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Glycated hemoglobin level is an independent predictor of major adverse cardiac events after nonfatal acute myocardial infarction in nondiabetic patients

A retrospective observational study

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Abstract

The effect of glycemic control on the prognosis of nondiabetic patients after acute myocardial infarction (AMI) remains uncertain. We investigated whether glycated hemoglobin (HbA1c) is associated with adverse outcomes after AMI in nondiabetic patients. In this observational study, we enrolled nondiabetic patients with AMI in the emergency department of 2 medical centers from January 2011 to September 2014. All patients received primary percutaneous coronary intervention and were divided into 4 groups according to the interquartile range of average HbA1c level (Group I, ≤5.6%; Group II, 5.6%–5.8%; Group III, 5.8%–6.0%; and Group IV, >6.0%). Multivariate logistic analysis was performed to estimate the correlation of HbA1c with major adverse cardiac events (MACEs) after AMI. In total, 267 eligible patients were enrolled; 48 patients (18%) developed MACEs within a median follow-up of 178 days. Univariate analysis showed HbA1c > 6.0%, with a higher risk of MACEs in Group IV than in Group I (odds ratio [OR]: 2.733; 95% confidence interval [CI]: 1.123–6.651 vs OR: 1.511; 95% CI: 0.595–3.835). Multivariate analysis revealed an approximately 3.8 times higher risk of MACEs in Group IV than in Group I (OR: 3.769; 95% CI: 1.30–10.86). The HbA1 level is a significant predictor of MACEs after AMI in nondiabetic patients.

Abbreviations: ADA = American Diabetes Association, AMI = acute myocardial infarction, AUC = area under curve, BMI = body mass index, CABG = coronary artery bypass grafting, CI = 95% confidence interval, CK = creatine kinase, CVD = cardiovascular disease, DM = diabetes mellitus, ECG = electrocardiography, GFR = glomerular filtration rate, GRACE = Global Registry of Acute Coronary Events, HbA1c = glycated hemoglobin, HF = heart failure, MACE = major adverse cardiac event, MI = myocardial infarction, NSTEMI = non-ST elevation MI, OR = odds ratio, PCI = percutaneous coronary intervention, ROC = receiver operating characteristic, STEMI = ST-segment elevation MI, TIMI = thrombolysis in MI.

Keywords: acute myocardial infarction, glycated hemoglobin, MACEs, nondiabetic

1. Introduction

Acute myocardial infarction (AMI) is a leading cause of mortality and morbidity worldwide.[1] Since the foundation of clinical guidelines for AMI management,[2] hospitalization and in-hospital mortality rates have significantly declined in recent decades.[3–5] However, the prognosis of patients after AMI requires improvement.

Studies have indicated that the nonfatal AMI population may have a 1.5 to 15 times higher mortality rate than the general population; approximately 10% to 20% of patients experience

secondary myocardial infarction (MI) and severe coronary heart disease, and 15% to 20% will experience heart failure (HF) within 5 years of AMI diagnosis.[1,6–9] Comorbidities and severity were significantly higher in recurrent AMI patients than in first MI patients.[10] Moreover, recurrent AMI patients encountered a higher risk of cardiovascular death, cardiogenic shock, and reinfarction but were less likely to receive evidence-based treatment than were first MI patients.[11] Therefore, it is essential to identify AMI patients who have the potential to develop secondary adverse prognosis and to provide prompt preventive intervention to avoid death or severe cardiovascular events.

Several risk prediction tools, such as the thrombolysis in MI (TIMI) risk score,[12] Global Registry of Acute Coronary Events (GRACE) risk score,[13,14] and Acute Physiology and Chronic Health Evaluation II (APACHE II) score, have been widely used and considered as reliable indicators of cardiovascular or all-cause outcomes. However, multiple complicated elements of these tools might affect prediction results, and the validity periods of the predictions are short.

Glycated hemoglobin (HbA1c) is formed by a series of chemical reactions between Hb and blood glucose. It represents the average blood glucose over 2 to 3 months, facilitates assessing the long-term glycemic control status in patients with diabetes, and can be determined by a simple blood examination. The type 2 diabetes mellitus (DM) population has a higher risk of cardiovascular disease (CVD) and shows poorer outcomes than does the general population.[15–17] Possible reasons may be endothelial and coagulation system dysfunction and inflammation exacerbation promoted by poor glycemic control.[18–20] Although the correlation of long-term glycemic control with coronary artery disease prognosis has been extensively studied,[21–24] few studies have focused on nondiabetic patients, and the results of analogous research remain unclear and controversial.[25–29]

Considering the limited information on and uncertain effects of long-term glycemic control on prognosis after AMI, we sought to determine whether HbA1c is associated with the outcomes after nonfatal MI and whether it can be an effective prognostic indicator and thereby provide a precise clinical guideline for identifying patients requiring early intervention.

2. Material and methods

2.1. Study design

In this retrospective observational study, we enrolled patients from the emergency department of 2 large medical centers, Taipei Veterans General Hospital and Taipei Municipal Wanfang Hospital; the annual average number of patients in the emergency departments of these hospitals is 85,000 and 66,000, respectively. We included nondiabetic patients hospitalized because of non-ST elevation MI (NSTEMI) or ST-segment elevation MI (STEMI) who received primary percutaneous coronary intervention (PCI) between January 2011 and September 2014.

2.2. Data collection

Specially trained nurses and a medical record technologist abstracted detailed information from the medical records of each enrolled patient. All the demographic and clinical data, namely, baseline characteristics (age, sex, and body mass index [BMI]), medical history (underlying comorbidities, risk factors for CVD, PCI process record, in-hospital medicine use, and risk assessment score), and laboratory tests (renal function, lipid profile, cardiac enzyme, HbA1c, and admission glucose) were collected from the medical records. All the patients were followed for 1 year from the AMI index date. Data were collected on the HbA1c level measured during the follow-up period and first major adverse cardiac events (MACEs) after nonfatal MI. HbA1c level was calculated and presented as a mean if it was measured more than once during the follow-up period. The periodic meetings would be held with the chart abstractors and all the study members to ensure the accuracy of the research process. In this study, HbA1c was measured an average of 1.4 times for each patient. The whole blood samples of each patient from peripheral venous vessels were collected into a sterile tube containing ethylenediaminetetra-acetic acid.[30] HbA1c analyses were performed using Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 (Tosoh Corporation, Tokyo, Japan) and the Capillarys 2 Flex Piercing analyzer (Sebia, Lisses, France) in Taipei Veterans General Hospital and Taipei Municipal Wanfang Hospital, respectively. These instruments are certified by the National Glycohemoglobin Standardization Program and standardized to the Diabetes Control and Complications Trial reference assay.[31] This study was approved by the institutional review boards of Taipei Medical University and Taipei Veterans General Hospital. All the data were obtained from the application of 2 centers after the approval of the both institutional review boards. In addition, the process of data collecting and analyzing was monitored by the institutional review boards periodically.

2.3. Definitions

Nondiabetic patients were defined as those without a history of diabetes at admission, who never received antidiabetic treatment, and with HbA1c < 6.5%.[31] STEMI was defined as a new ST-segment–T wave changes of >2 mm in 2 or more V1 to V3 leads or of >1 mm in 2 or more limb leads, a new presumed left bundle branch block on 12-lead electrocardiography (ECG), an increase in at least 1 cardiac biomarker (creatine kinase [CK], creatine kinase-MB fraction, and troponin I). NSTEMI was defined as patients with typical chest pain with cardiac enzyme elevation and no ST-segment elevation on ECG.[32] Furthermore, we recorded intra-aortic balloon pump use and coronary artery bypass grafting (CABG) of the patients during hospitalization for nonfatal AMI. MACEs were defined as all-cause mortality, repeated PCI, (such as target vessel revascularization, the progression of stenosis that needs PCI intervention or CABG), recurrent AMI (the second-time AMI occurrence that needed Percutaneous Transluminal Coronary Angioplasty intervention within a year from the AMI index date), and HF requiring hospitalization (patients hospitalized with the major diagnosis of acute HF after the first-time AMI).

2.4. Inclusion criteria

We enrolled nondiabetic patients who regularly underwent conventional examination in outpatient clinics for at least 1 year. The patients who underwent HbA1c measurement at least once during the follow-up period were enrolled. All the patients had received PCI and complete post-AMI treatment during hospitalization.

2.5. Exclusion criteria

Patients with in- and out-of-hospital cardiac arrest or refused PCI were considered to have predictable poor prognosis and were

therefore excluded. To avoid including undiagnosed or potentially diabetic patients in the study population, patients with newly diagnosed DM within 1 year of follow-up were also excluded.

2.6. Statistical analysis

The statistical methods used to determine the size of the sample is 2 independent t tests with the setting parameters as follows— effect size: 0.5, power: 0.8, and ratio of MACEs/without MACEs: 0.25. The predicted number of patients without MACEs is 160, and predicted number of patients with MACEs is 40. Continuous variables are expressed as mean and standard deviation. Categorical variables are expressed as frequency and percentage. The normality of variables was analyzed using the Kolmogorov– Smirnov test. Chi-squared or Fisher exact tests were used to compare categorical variables. Independent samples t tests and one-way analysis of variance were used to compare normally distributed continuous variables. The Mann–Whitney U and Kruskal–Wallis tests were used to compare nonnormally distributed continuous variables. Multivariate logistic regression analysis was performed to assess the correlation of HbA1c categories with MACEs. The receiver operating characteristic (ROC) curve was plotted to determine the cutoff value of HbA1c, and the area under curve (AUC) was calculated to analyze the predictive accuracy of HbA1c for MACEs. All the values were 2-tailed, and $P < .05$ was considered statistically significant in all the analyses. All the statistical analyses were conducted using the IBM SPSS program (Version 22.0; SPSS, Chicago, IL).

3. Results

3.1. Patient baseline demographic and characteristics

We enrolled 341 patients in our study, and 74 were excluded because of newly diagnosed DM in the following year (n = 42), in- and out-of-hospital cardiac arrest (n = 24), and refusal to receive PCI (n = 8). The median number of days for MACEs was 178. Overall, we analyzed 267 patients (Fig. 1). Table 1 compares the baseline characteristics of patients with (n = 48, 18%) and without (n = 219, 82%) MACEs. The mean age of the patients was 65 ± 1.26 (30–97) years, and 223 (83.5%) patients were males. The average BMI of the patients was $24.69 \pm 4.0 \, kg/m^2$. A total of 122 (45.7%) patients experienced STEMI and 145 (54.3%) experienced NSTEMI. History (CVD history, hypertension, and hyperlipidemia), hemodynamics (systolic blood pressure, diastolic blood pressure, and heart rate), smoking, alcohol consumption, lipid profile, cardiac enzyme, and medical use did not differ significantly between the 2 groups. The GRACE risk, APACHE II scores, and Killip class III were significantly higher in the patients with MACEs. In addition, these patients were more likely to have more hospitalized days during nonfatal AMI treatment and higher creatinine levels and glomerular filtration rates (GFRs). The mean HbA1c value of the patients with MACEs was significantly higher than that of the patients without MACEs ($5.91\% \pm 0.34\%$ vs $5.77\% \pm 0.36\%$; $P = .012$; Table 1).

3.2. Glycated hemoglobin predicts major adverse cardiac events

We divided the patients into 4 groups according to HbA1c interquartile range (Group I, $\leq 5.6\%$; Group II, 5.6%–5.8%; Group III, 5.8%–6.0%; and Group IV, >6.0%); these groups included 77 (28.8%), 72 (27.0%), 54 (20.2%), and 64 (24.0%)
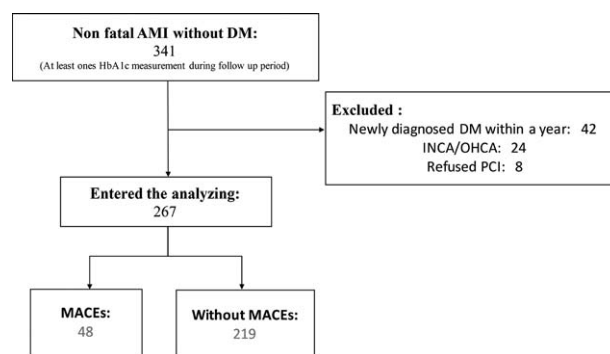

Figure 1. Flowchart of patient enrollment. AMI = acute myocardial infarction, DM = diabetes mellitus, HbA1c = glycated hemoglobin, INCA and OHCA = in- and out-of-hospital cardiac arrest, respectively, MACE = major adverse cardiac event, PCI = primary percutaneous coronary intervention.

patients, respectively. The distribution of the MACE occurrence rate in each group is shown in Fig. 2. MACE occurrence increased with HbA1c level, exhibiting a significant positive correlation (chi-squared test for trend, $P = .024$; Fig. 2). Univariate logistic analysis revealed creatinine, GFR, HbA1c > 6.0%, and GRACE, APACHE II scores, and Killip class III as significant predictors. Multivariate analysis revealed that BMI (odds ratio [OR]: 0.883, 95% confidence interval [CI]: 0.791–0.987, $P = .028$), HbA1c > 6.0% (OR: 3.763, 95% CI: 1.304–10.862, $P = .014$), and Killip class III score (OR: 4.676, 95% CI: 1.254–17.439, $P = .022$) were independent predictors of MACEs (Table 2). Regarding the predictive ability of HbA1c in different models, the results of logistic regression analysis adjusted for distinct variables in the 4 models are presented in Table 3. HbA1c > 6.0% showed significant predictive efficacy in all models, with model 3 exhibiting the highest significance. The risk of MACEs considering HbA1c > 6.0% was approximately 3.8 times higher than that considering HbA1c $\leq$ 5.6% after adjustment for age, sex, BMI, CVD history, hypertension, smoking, creatinine, hyperlipidemia, GFR, CK, troponin I, and GRACE, Killip class III, APACHE II scores (OR: 3.763, 95% CI: 1.304–10.862, $P = .014$; Table 3).

3.3. Receiver operating characteristic curve with the cutoff value of HbA1c for detecting major adverse cardiac events

We plotted the ROC curve with a cutoff value of HbA1c for predicting MACEs after AMI. The AUC was 0.615 (95% CI: 0.529–0.701, $P = .013$). The cutoff value of HbA1c was 5.78%; the corresponding sensitivity and specificity were 0.729 and 0.452, respectively (Fig. 3).

4. Discussion

In the present study, the HbA1c value and MACEs after AMI were significantly associated in nondiabetic patients. Our findings reveal that Groups II and III were not significantly correlated with the risk of MACEs compared with Group I. However, Group IV was at a significantly higher risk of MACEs than Group I, and the cutoff value obtained from the ROC curve was 5.78%. This value is within the normal range for diabetes detection. Thus, this value is easily neglected during the post-AMI follow-up, particularly in nondiabetic patients who are considered a comparatively healthy population. Hence, this cutoff value may serve as an indicator of

Table 1

Comparison of the baseline characteristics of patients with and without MACEs.

	Total (n=267)	Without MACEs (n=219)	Occurred MACEs (n=48)	P
Baseline characteristics				
Age, y	65.01±1.26	64.26±15.08	68.31±15.81	.098
Sex (male)	223 (83.5)	184 (84.0)	39 (81.3)	.668
BMI, kg/m^2	24.69±4.00	24.81±4.08	24.09±3.60	.404
AMI type (STEMI)	122 (45.7)	102 (46.6)	20 (47.1)	.536
SBP, mm Hg	137.64±60.76	139.62±64.93	128.58±35.16	.225
DBP, mm Hg	79.05±18.05	79.74±18.32	75.94±16.63	.162
HR, bpm	83.78±53.44	84.62±58.29	79.96±16.69	.881
Medical history				
CVD history	84 (31.5)	65 (29.7)	19 (39.6)	.181
Hypertension	165 (61.8)	131 (59.8)	34 (70.8)	.155
Smoking				
Never	107 (40.1)	89 (40.6)	18 (37.5)	.541
Former	48 (18)	36 (16.4)	12 (25.0)	
Current	111 (41.6)	93 (42.5)	18 (37.5)	
Alcohol use				
Never	181 (67.8)	151 (68.9)	30 (62.5)	.81
Former	18 (6.7)	14 (6.4)	4 (8.3)	
Current	68 (25.5)	54 (24.7)	14 (29.2)	
Hyperlipidemia	155 (43.1)	19 (39.6)	96 (43.8)	.59
ICU stay, d	3.19±2.75	3.10±2.69	3.60±2.97	.151
Total hospitalized, d	7.42±6.59	7.00±5.97	9.33±8.74	.003[*]
Killip class				
I	172 (64.4)	151 (68.9)	21 (43.8)	.002[*]
II	44 (16.5)	34 (15.5)	10 (20.8)	
III	23 (8.6)	13 (5.9)	10 (20.8)	
IV	28 (10.5)	21 (9.6)	7 (14.6)	
IABP use	16 (6.0)	12 (5.5)	4 (8.3)	.499
CABG use	15 (5.6)	12 (5.5)	3 (6.3)	.738
LVEF, %	50.86±11.74	51.53±11.48	47.71±12.55	.058
Laboratory data				
Total cholesterol, mg/dL	175.70±122.24	168.66±37.77	207.52±275.89	.797
LDL, mg/dL	121.23±172.84	115.68±124.01	146.32±272.66	.877
HDL, mg/dL	41.18±12.04	41.11±11.64	41.51±13.81	.848
Triglycerides, mg/dL	113.95±72.35	117.26±79.92	98.98±51.35	.147
Creatinine, mg/dL	1.617±2.73	1.5098±2.67	2.11±2.94	.003[*]
GFR, mL/min	65.94±25.30	68.33±24.70	55.05±25.71	.001[*]
Admission glucose, mg/dL	138.97±43.70	138.69±43.33	140.21±45.74	.797
HbA1c, %	5.79±0.36	5.77±0.36	5.91±0.34	.012[*]
CK-MB, ng/mL	46.59±68.51	46.229±70.02	48.23±61.88	.773
CK, U/L	500.89±718.56	476.49±707.99	611.21±762.50	.077
Troponin-I, ng/mL	9.716±26.06	9.09±26.79	12.53±22.48	.068
Risk assessment scoring system				
TIMI risk score	3.84±1.94	3.76±1.91	4.21±2.07	.181
GRACE score	119.49±37.87	116.71±37.50	132.19±37.35	.009[*]
APACHE II	9.02±4.40	8.67±4.08	10.68±5.43	.028[*]
Medicine use				
Aspirin	264 (98.9)	216 (98.6)	48 (100)	>.999
Clopidogrel	215 (80.5)	176 (80.4)	39 (81.3)	.889
Statin	246 (92.1)	42 (93.2)	204 (87.5)	.188
Beta blocker	212 (79.4)	176 (80.4)	36 (75.0)	.405
Ticagrelor	69 (25.8)	58 (26.5)	11 (22.9)	.609
ACEI/ARB	223 (83.5)	182 (83.1)	41 (85.4)	.696
CCB	47 (17.6)	34 (15.5)	13 (27.1)	.057
Nitrate	136 (50.9)	107 (48.9)	29 (60.4)	.147

Data are presented as mean±standard deviation or numbers (%). ACEI and ARB = angiotensin-converting enzyme inhibitor and angiotensin receptor blocker, respectively, AMI = acute myocardial infarction, APACHE II = acute physiology and chronic health evaluation II, BMI = body mass index, CABG = coronary artery bypass grafting, CCB = calcium-channel blocker, CK = creatinine kinase, CVD = cardiovascular disease, DBP = diastolic blood pressure, GFR = glomerular filtration rate, GRACE score = Global Registry of Acute Coronary Events score, HbA1c = glycated hemoglobin, HDL = high-density lipoprotein, HR = heart rate, IABP = intra-aortic balloon pump, ICU = intensive care unit, Killip class = Killip–Kimball classification, LDL = low-density lipoprotein, LVEF = left ventricular ejection fraction, MACE = major adverse cardiac event, SBP = systolic blood pressure, STEMI = ST-segment elevation MI.
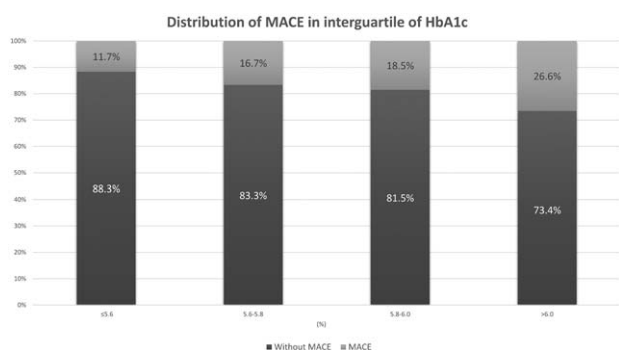
[*] $P < .05$.

Figure 2. Distribution of major adverse cardiac events among each glycated hemoglobin category. Chi-squared test for trend, P = .024. HbA1c = glycated hemoglobin, MACE = major adverse cardiac event.

clinical reference for secondary prevention for improving the prognosis after AMI.

When considering other risk assessment scoring systems that have frequently been used in clinical studies, HbA1c is a more favorable predictor than TIMI, GRACE risk, and APACHE II scores. GRACE and APACHE II scores appear to be effective predictive tools in univariate analysis, whereas only HbA1c showed statistical significance in multivariate analysis. Therefore, we consider HbA1c to be a more efficient indicator of 1 year outcomes for AMI, which is more stable and easily obtained.

The glycemic control status is significantly correlated to the prognosis of AMI in the nondiabetic population, which may be attributed to the damage of vascular structures caused by poor glycemic status, which may occur before DM onset. The mechanisms might include severe coronary endothelial dysfunction because of increased oxidative stress caused by high

Table 2

Logistic regression analysis of predictors of MACEs.

	Univariate analysis Odds ratio (95% CI)	P	Multivariate analysis Odds ratio (95%CI)	P
Baseline characteristics				
Age, y	1.018 (0.997–1.039)	.100	0.981 (0.944–1.024)	.519
Sex (male)	0.824 (0.367–1.853)	.640	1.150 (0.357–3.701)	.815
BMI, kg/m^2	0.954 (0.879–1.035)	.258	0.883 (0.791–0.987)	.028[*]
AMI type (STEMI)	0.819 (0.435–1.542)	.537		
SBP, mm Hg	0.994 (0.984–1.005)	.279		
DBP, mm Hg	0.988 (0.971–1.006)	.188		
HR, bpm	0.997 (0.980–1.014)	.744		
Medical history				
CVD history	1.552 (0.813–2.965)	.183	1.326 (0.618–2.848)	.469
Hypertension	1.631 (0.828–3.215)	.157	1.041 (0.459–2.362)	.923
Smoking				
Never	1 (reference)	–	1 (reference)	–
Former	1.648 (0.721–3.767)	.236	1.796 (0.640–5.042)	.266
Current	0.947 (0.463–1.935)	.881	1.167 (0.443–3.072)	.755
Alcohol use				
Never	1 (reference)	–		
Former	1.438 (0.443–4.672)	.546		
Current	1.305 (0.644–2.645)	.460		
Hyperlipidemia	0.839 (0.444–1.587)	.590	1.088 (0.501–2.359)	.832
ICU stay, d	1.058 (0.959–1.166)	.259		
Killip class				
I	1 (reference)	–	1 (reference)	–
II	1.011 (1.002–1.019)	.081	2.359 (0.903–6.168)	.080
III	5.531 (2.156–14.193)	<.001[*]	4.676 (1.254–17.439)	.022[*]
IV	2.397 (0.909–6.320)	.077	2.649 (0.616–11.40)	.191
IABP use	1.568 (0.483–5.090)	.454		
CABG use	1.150 (0.312–4.243)	.834		
LVEF, %	0.973 (0.945–1.001)	.060		
Laboratory data				
Total cholesterol, mg/dL	1.002 (0.999–1.006)	.241		
LDL, mg/dL	1.001 (0.999–1.002)	.304		
HDL, mg/dL	1.003 (0.977–1.029)	.840		
Triglycerides, mg/dL	0.996 (0.990–1.001)	.116		
Creatinine, mg/dL	1.254 (1.044–1.506)	.015[*]	1.049 (0.813–1.353)	.715
GFR, mL/min	0.979 (0.966–0.991)	.001[*]	0.981 (0.959–1.004)	.102
Admission glucose, mg/dL	1.001 (0.994–1.008)	.828		
HbA1c interquartile, %				
Group I ≤5.6	1 (reference)	–	1 (reference)	–
Group II 5.6–5.8	1.511 (0.595–3.835)	.385	1.994 (0.704–5.648)	.194
Group III 5.8–6.0	1.717 (0.646–4.562)	.278	1.993 (0.667–5.953)	.217
Group IV >6.0	2.733 (1.123–6.651)	.027[*]	3.763 (1.304–10.862)	.014[*]

Table 2

(continued).

	Univariate analysis Odds ratio (95% CI)	Multivariate analysis P	Odds ratio (95%CI)	P
CK-MB, ng/mL	1.000 (0.990–1.005)	.855		
CK, U/L	1.000 (1.000–1.001)	.246	1.001 (1.000–1.001)	.091
Troponin-I, ng/mL	1.004 (0.994–1.014)	.418	0.991 (0.972–1.010)	.352
Risk assessment scoring system				
TIMI risk score	1.115 (0.961–1.293)	.150		
GRACE score	1.011 (1.002–1.019)	.011*	0.999 (0.982–1.017)	.99
APACHE II	1.104 (1.030–1.183)	.005*	1.060 (0.966–1.163)	.219
Medicine use				
Clopidogrel	1.059 (0.477–2.351)	.889		
Statin	0.515 (0.189–1.404)	.194		
Beta blocker	0.733 (0.352–1.526)	.406		
Ticagrelor	0.825 (0.395–1.724)	.610		
ACEI/ARB	1.191 (0.496–2.859)	.696		
CCB	2.021 (0.970–4.211)	.060		
Nitrate	1.598 (0.846–3.019)	.149		

95% CI = 95% confidence interval, ACEI and ARB = angiotensin-converting enzyme inhibitor and angiotensin receptor blocker, respectively, AMI = acute myocardial infarction, APACHE II = acute physiology and chronic health evaluation II, BMI = body mass index, CABG = coronary artery bypass grafting, CCB = calcium-channel blocker, CK = creatinine kinase, CVD = cardiovascular disease, DBP = diastolic blood pressure, GFR = glomerular filtration rate, GRACE score = Global Registry of Acute Coronary Events score, HbA1c = glycated hemoglobin, HDL = high-density lipoprotein, HR = heart rate, IABP = intra-aortic balloon pump, ICU = intensive care unit, Killip class = Killip–Kimball classification, LDL = low-density lipoprotein, LVEF = left ventricular ejection fraction, MACE = major adverse cardiac event, SBP = systolic blood pressure, STEMI = ST-segment elevation MI, TIMI risk score = thrombolysis in myocardial infarction risk score.
* P < .05.

glucose,[18,33] increased platelet adhesion that promotes venous thrombosis,[19,34] and enhanced inflammatory responses, which cause the progression of atherosclerosis or vascular injury.[20,35,36] Furthermore, poor glycemic control may lead to an increased conformation of advanced glycation end products, which may cause severe vascular damage.[18] Therefore, HbA1c, which reflects metabolic control and embedded ongoing vascular injury or atherosclerosis, may be considered a reliable indicator of adverse outcomes in nondiabetic populations after AMI.

Our study showed that only HbA1c but not glucose was associated with MACEs. These results have notable interpretations. First, the effect on an unequal diet condition when patients admitted to an emergency room and acute stress because of severe diseases may contribute to inaccurate glucose values. Comparatively, HbA1c is a steady biomarker that is less likely to be disrupted and may be considered a more efficient clinical indicator. Second, the influence of elevated blood glucose on the prognosis of AMI may be classified into different mechanisms and represent distinct significance compared with HbA1c. Several studies have reported that elevated glucose more strongly represents the acute phase of diseases, whereas HbA1c represents long-term metabolic disorders. Timmer et al reported that in patients without diabetes, admission glucose levels are more associated with acute and short-term prognosis of AMI, such as

infarct size of the myocardium and 30-day mortality, compared with HbA1c. In long-term mortality (approximately 3-year follow-up), only HbA1c was correlated.[37] Liu et al[38] revealed that glucose is a significant predictor of 7- and 30-day mortality, rather than HbA1c. Selvin et al[39] conducted a median 14-year follow-up study and indicated that the HbA1c value is associated with the risk of DM and more closely with risks of CVD and death compared with fasting glucose in the nondiabetic population.

The American Diabetes Association (ADA) indicated that patients with HbA1c of 5.7% to 6.4% might have a prediabetic status and an increased risk of diabetes and cardiovascular mortality.[31,40] HbA1c of 6.0% to 6.5% confers a 25% to 50% 5-year risk of diabetes.[41] To avoid the effect of enrolling unrecognized DM or prediabetic patients on our study results (we reported newly diagnosed DM in 12% of the patients within 1 year after AMI), we included patients who fit the ADA definition of nondiabetes and excluded those who were newly diagnosed with diabetes within 1 year of follow-up.[31] Therefore, our study results may more strongly represent responses presented by the nondiabetic population.

Our study has several limitations. First, this was a retrospective observational study, which may have caused inevitable selection bias. Second, because of the rigorous population screening

Table 3

Odds ratios of MACEs among HbA1c interquartile range with adjustment of different variables.

HbA1c interquartile, %	Model 0 Odds ratio (95% CI)	P	Model 1 Odds ratio (95% CI)	P	Model 2 Odds ratio (95% CI)	P	Model 3 Odds ratio (95% CI)	P
Group I	≤5.6	1 (reference)	–	1 (reference)	–	1 (reference)	–	1 (reference)	–
Group II	5.6–5.8	1.511 (0.595–3.835)	.385	1.492 (0.585–3.804)	.403	1.763 (0.666–4.668)	.254	1.994 (0.704–5.648)	.194
Group III	5.8–6.0	1.717 (0.646–4.562)	.278	1.638 (0.610–4.397)	.327	1.694 (0.607–4.728)	.315	1.993 (0.667–5.953)	.217
Group IV	>6.0	2.733 (1.123–6.651)	.027*	2.662 (1.077–6.580)	.034*	2.942 (1.133–7.643)	.027*	3.763 (1.304–10.862)	.014*

Model 0 = unadjusted. Model 1 = adjusted age, sex, and BMI. Model 2 = adjusted Model 1 plus CVD history, hypertension, smoking, creatinine, hyperlipidemia, and GFR. Model 3 = adjusted Model 2 plus GRACE score, Killip class, APACHE II, troponin I, and CK. 95% CI= 95% confidence interval, APACHE II = acute physiology and chronic health evaluation II, HbA1c = glycated hemoglobin.
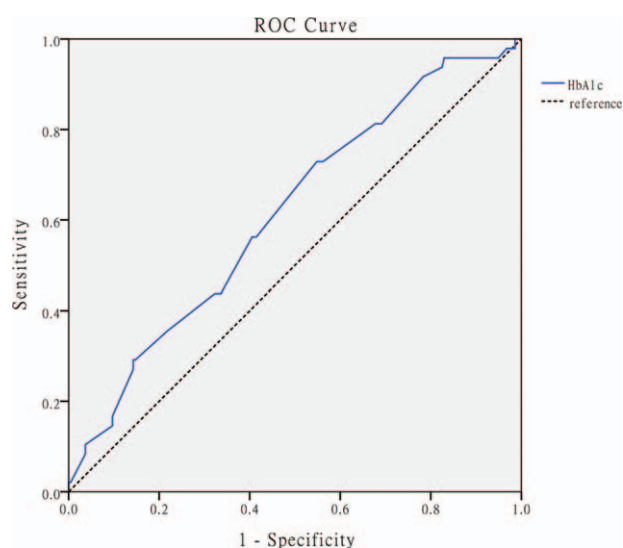* P < .05.

Figure 3. Receiver operating characteristic curve with the cutoff value of glycated hemoglobin for detecting major adverse cardiac events. Area under curve: 0.616, 95% confidence interval: 0.529 to 0.701; cutoff value: 5.78; $P = .013$ (sensitivity: 0.729 and specificity: 0.452).

process, the study sample size was relatively small despite including 2 large medical centers. Third, the follow-up period of the patients was only 1 year; thus, it is necessary to investigate the longer term relationship between HbA1c and MACEs in the nondiabetic population. Fourth, the time and frequency of conducting HbA1c examination for the patients during the study were inconsistent[42,43]; therefore, a randomized clinical study with a fixed frequency and time of HbA1c examination is required in the future.

5. Conclusion

Our study showed that HbA1c is a significant predictor of MACEs after AMI in nondiabetic patients. This biomarker may strengthen the accuracy of clinical care in early intervention and secondary prevention. HbA1c may be considered an effective indicator that facilitates the early detection of patients with potential adverse prognosis after nonfatal MI.

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