) patients with Killip class I treated with pPCI. **Methods**: The Chinese STEMI pPCI Registry (NCT04996901) enrolled 5586 STEMI patients undergoing pPCI from January 2015 to August 2021. Patients were divided into three groups after excluding those with hyperglycemia (ABG $\geq$11 mmol/L) and a history of diabetes. MACE was defined by re-infarction, stroke, and cardiovascular death. The association between ABG and in-hospital MACE was assessed using Logistic regression analysis. **Results**: 2890 non-diabetic STEMI patients with Killip class I treated with pPCI were identified. Patients were divided into three groups based on ABG (Q1: 2.5–5.72 mmol/L; Q2: 5.73–7.0 mmol/L; Q3: 7.01–11.0 mmol/L). After multivariate adjustment for age, gender, Diastolic Blood Pressure (DBP), Heart Rate (HR), smoking, and hypertension, the OR of MACE in Q2 and Q3 were 1.43–1.62 times of Q1 in the calibration Model II to IV. Subgroup analysis showed that the OR of Q2 was 3.52-fold of Q1 in females and 1.54-fold in the elder ($\geq$60 years). Sensitivity analysis showed that after excluding patients with ABG less than 4 mmol/L, elevated ABG was still associated with a significant increase in the risk of MACE. The area under the ROC curve of ABG in predicting the occurrence of MACE after pPCI was 0.668, and the C-index was 0.666. The cubic spline confirmed MACE risk decreased significantly with ABG below 6.3 mmol/L. **Conclusions**: Elevated ABG is associated with increased risk of in-hospital MACE in non-diabetic STEMI patients treated with pPCI, particularly females and the elderly. This retrospective observational study was registered in Clinical Trials (NCT04996901).

Keywords

admission blood glucose; non-diabetic; major adverse cardiovascular events; ST-segment elevation myocardial infarction; primary PCI

Introduction

Percutaneous coronary intervention (PCI), is widely used in the clinical treatment of ST-segment elevation my-

ocardial infarction (STEMI) patients. Heart failure (HF), a common adverse cardiovascular event, occurs in nearly 6% of STEMI patients treated with pPCI [1], leading to an unacceptably high incidence of cardiovascular mortality [2]. By improving the ability to identify high-risk patients with major adverse cardiovascular events (MACE), timely intervention measures can be made to ensure the positive therapeutic effects of coronary re-canalization after PCI.

Admission blood glucose (ABG), an inexpensive and rapidly available laboratory parameter, is frequently increased in critically ill patients. It is well known that blood glucose levels are associated with the risk of various cardiovascular diseases. A strong positive association has been observed between ABG and mortality in acute MI patients [3]. In addition, patients with diabetes have a relatively higher risk of adverse outcomes after myocardial infarction [4]. High blood glucose levels are a risk factor for heart failure and increased morbidity and mortality [5]. Impaired fasting blood glucose is associated with an increased risk of coronary artery disease [6]. However, the relationship between dysglycemia and adverse outcomes in non-diabetics with STEMI is still controversial. Dysglycemia, significantly impairs fasting glucose or glucose tolerance, in patients with prediabetes [7]. Several studies have found that dysglycemia is not immediately associated with adverse cardiovascular outcomes [8]. Other studies have found that among non-diabetic patients undergoing PCI, one-third have abnormal blood glucose levels, and the risk of adverse events, such as myocardial infarction, is four times higher compared to those with normal blood glucose levels [9]. Ritsinger V *et al*. [10] also discovered that elevated ABG levels identifies an increased risk of long-term complications in non-diabetics with an MI. At the time of a PCI, dysglycemia is even more likely to result in adverse outcomes [11]. The correlation between ABG and MACE after PCI in non-diabetic STEMI patients has not been adequately reported.

We conducted this large scale, multi-center clinical study to further explore the correlation between ABG levels and MACE, defined as re-infarction, stroke, and cardiovascular death, and to determine whether ABG could serve as a valuable marker for identifying the risk of MACE in non-diabetic STEMI patients treated with PCI, as well as to assess whether there are age or gender-related differences.

Methods

Data Source and Selected Patient Cohort

This study protocol was reviewed and approved by the Ethics committee of Wuhan University People's Hospital (approval number: WDRY2021-K054) and the Medical Ethics Committee of Yichang Central People's Hospital (approval number: 2021-043-01). Written informed consent was obtained from all participants (or their parent/legal guardian/next of kin) to participate in this study.

This retrospective observational study was registered in Clinical Trials (NCT04996901). A total of seven research centers participated, all of which are located in Hubei Province. The patient distribution is also primarily concentrated within this province. Patients admitted for the first time or transferred from another hospital were included in this study. Non-diabetic patients diagnosed with STEMI and who underwent PCI from January 2015 to August 2021 were the target population.

5586 STEMI patients treated with PCI were included in this study. Patients with available random blood sugars reported on the first day of hospitalization were enrolled. The exclusion criteria included ABG $\geq$11.1 mmol/L, Killip class $\geq$2 on admission, symptom onset time beyond 24 h, without or failed PCI, and missing HF or other information. Ultimately, 2890 participants were eligible for inclusion to assess the association between ABG and the risk of in-hospital MACE.

Definitions

Non-diabetics: Information on non-diabetics was obtained from this multi-center study. Patients with an ABG of less than 11 mmol/L or no preexisting diabetes were the targeted population.

Patients diagnosed as non-diabetics, STEMI, Killip class 1, and underwent PCI that could be retrieved from the corresponding disease code in the hospital's case system. In the included patients, ABG between 2.5 and 11.0 mmol/L were categorized into the following three groups: Q1 ABG: 2.5–5.72 mmol/L (45–102.96 mg/dL). Q2 ABG: 5.73–7.01 mmol/L (102.97–126.18 mg/dL). Q3 ABG: 7.02–11.0 mmol/L (126.19–198 mg/dL).

MACE included death and new-onset HF. Patients who died in the hospital from any cause and terminal patients who chose to withdraw treatment were excluded from the study. During the hospitalization of patients, once new-onset HF and an in-hospital death occurred, clinicians would enter the corresponding disease code in the medical record system.

Statistical Analysis

Baseline characteristics of non-diabetic STEMI patients with PCI were analyzed by stratified glucose levels. Continuous variables are presented as mean $\pm$ standard deviation or median [P25, P75], and categorical variables are reported as numbers (percentages). One-way ANOVA, χ^2, and Kruskal-Wallis H tests were used in the data analysis. The association between different groups of ABG levels and the risk of in-hospital MACE was assessed in an adjusted Logistic regression model, in which Q1 (ABG 2.5–5.72 mmol/L [45–102.96 mg/dL]) served as a refer-

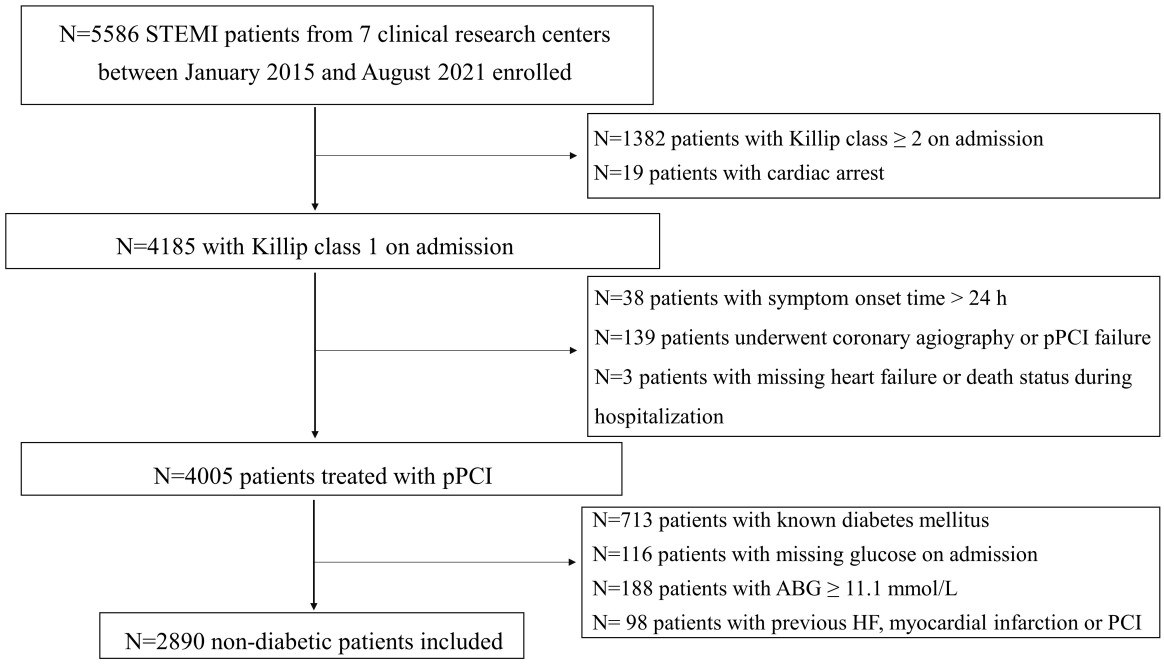

Fig. 1. Flowcharts of patient's screening process in this study. STEMI, ST-segment elevation myocardial infarction; pPCI, primary percutaneous coronary intervention; ABG, admission blood glucose; HF, heart failure; PCI, percutaneous coronary intervention.

ence. We fitted four statistical models based on the Model I. Model II was adjusted for age, gender (man/female), Systolic Blood Pressure (SBP), DBP, and HR; Model III was further adjusted for smoking, hypertension, hyperlipidemia, atrial fibrillation, myocardial infarction, PCI, and stroke; Model IV was further adjusted based on Model III for onset to balloon time, malignant arrhythmia, syncope, ventricular arrhythmia, bradyarrhythmia, cardiac arrest; Model V added a few more factors, including TIMI flow after PCI, infarct-related coronary artery condition, type of operation, in hospital non-infarct-related artery operational management. Analysis of p for trend was conducted in the form of a median. Restricted cubic spline showed the dose-response relationship between ABG and the risk of MACE. Subgroup analysis of gender and age was carried out based on mode IV. Sensitivity analyses were made after excluding the patients whose ABG level was less than 4 mmol/L and the patients who had a prior MACE. ROC curves and calibration plots were used to test model differentiation and the degree of calibration. All analyses were performed using R software http://www.R-project.org (4.2.1). Statistical significance was determined by a two-sided p value < 0.05.

Included Population

In all, 5586 patients were identified during the study period. We excluded patients with Killip class $\geq$2 on admission (n = 1382, and another 19 patients with cardiac arrest), symptom onset time beyond 24 h (n = 38), without or failure PCI (n = 139), ABG $\geq$11.1 mmol/L (n = 188). A total of 2890 patients were ultimately included (Fig. 1).

Baseline Characteristics

The baseline characteristics and dual anti-platelet therapy are shown in Table 1. Detailed information was collected on all study participants, including sociodemographic characteristics (age, gender), lifestyle factors (smoking), clinical indicators (Systolic blood pressure, Diastolic blood pressure, Heart rate, Hypertension, Hyperlipidaemia, Preoperative malignant arrhythmia, Ventricular arrhythmia, Bradyarrhythmia, Cardiac arrest, and Syncope), combined disease (previous atrial fibrillation, heart failure, and stroke) and oral medication (Statin, β-blocker) through the inpatient medical record system and telephone consultation. The patients were divided into three groups according to the trilateral method (Q1: 2.01–5.72 mmol/L; Q2: 5.73–7.01 mmol/L; Q3: 7.02–11 mmol/L). 10.14% of patients developed in-hospital MACE, the mean age was 59.677 $\pm$ 12.110 years, 83.87% were male, 95.67% of patients had no prior PCI, and 55.3% had a smoking history. Significant differences existed in in-hospital MACE, gender, SBP, DBP, HR, smoking history, hyperlipidemia, and other indexes among the three groups.

Results

Correlation between ABG and the Risk of In-Hospital MACE

There was a correlation between ABG and the risk of in-hospital MACE (all $p < 0.05$) through unadjusted Model

Table 1. Baseline characteristics by glucose (mmol/L) level strata.

Variable	No. (%)				*p*-value
	Overall	Q1 (2.50–5.72 mmol/L)	Q2 (5.73–7.00 mmol/L)	Q3 (7.01–11.00 mmol/L)	
	(n = 2890)	(n = 959)	(n = 963)	(n = 968)	
Clinical Characteristic					
Age, median Interquartile Range (IQR), y	60 (51–68)	60 (52–68)	59 (51–68)	60 (52–69)	0.0726
Female	477 (16.51)	132 (13.76)	144 (14.95)	201 (20.76)	0.0001
Smoking	1585 (54.84)	552 (57.56)	547 (56.80)	486 (50.21)	0.0017
Hypertension	1329 (45.99)	425 (44.32)	438 (45.48)	466 (48.14)	0.2251
Hyperlipidaemia	190 (6.57)	44 (4.59)	84 (8.72)	62 (6.40)	0.0012
Previous atrial fibrillation	48 (1.66)	14 (1.46)	17 (1.77)	17 (1.76)	0.8372
Previous stroke	156 (5.40)	40 (4.17)	56 (5.82)	60 (6.20)	0.1125
Presentation					
Anterior myocardial infarction	1365 (47.23)	419 (43.69)	482 (50.05)	464 (47.93)	0.0175
Symptom onset to balloon time, median (IQR), h	5 (3–7)	5 (3–7)	5 (3–8)	4 (3–7)	0.0542
Malignant arrhythmia before primary Percutaneous Coronary Intervention (pPCI)	189 (6.54)	63 (6.57)	55 (5.71)	71 (7.33)	0.3528
Ventricular arrhythmia before pPCI	74 (2.56)	21 (2.19)	17 (1.77)	36 (3.72)	0.0168
Bradyarrhythmia before pPCI	98 (3.39)	30 (3.13)	35 (3.63)	33 (3.41)	0.8281
Syncope before pPCI	41 (1.42)	20 (2.09)	8 (0.83)	13 (1.34)	0.0649
Hemodynamic parameters on admission					
Systolic Blood Pressure (SBP), median (IQR), mmHg	122 (110–138)	120 (106–135)	122 (110–137)	123 (110–140)	0.0007
Diastolic Blood Pressure (DBP), median (IQR), mmHg	78 (69–86)	76 (68–85)	78 (70–88)	78 (69–87)	0.0059
Heart Rate (HR), median (IQR), bpm	76 (68–85)	75 (66–84)	76 (68–85)	78 (68–86)	0.007
Laboratory indexes on admission					
White blood cell count, median (IQR), 10^9/L	10.29 (8.36–12.45)	9.89 (8.01–11.90)	10.45 (8.48–12.59)	10.49 (8.56–3.02)	<0.0001
Neutrophil count, median (IQR), 10^9/L	8.18 (6.27–10.40)	7.63 (5.91–9.55)	8.40 (6.46–10.50)	8.44 (6.61–10.84)	<0.0001
Lymphocyte count, median (IQR), 10^9/L	1.20 (0.87–1.75)	1.27 (0.91–1.81)	1.20 (0.89–1.69)	1.15 (0.82, 1.71)	0.0878
Platelet count, median (IQR), 10^9/L	207.00 (170.00–247.50)	205.00 (170.00–243.50)	206.00 (169.00–253.00)	208.00 (172.00–246.00)	0.4965
Haemoglobin count, median (IQR), g/L	141.00 (129.00–152.00)	140.00 (128.00–150.00)	143.00 (130.00–153.00)	141.00 (129.25–152.00)	0.0011
Alanine Aminotransferase (ALT), median (IQR), U/L	39.85 (25.00–61.00)	40.00 (26.00–59.00)	40.00 (26.00–64.85)	39.00 (24.20–60.00)	0.2492
Aspartate Aminotransferase (AST), median (IQR), U/L	126.00 (49.00–264.00)	131.00 (60.00–255.00)	139.00 (51.02–297.75)	95.15 (41.90–252.25)	0.0001
Uric acid, median (IQR), μmol/L	358.89 (299.00–426.60)	357.00 (298.91–430.00)	365.30 (309.00–430.40)	354.59 (292.24–421.62)	0.0411
Total Cholesterol (TC), median (IQR), mmol/L	4.63 (4.00–5.32)	4.52 (3.90–5.22)	4.63 (4.03–5.31)	4.74 (4.09–5.42)	<0.0001
Triglycerides (TG), median (IQR), mmol/L	1.30 (0.89–1.92)	1.35 (0.97–1.91)	1.29 (0.89–1.91)	1.29 (0.81–1.93)	0.0634
High-Density Lipoprotein Cholesterol (HDL-C), median (IQR), mmol/L	1.11 (0.93–1.32)	1.10 (0.93–1.32)	1.10 (0.92–1.31)	1.11 (0.95–1.32)	0.1705
Low-Density Lipoprotein Cholesterol (LDL-C), median (IQR), mmol/L	2.82 (2.30–3.35)	2.70 (2.27–3.18)	2.83 (2.29–3.41)	2.91 (2.37–3.47)	<0.0001
Serum creatine, median (IQR), μmol/L	71.40 (62.00–84.00)	72.00 (63.00–85.00)	71.00 (62.00–82.80)	71.00 (61.00–84.00)	0.1003

Table 1. Continued.

Variable	No. (%)				*p*-value
	Overall (n = 2890)	Q1 (2.50–5.72 mmol/L) (n = 959)	Q2 (5.73–7.00 mmol/L) (n = 963)	Q3 (7.01–11.00 mmol/L) (n = 968)	
Procedure characteristics					
Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 before pPCI	2048 (70.87)	636 (66.32)	686 (71.24)	726 (75.00)	0.0001
TIMI flow grade 3 after pPCI	2852 (98.69)	949 (98.96)	951 (98.75)	952 (98.35)	0.8315
Multivessel disease					
1–vessel lesion	1492 (51.63)	532 (55.47)	527 (54.72)	433 (44.73)	
2–vessel lesion	844 (29.20)	274 (28.57)	253 (26.27)	317 (32.75)	<0.0001
3–vessel lesion	554 (19.17)	153 (15.95)	183 (19.00)	218 (22.52)	
Infarct-Related Artery (IRA)					
Left anterior descending	1388 (48.03)	430 (44.84)	487 (50.57)	471 (48.66)	
Left circumflex	354 (12.25)	136 (14.18)	108 (11.21)	110 (11.36)	0.0582
Left main	4 (0.14)	3 (0.31)	1 (0.10)	0 (0.00)	
Right	1144 (39.58)	390 (40.67)	367 (38.11)	387 (39.98)	
Stent implantation for IRA	2698 (93.36)	914 (95.31)	882 (91.59)	902 (93.18)	0.0045
Non-IRA PCI management	232 (8.03)	75 (7.82)	81 (8.41)	76 (7.85)	0.8657
Complete revascularization	1791 (61.97)	652 (67.99)	616 (63.97)	523 (54.03)	<0.0001
Treatment					
Dual antiplatelet	2871 (99.34)	955 (99.58)	958 (99.48)	958 (98.97)	0.1998
Statin	2874 (99.45)	959 (100.00)	957 (99.38)	958 (98.97)	0.0088
β-blocker	2412 (83.46)	767 (79.98)	792 (82.24)	853 (88.12)	<0.0001
Angiotensin-Converting Enzyme Inhibitor (ACEI)/Angiotensin II Receptor Blocker (ARB)/Angiotensin Receptor-Neprilysin Inhibitor (ARNI)	1925 (66.61)	616 (64.23)	621 (64.49)	688 (71.07)	0.0015
Cardiotonic drugs	75 (2.60)	26 (2.71)	21 (2.18)	28 (2.89)	0.5933
Diuretics	345 (11.94)	94 (9.80)	122 (12.67)	129 (13.33)	0.0402
Sprironolactone	387 (13.39)	92 (9.59)	136 (14.12)	159 (16.43)	<0.0001
Calcium channel blocker	341 (11.80)	85 (8.86)	129 (13.40)	127 (13.12)	0.0026
Intra-Aortic Balloon Pump (IABP)	7 (0.24)	2 (0.21)	1 (0.10)	4 (0.41)	0.3716
Respirator	12 (0.42)	2 (0.21)	2 (0.21)	8 (0.83)	0.051
Continuous Renal Replacement Therapy (CRRT)	4 (0.14)	3 (0.31)	1 (0.10)	0 (0.00)	0.1707
In-hospital outcomes					
Death of all cause and treatment withdraw	23 (0.80)	4 (0.42)	9 (0.93)	10 (1.03)	0.2635
New-onset heart failure	280 (9.69)	70 (7.30)	105 (10.90)	105 (10.85)	0.0093
Major Adverse Cardiovascular Events (MACE)	293 (10.14)	73 (7.61)	110 (11.42)	110 (11.36)	0.0066

Table 2. Unadjusted and adjusted risk (OR 95%CI) of MACE (new-onset HF, death) in STEMI patients who underwent pPCI stratifiedby glucose levels.

Glucose level	Model 1		Model 2		Model 3		Model 4		Model 5	
	OR (95% CI)	*p*	adj. OR (95% CI)	*p*	adj. OR (95% CI)	*p*	adj. OR (95% CI)	*p*	adj. OR (95% CI)	*p*
Q1 (2.50–5.72 mmol/L)	1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Q2 (5.73–7.00 mmol/L)	1.57 (1.15, 2.13)	0.005	1.62 (1.18, 2.22)	0.003	1.59 (1.16, 2.18)	0.004	1.59 (1.16, 2.19)	0.004	1.56 (1.14, 2.15)	0.006
Q3 (7.01–11.00 mmol/L)	1.56 (1.14, 2.12)	0.005	1.49 (1.09, 2.04)	0.014	1.46 (1.06, 2.01)	0.019	1.48 (1.08, 2.03)	0.016	1.43 (1.04, 1.97)	0.027

Model 1 unadjusted; Model 2 adjusted for age, gender, DBP, and HR; Model 3 adjusted for age, gender, DBP, HR, smoking, hypertension, hyperlipidemia, previous atrial fibrillation, and previous stroke; Model 4 adjusted for age, gender, DBP, HR, smoking, hypertension, hyperlipidemia, previous atrial fibrillation, previous stroke, symptom onset to balloon time, and malignant arrhythmia before pPCI; Model 5 adjusted for age, gender, DBP, HR, smoking, hypertension, hyperlipidemia, previous atrial fibrillation, previous stroke, symptom onset to balloon time, malignant arrhythmia before pPCI, TIMI flow grade 0 before pPCI, TIMI flow grade 3 after pPCI, stent implantation for IRA, and non-IRA PCI management. Patients with a blood glucose of 2.50–5.72 mmol/L were a reference group with OR = 1.

Table 3. Adjusted risk (OR 95% CI) of MACE (new-onset HF, death) in different gender or age of STEMI patients underwent pPCI stratified by glucose levels.

Glucose level (mmol/L)	Male*		Female*		<60 years[#]		≥60 years[#]	
	adj. OR (95% CI)	*p*	adj. OR (95% CI)	*p*	adj. OR (95% CI)	*p*	adj. OR (95% CI)	*p*
Q1 (2.50–5.72 mmol/L)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Q2 (5.73–7.00 mmol/L)	1.31 (0.92, 1.86)	0.136	3.52 (1.53, 8.06)	0.003	1.67 (0.95, 2.93)	0.075	1.54 (1.05, 2.27)	0.029
Q3 (7.01–11.00 mmol/L)	1.31 (0.91, 1.87)	0.141	2.09 (0.92, 4.75)	0.078	1.4 (0.78, 2.51)	0.266	1.53 (1.04, 2.24)	0.029

*Adjusted for age, DBP, HR, smoking, hypertension, hyperlipidaemia, previous atrial fibrillation, previous stroke, symptom onset to balloon time, malignant arrhythmia before pPCI, TIMI flow grade 0 before pPCI, TIMI flow grade 3 after pPCI, stent implantation for IRA, and Non-IRA PCI management. [#]Adjusted for gender, DBP, HR, smoking, hypertension, hyperlipidaemia, previous atrial fibrillation, previous stroke, symptom onset to balloon time, malignant arrhythmia before pPCI, TIMI flow grade 0 before pPCI, TIMI flow grade 3 after pPCI, stent implantation for IRA, and non-IRA PCI management. Patients with blood glucose of 2.50–5.72 mmol/L served as a reference group with OR = 1.

Table 4. Unadjusted and adjusted risk (OR 95%CI) of MACE (new-onset HF, death) in STEMI patients underwent pPCI with admission blood glucose level ≥4 mmol/L.

Glucose level	Model I		Model II		Model III		Model IV		Model V	
	OR (95% CI)	*p*	adj. OR (95% CI)	*p*	adj. OR (95% CI)	*p*	adj. OR (95% CI)	*p*	adj. OR (95% CI)	*p*
Q1 (4.00–5.72 mmol/L)	1 (reference)		1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Q2 (5.73–7.00 mmol/L)	1.53 (1.12, 2.09)	0.008	1.62 (1.18, 2.22)	0.003	1.59 (1.16, 2.18)	0.004	1.59 (1.16, 2.19)	0.004	1.56 (1.14, 2.15)	0.006
Q3 (7.01–11.00 mmol/L)	1.52 (1.11, 2.07)	0.009	1.49 (1.09, 2.04)	0.014	1.46 (1.06, 2.01)	0.019	1.48 (1.08, 2.03)	0.016	1.43 (1.04, 1.97)	0.027

Model I unadjusted; Model II adjusted for age, gender, DBP and HR; Model III adjusted for age, gender, DBP, HR, smoking, hypertension, hyperlipidaemia, previous atrial fibrillation, and previous stroke; Model IV adjusted for age, gender, DBP, HR, smoking, hypertension, hyperlipidaemia, previous atrial fibrillation, previous stroke, symptom onset to balloon time, and malignant arrhythmia before pPCI; Model V adjusted for age, gende, DBP, HR, smoking, hypertension, hyperlipidaemia, previous atrial fibrillation, previous stroke, symptom onset to balloon time, malignant arrhythmia before pPCI, TIMI flow grade 0 before pPCI, TIMI flow grade 3 after pPCI, stent implantation for IRA, and non-IRA PCI management. Patients with blood glucose of 4.00–5.72 mmol/L served as a reference group with OR = 1. There were 34 cases of admission blood glucose level <4 mmol/L.

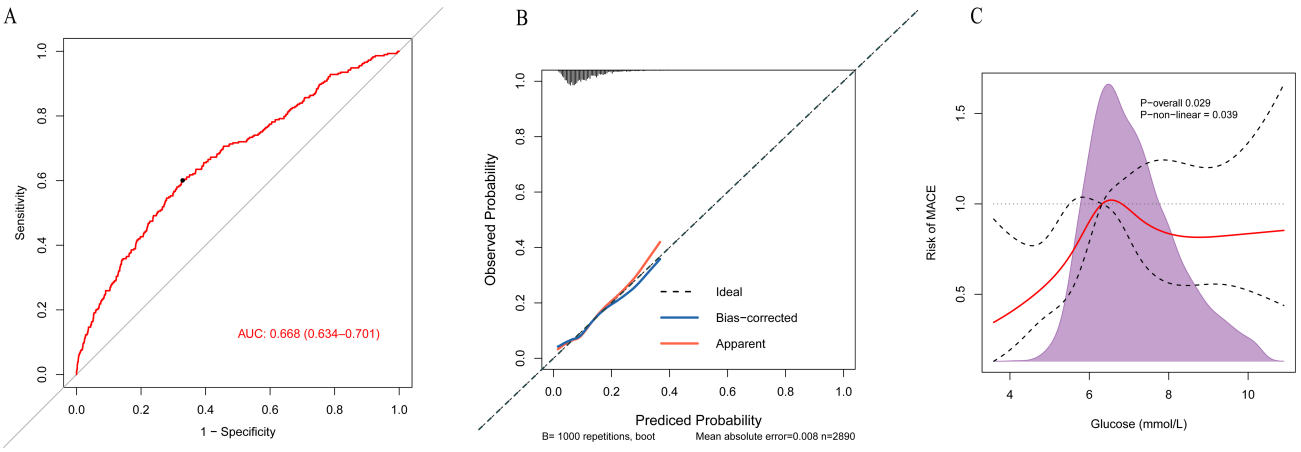

Fig. 2. The association between admission blood glucose and in-hospital MACE (new-onset heart failure, death) for non-diabetic STEMI patients who underwent pPCI. The association between admission blood glucose level and in-hospital MACE (new-onset heart failure, death) is adjusted for age, gender, DBP, HR, smoking, hypertension, hyperlipidemia, previous atrial fibrillation, previous stroke, symptom onset to balloon time, malignant arrhythmia before pPCI, TIMI flow grade 0 before pPCI, TIMI flow grade 3 after pPCI, stent implantation for IRA, and non-IRA PCI management. The area under the ROC curve is 0.688 (A). The calibration plot demonstrates the predicted probability and observed incidence of in-hospital MACE (B). Repeated sampling performs 1000 times using the bootstrap method. The c-index of the adjusted model is 0.666. Restricted cubic spline displays an association between continuous admission blood glucose level and in-hospital MACE (C). The solid line illustrates the odds ratio (OR). The dotted lines demonstrate the 95% confidence interval. A glucose of 6.78 mmol/L served as a reference (OR = 1.0).

I. Setting the OR of Q1 for 1 as a reference, the OR was 1.57 in Q2 and 1.56 in Q3. Model II was established after adjusting age, gender, DBP, and HR, and the OR was 1.62 in Q2 and 1.49 in Q3. The same result was found in Model III after adding several factors, including smoking, hypertension, hyperlipidemia, previous atrial fibrillation, and previous stroke. We made two more model adjustments, adding symptom onset to balloon time and malignant arrhythmia before PCI as Model IV and continuing to add TIMI flow grade 0 before PCI, TIMI flow grade 3 after PCI, stent implantation for IRA and non-IRA PCI management as Model V. All five Models showed stability that the risk of MACE was higher in Q2 and Q3 than in Q1 (Table 2).

Differentiation and Calibration of ABG in Predicting MACE

Predicted and actual in-hospital MACE incidences are depicted in Fig. 2B, which showed that the selection of ABG was appropriate and accurate in the prediction of in-hospital MACE with a c-index of 0.666. ROC curves (Fig. 2A) showed that the c-index was 0.668 (95% CI = 0.634–0.701). Restricted cubic spline (Fig. 2C) showed that ABG <5.5 mmol/L is the protective factor for in-hospital MACE.

Subgroup Analysis—ABG and MACE in Different Ages and Gender

Subgroup analysis of gender was performed by adjusting for certain factors, including age, DBP, HR, smoking, hypertension, hyperlipidemia, previous atrial fibrillation, previous stroke, symptom onset to balloon time, malignant arrhythmia before PCI, TIMI flow grade 0 before PCI, TIMI flow grade 3 after PCI, stent implantation for IRA, and Non-IRA PCI management. The result was that Q2 was 3.52-fold of Q1 in females ($p < 0.05$).

Subgroup analysis of age was performed by adjusting for other factors, including gender, DBP, HR, smoking, hypertension, hyperlipidemia, previous atrial fibrillation, previous stroke, symptom onset to balloon time, malignant arrhythmia before PCI, TIMI flow grade 0 before PCI, TIMI flow grade 3 after PCI, stent implantation for IRA, and non-IRA PCI management. We found that Q2 and Q3 were 1.54-fold and 1.53-fold of Q1 in the elder (≥60 years), respectively ($p < 0.05$) (Table 3).

Sensitivity Analysis—After Excluding Patients with ABG less than 4 mmol/L

Hypoglycemia is defined as a blood sugar of 3.9 mmol/L or less. Previous studies have found that hypoglycemia is associated with a higher risk of mortality in non-diabetic STEMI patients [12]. Thus, the relationship between ABG and MACE was analyzed again after excluding patients with ABG less than 4 mmol/L (n = 34). Calibration was again conducted for four more models based on model 1. The results showed that all models were statistically significant, which suggested that ABG was related to the occurrence of MACE in non-diabetics with normal blood glucose (Table 4).

Discussion

This analysis explored the relationship between ABG and in-hospital MACE in non-diabetic STEMI patients (Killip I) who underwent PCI. By analyzing patients' sociodemographic characteristics, clinical indicators, combined disease, and oral medication, we found a correlation between ABG and the occurrence of MACE. The incidence of MACE decreased with the reduction of blood glucose when the patient's ABG was below 6.3 mmol/L, especially in females and in elder patients.

A previous study stated that prediabetes was independently associated with an increased risk of MACE after PCI [13]. However, only five studies on primary PCI showed high heterogeneity (I^2 = 52%). The main reason for the high heterogeneity was the insufficient sample size. Therefore, conducting clinical research on ABG and in-hospital MACE is necessary. Our study is highly sensitive and calibrated, which would be a helpful reference in clinical practice. Moreover, our study adopted the third percentile method to group patients with different values of ABG, which can better explain the role of blood glucose and the risk of in-hospital MACE.

The present study extends previous knowledge on the association between ABG level and in-hospital MACE. We concluded that the higher the elevated ABG level, the higher the occurrence of in-hospital MACE, consistent with previous research [14,15]. The increase of ABG in non-diabetic patients receiving PCI can be regarded as a stress-induced increase in blood glucose. The pathogenesis between elevated ABG and in-hospital MACE may be as follows: First, acute hyperglycemia at the time of hospital admission is reflective of severely damaged myocardium, and the elevated ABG is associated with higher Killip class and lower cardiac ejection fraction [16]. Admission hyperglycemia may be associated with sympathetic hyperactivity, which could alter the microbiota (including gut and thrombus microbiota) and have adverse effects on STEMI patients [17,18].

Hyperglycemia is an important predictor of impaired coronary flow, which can further affect myocardial perfusion and cardiac function [19]. Second, Esposito *et al*. [20] found that elevated ABG exacerbates oxidative stress and inflammation, thus leading to the expression of cytokines, including IL-6, IL-8, and TNF-α. The elevated cytokines could be prevented by an infusion of the antioxidant glutathione [21]. Furthermore, Marwah ST *et al*. [22] found that hyperglycemia could cause endothelial dysfunction by increasing oxidative stress via multiple pathways. They concluded that the likelihood of post-myocardial infarction complications was higher with hyperglycemia. Third, apoptosis of myocardial cells was also found to be associated with elevated ABG levels. This might be related to the cytochrome c-activated caspase-3 pathway, which is activated by reactive oxygen species (ROS) derived from high levels of glucose [23]. Fourth, endothelial dysfunction is also caused by acute hyperglycemia, resulting not only in endothelial apoptosis [24] but also endothelial dysfunction, which may further decrease retrograde coronary collateral blood flow by adversely affecting nitric oxide availability [25]. Fifth, elevated ABG stimulates coagulation and platelet aggregation [21], which is not conducive to the improvement of coronary microcirculation, thus leading to adverse events [26]. The inhibition of platelet aggregation by the NO donor sodium nitroprusside is decreased as the admission blood glucose level increases [27]. In addition, patients with hyperglycemia have larger thrombus sizes, increased inflammation, and worse clinical outcomes, which may be related to excessive endothelial (coronary) inflammation and oxidative stress in STEMI patients [28]. Marfella R *et al*. [29] found that tight glycemic control (glucose 80 to 140 mg/dL) could reduce heart inflammation and remodeling during acute myocardial infarction in hyperglycemic patients. Therefore, effective control of blood glucose levels plays an important role in the stabilization of atherosclerotic lesions. Maintaining optimal glycemic control not only improves systemic metabolic status, but also plays an important role in atherosclerotic cap and plaque stabilization [30].

With the increase of ABG, the increasing range of OR was also increased [31]. It was found that there was a linear relationship between ABG and in-hospital mortality [21]. In contrast, our study is the first to find that the increasing rate of MACE decreases with the increasing level of ABG. The four models have consistent OR levels (Model I: Q2 = 1.52, Q3 = 1.48; Model II: Q2 = 1.5, Q3 = 1.46; Model III: Q2 = 1.54, Q3 = 1.46; Model IV: Q2 = 1.5, Q3 = 1.44). It can be concluded that the OR values in Q3 were lower than in the Q2 group. Thus patients with ABG levels of 7.02–11.0 mmol/L have a lower risk of in-hospital MACE than the Q2 group (5.72–7.01 mmol/L). Mi *et al*. [14] conducted a study on the division of blood glucose values, and found that the OR of these two ABG segments (7.0–7.7 mmol/L, 7.8–11.0 mmol/L) was 1.1 and 1.17, respectively. Therefore, ABG between 6.3–7.8 mmol/L may play a protective role in preventing the occurrence of in-hospital MACE. The administration of a glucose solution can be related to increased cardiac output, blood pressure, and improved survival [32]. Hyperglycemia could induce free radical generation, leading to oxidative stress and adverse outcomes [33]. These results suggest that maintaining ABG within an optimal range (6.3–7.8 mmol/L) could potentially reduce the risk of in-hospital MACE. For patients with ABG levels exceeding this range, early interventions such as glucose-lowering therapies and antioxidant treatments might help mitigate adverse outcomes.

In the subgroup analysis, we found that the relationship between ABG and in-hospital MACE is pronounced in females and elder patients. Older patients have more se-

vere and extensive coronary artery disease which increases MACE outcomes. In addition, estrogen has a significant impact on blood glucose levels and cardiovascular diseases. For example, longer estrogen exposure is associated with a lower risk of cardiovascular disease [34]. At the same time, estrogen plays a crucial role in maintaining normal glucose homeostasis [35]. Hara H *et al*. [36] found that females had a higher 10-year mortality rate than males (32.8% vs. 24.7%). Moreover, female patients had a higher risk of in-hospital mortality and 30-day adverse outcomes [37]. Denkmann *et al*. [38] demonstrated that the risk factors for primary PCI were female and age $\geq$75, which was very similar to our subgroup analysis.

Strengths and Limitations

This study is the first to investigate the correlation between ABG and MACE in non-diabetic STEMI patients who underwent PCI. A strength of this study is the exclusion criteria of Killip class $\geq$2. The inclusion of only Killip I patients ensures the accuracy of this study.

There are several limitations to our study. First, more information is needed on oral glucose tolerance tests and glycosylated hemoglobin (HbA1c) levels. We could only screen non-diabetics based on whether they have a history of diabetes and an ABG level $<$11.0 mmol/L, which limits the accuracy of classifying non-diabetic patients. Second, the study was conducted in Hubei (China), which may limit its global replication. Third, patients with significant hypoglycemia (ABG $<$4 mmol/L) were excluded, which may affect the relationship between ABG and MACE. Finally, the study focuses on in-hospital events without long-term data.

Conclusions

In conclusion, elevated ABG in non-diabetic STEMI patients who underwent PCI identifies individuals with an increased risk of MACE. This correlation was most apparent in females and the elderly. This result emphasizes that ABG should be considered a risk factor for MACE, even in non-diabetic patients.

Availability of Data and Materials

The data that supported the findings of this study were not publicly available due to the potential risk of disclosing participants' private information. Upon reasonable request, the research data could be obtained from the corresponding author (JZ).

Author Contributions

This study design was developed by JZ, JY and JC. JZ, PZ and JJY completed the initial draft. PZ, RHH, XYC, LS, FYL, CYH, YHL, DSL, XJ, ZH, XZC, CZZ and JJY participated in data collection. JJY, PZ, JZ, CYH and CZZ analyzed the data. JZ, JY, JC, CZZ, JJY, PZ and CYH revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Wuhan University People's Hospital (approval number: WDRY2021-K054) and the Medical Ethics Committee of Yichang Central People's Hospital (approval number: 2021-043-01). Written informed consent was obtained from all participants (or their parent/legal guardian/next of kin) to participate in this study.

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Conflict of Interest

The authors declare no conflict of interest.

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