Diabetology & Metabolic Syndrome

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Association of hemoglobin glycation index with clinical outcomes in patients with coronary artery disease: a prospective cohort study

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Abstract

Background To analyze the association between the hemoglobin glycation index (HGI) and the long-term prognosis of patients with coronary artery disease (CAD).

Methods HGI represented the difference between laboratory measured Hemoglobin A1c (HbA1c) and predicted HbA1c based on a liner regression between Hb1Ac and fasting plasma glucose (FPG). A total of 10 598 patients who treated with percutaneous coronary intervention (PCI) were stratified into three groups (low HGI group: HGI<-0.506, medium HGI group: -0.506 ≤ HGI < 0.179, and high HGI group: HGI ≥ 0.179). The primary endpoints includes all-cause mortality (ACM) and cardiac mortality (CM). The secondary endpoints were major adverse cardiac events (MACEs) and major adverse cardiac and cerebrovascular events (MACCEs).

Results A total of 321 ACMs, 243 CMs, 774 MACEs, and 854 MACCEs were recorded during a 60-month follow-up period. After adjusting for confounders using a multivariate Cox regression analysis, the patients in the low HGI group had a significantly increased risk of ACM (adjusted HR = 1.683, 95%CI:1.179–2.404, *P* = 0.004) and CM (HR = 1.604, 95%CI:1.064–2.417, *P* = 0.024) as compared with patients in the medium HGI group. Similarly, the patients in the high HGI group had an increased risk of MACEs (HR = 1.247, 95% CI: 1.023–1.521, *P* = 0.029) as compared with patients in the medium HGI group. For ACM, CM, and MACEs, a U-shaped relation were found among these three groups. However, we did not find significant differences in the incidence of MACCEs among these three groups.

Conclusion The present study indicates that HGI could be an independent predictor for the risk of mortality and MACEs in patients with CAD.

Keywords Coronary artery disease, Hemoglobin glycosylation index, Major adverse cardiovascular events, Mortality

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Introduction

Coronary artery disease (CAD) is the leading cause of death worldwide [1]. Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) therapy can improve the quality of life for CAD patients [2]. However, the patients with established CAD still have high residual risk for future vascular events that varies widely and poses a challenge in its accurate estimation [3]. Therefore, it is essential to identify the predictors for adverse clinical outcomes in the patients with CAD who underwent PCI. Several traditional indicators for prognosis of CAD including obesity [4], smoking [5], hypertension [6], hyperlipidemia [7], and hyperglycemia [8] have been reported previously. Among these factors, hyperglycemia, either expressed as impaired glucose regulation or diabetes mellitus, has been independently associated with mortality in CAD patients [9]. At present, blood glucose and Hemoglobin A1c (HbA1c) are two commonly used indicators for diabetes in clinical practice. However, the discrepancy between Hb1Ac [10] and blood glucose [11] affects their clinical application. A new indicator, hemoglobin glycation index (HGI) was introduced to quantify this variation [12].Some researches have proven the association of HGI with cardiovascular disease and outcomes. Li`s research showed that the lower and higher HGI would increase the risk of adverse outcomes in patients with acute coronary syndrome(ACS) [13].And previously, Cheng's study indicated that HGI was an independent predictor for poor prognosis at levels<-0.4 or ≥0.12 for CAD patients who underwent PCI [14]. However, the sample size in Cheng's study was very small. To clarify the relation between HGI and clinical outcomes of CAD patients, we conducted a large-sample size study including 10 598 CAD patients who underwent PCI in the present study.

Methods

Study population

All of the patients in this study came from a large, single-center prospective cohort study named the PRACTICE based on case records and a follow-up registry that was conducted at the First Affiliated Hospital of Xinjiang Medical University during the December 2016 to October 2021. The details of the design have been registered on http://Clinicaltrials.gov (Identifier: NCT05174143). In this study, we enrolled 15 250 CAD patients who had a definitive diagnosis using coronary angiography and underwent PCI as described previously [15], including ACS and stable coronary artery disease (SCAD). We excluded the patients with sever heart failure, malignant tumor, hematologic diseases, congenital heart disease, rheumatic heart disease, valvular heart disease, serious dysfunction of liver or kidney and missing data of HbA1c and fasting plasma glucose (FPG). Finally, we recruited 10 598 patients, who were divided into 3 groups according to the HGI levels: low HGI subgroup (HGI<-0.506, $n=3503$), medium group (-0.506≤HGI<0.179, $n=3565$), and high group (HGI≥0.179, $n=3530$). The flowchart of inclusion and exclusion of patients was shown in Fig. 1.

Data collection

The demographic characteristics of all participants including age, sex, drinking status, smoking status, history of diabetes and hypertension, drug prescription, multiple vessel lesions (MVL), and family history of CAD, were collected and recorded. Diabetes mellitus was defined as the use of hypoglycemic agents, a documented history of diabetes, fasting blood glucose≥7.0 mmol/L, or two-hour postprandial glucose≥11.1 mmol/L. These definitions were consistent with those reported in a previous study [16]. Hypertension was defined as systolic blood pressure≥140 mmHg and/or diastolic blood pressure≥90 mmHg on three separate days or the use of antihypertensive drugs [17].

Overnight fasting blood samples were collected to measure FPG, HbA1c, serum creatinine (Scr), uric acid (UA), Triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). The detection of all indices was performed using chemical analysis equipment located in the Department of Clinical Laboratory of the First Affiliated Hospital of Xinjiang Medical University (Dimension AR/AVL Clinical Chemistry System, Newark, NJ, USA).

Definition of HGI

HGI was calculated using the formula [18]: HGI=measured HbA1c value - predicted HbA1c value. We used the linear regression equation derived from a previous study [14]. (Regression equation: HbA1c=0.435 × FPG (mmol/L)+4.023, $r=0.699$ and $P<0.001$). Predicted HbA1c levels were then calculated from this regression equation using each subject's FPG value. Finally, the participants were assigned to low, medium, or high HGI groups. HGI cut off value was as follows: low HGI group (< -0.506, $n=3503$), medium HGI group (-0.506 to 0.179, $n=3565$) and high HGI group (≥0.179, $n=3530$).

Endpoints

The primary endpoint of the study was defined as mortality: including all-cause mortality (ACM) and cardiac mortality (CM). The secondary endpoints were main cardiovascular adverse events (MACEs) and main cardiovascular and cerebrovascular adverse events (MACCEs). The MACEs were defined as the composite endpoint of cardiac death, stent thrombosis, target vessel reconstruction, and nonfatal myocardial infarction (NFMI). The

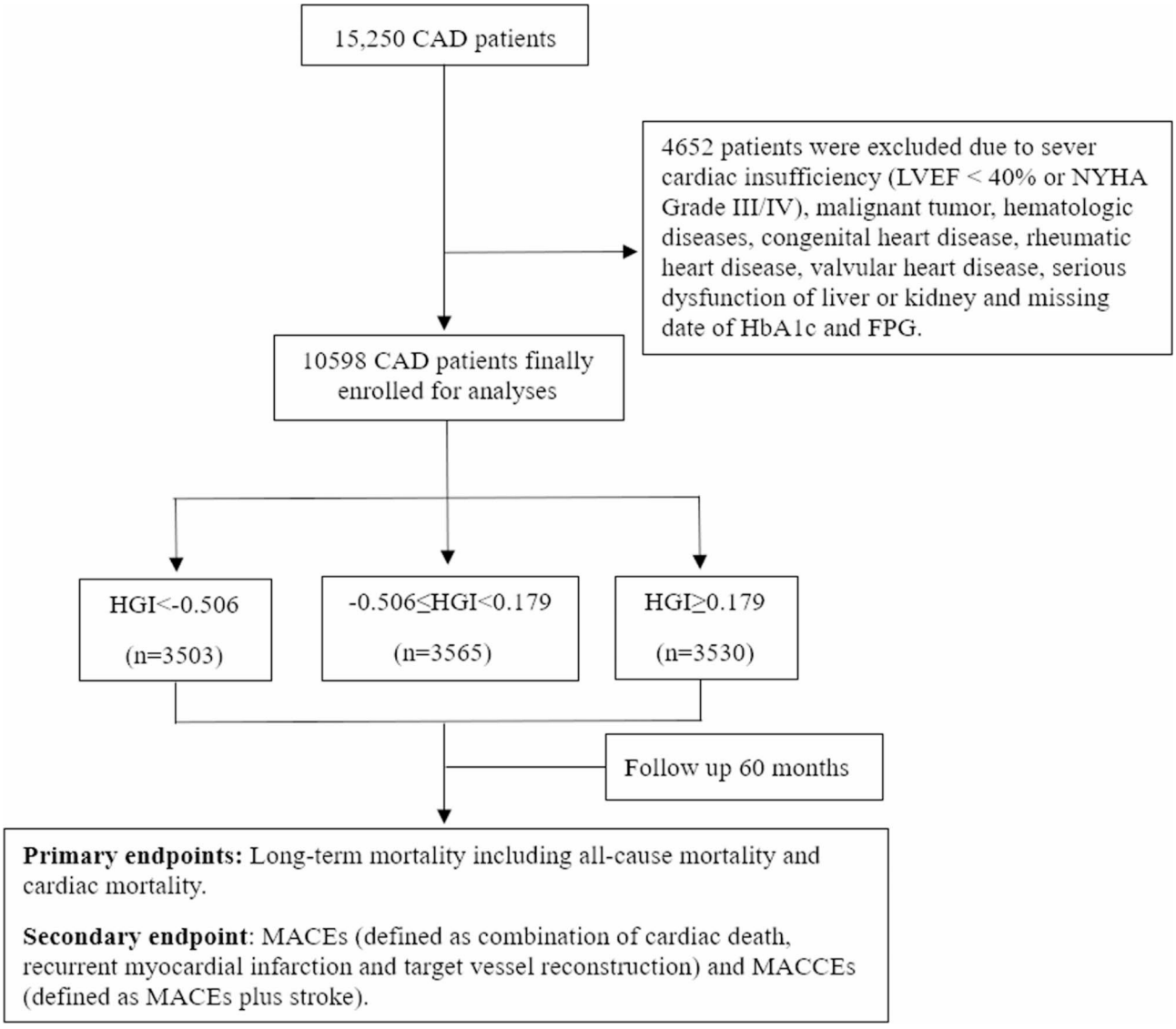

Fig. 1 Flowchart of patients inclusion, exclusion, and grouping

MACCEs were defined as MACE plus stroke as described previously [19].

Follow-up

In the PRACTICE study, all patients were followed-up regularly at 1 month, 3 months, 6 months, 1 year, 3 years, and 5 years from discharge. The median follow-up time was 24 months in the present study. The follow-up through office visits, phone calls, and questionnaires. Medication adherence and adverse events were assessed at each follow-up period.

Statistical analysis

All analyses were conducted using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). Normally distributed continuous variables are expressed as mean±standard deviation. Categorical variables are represented as numbers and percentages. The Chi-square test is used to compare categorical variables. ANOVA was used to examine continuous variables across and within groups. The Kaplan-Meier method was used to generate cumulative survival curves for the primary and secondary endpoints. A log-rank test was utilized to compare the differences between two groups. Multivariable Cox proportional hazards models were used to compute hazard ratios (HRs) and 95% CIs for clinical outcomes including ACM, CM, MACEs, and MACCEs. Individuals with HGI levels between −0.506 and 0.179 formed the reference. The models adjusted for sex, age, smoking, alcohol, family history, Scr, UA, TG, TC, HDL-C, LDL-C, MVL, renin-angiotensin system inhibitors (RASi), β blockers, calcium channel blocker (CCB), aspirin, statin usage, in terms

Table 1 Baseline characteristics by HGI categories

Variables	Low HGI (*n* = 3503)	Medium HGI (*n* = 3565)	High HGI (*n* = 3530)	*P* value
Female, n(%)	818 (23.4)	1023 (28.7)	986 (27.9)	**< 0.001**
Smoker, n(%)	1523 (43.5)	1435 (40.3)	1443 (40.9)	**0.014**
Alcohol, n(%)	913 (26.1)	893 (25.0)	892 (25.3)	0.589
Family History, n(%)	399 (12.0)	441 (13.0)	451 (13.5)	0.179
RASi, n(%)	1513 (43.2)	1556 (43.6)	1707 (48.4)	**< 0.001**
β-blocker, n(%)	1942 (57.6)	1970 (57.1)	2143 (63.3)	**< 0.001**
CCB, n(%)	608 (18.0)	787 (22.8)	779 (23.0)	**< 0.001**
Aspirin, n(%)	3284 (93.7)	3428 (96.2)	3321 (94.1)	**< 0.001**
Statins, n(%)	3197 (91.3)	3377 (94.7)	3255 (92.2)	**< 0.001**
Nitrates, n(%)	351 (10.4)	313 (9.1)	384 (11.3)	**0.009**
Tiagrelor, n(%)	1778 (50.8)	1731 (48.6)	1751 (49.6)	0.180
Clopidogrel, n(%)	1725 (49.2)	1834 (51.4)	1779 (50.4)	0.180
MVL, n(%)	2943 (84.0)	2977 (83.5)	3081 (87.3)	**< 0.001**
CAD				
SCAD, n(%)	1214 (34.7)	1608 (45.1)	1549 (43.9)	**< 0.001**
ACS, n(%)	2289 (65.3)	1957 (54.9)	1981 (56.1)	**< 0.001**
Hypertension, n(%)	2317 (66.1)	2482 (69.6)	2676 (75.8)	**< 0.001**
Diabetes, n(%)	1959 (55.9)	951 (26.7)	2552 (72.3)	**< 0.001**

Abbreviations: HGI, Hemoglobin glycation index; RASi, renin-angiotensin system inhibitors; CCB, Calcium channel blocker; MVL, multiple vascular lesions; CAD, coronary artery disease; SCAD, stable coronary artery disease; ACS, acute coronary syndrome; Note: The boldfaced *p*-Values are statistically different

Table 2 Outcomes comparison among the three subgroups

Variables	Low HGI(*N* = 3503)	Medium HGI(*N* = 3565)	High HGI(*N* = 3530)	*P* value
ACM (n, %)	120(3.4)	75(2.1)	126(3.6)	**< 0.001**
CM (n, %)	84(2.4)	57(1.6)	102(2.9)	**0.001**
MACEs (n, %)	253(7.2)	215(6.0)	306(8.7)	**< 0.001**
MACCEs n, %)	277(7.9)	247(6.9)	330(9.3)	**0.001**

Abbreviations: HGI: Hemoglobin glycation index; ACM, All-cause mortality; CM, Cardiac mortality; MACEs, The major adverse cardiovascular events; MACCEs, The major adverse cardiovascular and cerebrovascular events. Note: The boldfaced *p*-Values are statistically different

of ticagrelor or clopidogrel and hypertension. *P*-values < 0.05 are considered statistically significant.

Results

Baseline data and procedural characteristic

As shown in Table 1, there were significant differences among these three groups in sex, smoking, family history, RASi, β blockers, CCB, aspirin, statin usage, nitrates, MVL, CAD type [ACS or SCAD], hypertension and diabetes (all $P<0.05$).We did not find differences among the three groups in alcohol drinking, family history in CAD, in terms of ticagrelor and clopidogrel (all $P \geq 0.05$).

Clinical outcomes

A total of 321 ACMs, 243 CMs, 774 MACEs and 854 MACCEs were recorded during up to 60-months follow-up period. As shown in Table 2, for the endpoints, the incidence of ACM, CM, MACEs and MACCEs was significantly lower in the medium HGI group than that in the low group or that in the high HGI group (ACM:3.4%,2.1%,3.6%, $P<0.001$; CM:2.4%, 1.6%,2.9%, $P=0.001$; MACEs: 7.2%, 6.0%, 8.7%, $P<0.001$; MACCEs: 7.9%, 6.9%,9.3%, $P=0.001$). In Fig. 2, the Kaplan-Meier analyses suggested that patients with medium HGI tended to have a lower accumulated risk of ACM, CM, MACEs and MACCEs (all Log-rank $P<0.05$).

Univariate Cox regression models revealed a U-shape relation between HGI and ACM, CM and MACEs. Compared with the medium HGI group, those with low HGI group and high HGI group both had an increased risk of ACM, CM and MACEs (all $P<0.05$). In addition, a nonlinear relation was also observed between HGI and MACCEs, however, low HGI group did not show significant difference ($P=0.09$) as shown in Table 3.

After adjusting for the traditional clinical prognostic factors including sex, age, smoking, alcohol, family history, Scr, Uric acid, TG, TC, HDL-C, LDL-C, MVL, RASi, β blockers, CCB, aspirin, statin usage, in terms of ticagrelor or clopidogrel and hypertension, we found HGI could predict adverse clinical outcomes. Compared to the medium HGI group, patients in the low HGI group had a significantly increased risk of ACM(Table 4) and CM(Table 5) during the long-term follow-up (ACM: HR = 1.683, 95%CI:1.179–2.404, $P<0.05$, $P=0.004$, CM: HR = 1.604, 95%CI:1.064–2.417, $P<0.05$, $P=0.024$). Similary, the patients in the high HGI group had a significantly increased risk of MACEs during the long-term follow-up (HR = 1.247, 95%CI:1.023–1.521, $P<0.05$, $P=0.029$) (Table 6). But neither in the low HGI group nor in the high HGI group did the patients have a significantly increased risk of MACCEs during the long-term follow-up (Table 7).

Discussion

Our study investigated the association of HGI with adverse outcomes in patients with CAD. The main finding of our study was that HGI independently predicted adverse clinical outcomes in patients with CAD who underwent PCI. More specifically, the low HGI levels <-0.506 were associated with higher all-cause and cardiac mortality compared with the medium HGI group (-0.506 to 0.179) whereas the highest HGI levels ≥ 0.179 were independent predictors of MACEs in CAD patients. No significant differences were observed in terms of MACCEs among the three different HGI groups.

Hb1Ac is the gold standard used to evaluate the blood glucose control level in a short period of time. However,

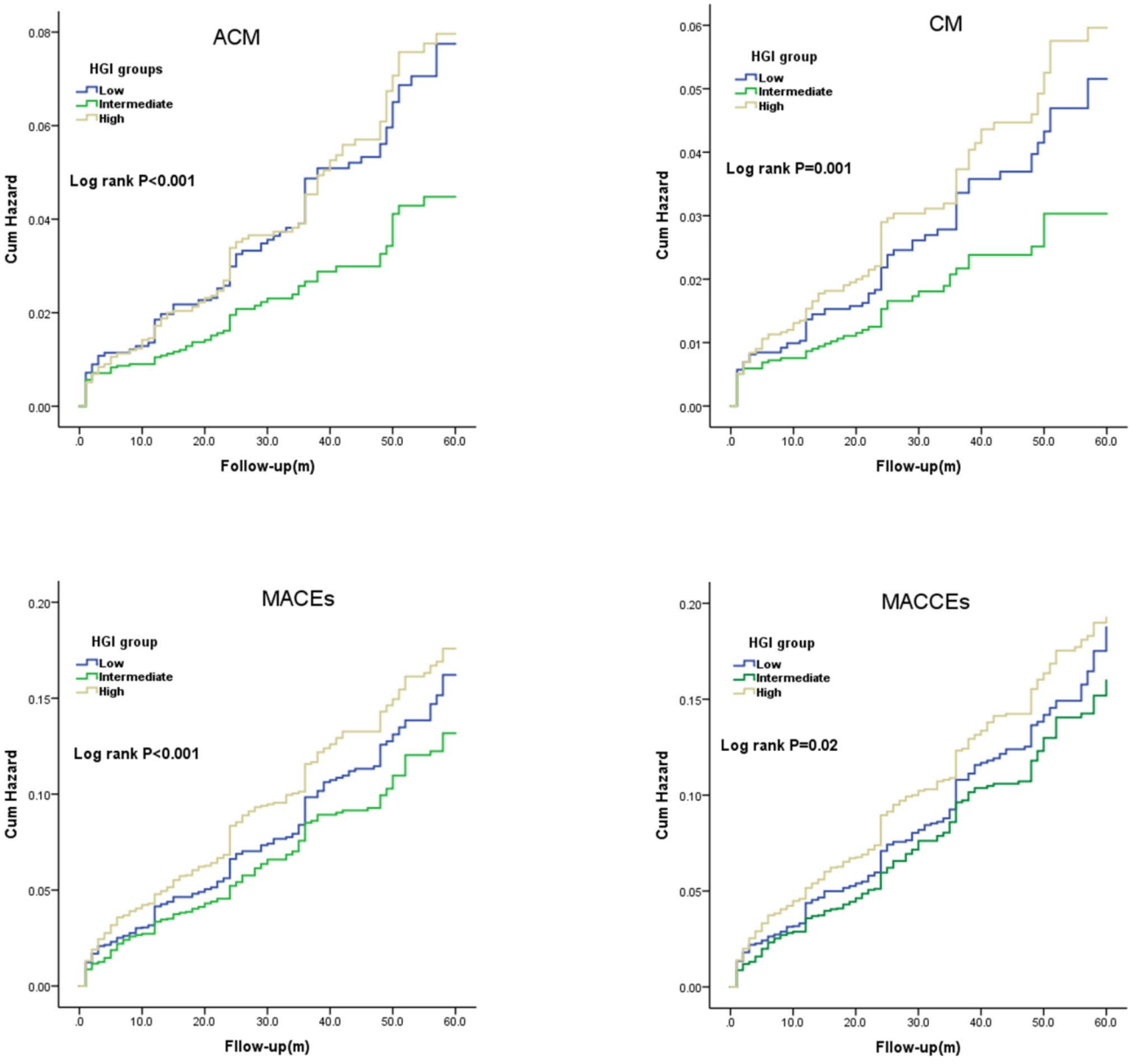

Fig. 2 Cumulative Kaplan-Meier curves of the time to the occurrence of clinical outcomes in all patients according to three HGI categories. ACM, all-cause mortality; CM, cardiac mortality; MACEs, major adverse cardiovascular events; MACCEs, major adverse cardiovascular and cerebrovascular events. Note: The boldfaced *p*-Values are statistically different

Table 3 Univariate COX regression analysis

Outcomes	Low HGI group		Medium HGI group	High HGI group	
	HR(95%CI)	*P* value	(reference)	HR(95%CI)	*P* value
ACM	1.652 (1.238–2.204)	**0.001**	1	1.690 (1.269–2.249)	**< 0.001**
CM	1.520 (1.086–2.128)	**0.015**	1	1.802 (1.303–2.492)	**< 0.001**
MACEs	1.216 (1.014–1.458)	**0.035**	1	1.432 (1.203–1.705)	**< 0.001**
MACCEs	1.160 (0.977–1.377)	0.090	1	1.345 (1.140–1.586)	**< 0.001**

Abbreviations: HGI: Hemoglobin glycation index; ACM, All-cause mortality; CM, Cardiac mortality; MACEs, The major adverse cardiovascular events; MACCEs, The major adverse cardiovascular and cerebrovascular events. Note: The boldfaced *p*-Values are statistically different

Table 4 Multivariate COX regression analysis in ACM

Variable	B	SE	Wald	HR (95%CI)	*P* value
HGI (low vs. medium)	0.521	0.182	8.212	1.683(1.179–2.404)	**0.004**
HGI (high vs. medium)	0.282	0.184	2.341	1.325(0.924–1.901)	0.126
Sex	-0.134	0.177	0.573	0.875(0.619–1.237)	0.449
Age	0.073	0.007	120.536	1.076(1.062–1.090)	**< 0.001**
Smoker	-0.051	0.184	0.076	0.950(0.663–1.363)	0.782
Alcohol	0.000	0.204	0.000	1.000(0.671–1.491)	1.000
Family history	0.099	0.203	0.238	1.104(0.742–1.643)	0.625
Creatinine	0.000	0.000	0.427	1.000(1.000–1.000)	0.514
UA	0.000	0.000	0.346	1.000(1.000–1.000)	0.556
TG	-0.347	0.108	10.321	0.707(0.572–0.873)	**0.001**
TC	0.096	0.246	0.152	1.101(0.679–1.784)	0.697
HDL-C	-1.471	0.315	21.824	0.230(0.124–0.426)	**< 0.001**
LDL-C	0.066	0.271	0.060	1.069(0.628–1.817)	0.806
MVL	0.826	0.300	7.566	2.285(1.268–4.118)	**0.006**
RASi	-0.107	0.152	0.498	0.898(0.667–1.210)	0.480
β-blocker	-0.452	0.147	9.431	0.637(0.477–0.849)	**0.002**
CCB	-0.514	0.192	7.157	0.598(0.410–0.872)	**0.007**
Antiplatelet	-0.453	0.301	2.272	0.635(0.352–1.146)	0.132
Statins	-0.427	0.223	3.668	0.652(0.421–1.010)	0.055
Clopidogrel or Tiagrelor	-0.356	0.141	6.387	0.701(0.532–0.923)	**0.011**
Hypertension	0.334	0.176	3.620	1.397(0.990–1.970)	0.057

Abbreviations: ACM, All-cause mortality; HGI, Hemoglobin glycation index; UA, Uric acid; TG, Triglyceride; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; MVL, multibranch vascular lesions ; RASi, renin-angiotensin system inhibitors; CCB, Calcium channel blocker; Note: The boldfaced *p*-Values are statistically different

Table 5 Multivariate COX regression analysis in CM

Variable	B	SE	Wald	HR (95%CI)	*P* value
HGI (low vs. medium)	0.472	0.209	5.092	1.604(1.064–2.417)	**0.024**
HGI (high vs. medium)	0.364	0.207	3.101	1.439(0.960–2.158)	0.078
Sex	0.035	0.194	0.033	1.036(0.708–1.516)	0.856
Age	0.066	0.008	76.469	1.069(1.053–1.085)	**< 0.001**
Smoker	-0.162	0.217	0.558	0.850(0.555–1.302)	0.455
Alcohol	0.093	0.238	0.154	1.098(0.689–1.750)	0.695
Family history	-0.097	0.247	0.155	0.907(0.559–1.472)	0.693
Creatinine	0.000	0.000	0.395	1.000(1.000–1.000)	0.530
Uric acid	0.000	0.000	1.012	1.000(1.000–1.000)	0.314
TG	-0.340	0.122	7.757	0.711(0.560–0.904)	**0.005**
TC	0.104	0.282	0.136	1.110(0.639–1.929)	0.712
HDL	-1.343	0.355	14.332	0.261(0.130–0.523)	**< 0.001**
LDL	0.013	0.310	0.002	1.013(0.552–1.858)	0.967
MVL	1.171	0.391	8.984	3.224(1.500-6.933)	**0.003**
RASi	-0.105	0.173	0.367	0.901(0.642–1.263)	0.545
β-blocker	-0.275	0.167	2.718	0.759(0.547–1.053)	0.099
CCB	-0.558	0.222	6.346	0.572(0.371–0.883)	**0.012**
Antiplatelet	-0.543	0.330	2.702	0.581(0.304–1.110)	0.100
Statins	-0.564	0.241	5.472	0.569(0.354–0.913)	**0.019**
Clopidogrel or Tiagrelor	-0.323	0.160	4.072	0.724(0.529–0.991)	**0.044**
Hypertension	0.280	0.199	1.975	1.323(0.896–1.954)	0.160

Abbreviations: CM, Cardiac mortality; HGI, Hemoglobin glycation index; UA, Uric acid; TG, Triglyceride; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; MVL, multibranch vascular lesions; RASi, renin-angiotensin system inhibitors; CCB, Calcium channel blocker; Note: The boldfaced *p*-Values are statistically different

Table 6 Multivariate COX regression analysis in MACEs

Variable	B	SE	Wald	HR(95%CI)	*P* value
HGI (low vs. medium)	0.183	0.105	3.052	1.201(0.978–1.474)	0.081
HGI (high vs. medium)	0.221	0.101	4.772	1.247(1.023–1.521)	**0.029**
Sex	-0.130	0.109	1.419	0.878(0.710–1.087)	0.234
Age	0.014	0.004	13.437	1.014(1.006–1.021)	**0.000**
Smoker	-0.095	0.107	0.797	0.909(0.738–1.121)	0.372
Alcohol	0.156	0.111	1.990	1.169(0.941–1.453)	0.158
Family history	0.015	0.113	0.017	1.015(0.812–1.267)	0.897
Creatinine	0.000	0.000	0.129	1.000(1.000–1.000)	0.719
Uric acid	0.000	0.000	0.005	1.000(1.000–1.000)	0.945
TG	-0.038	0.035	1.144	0.963(0.899–1.032)	0.285
TC	0.056	0.116	0.228	1.057(0.842–1.328)	0.633
HDL	-0.734	0.172	18.211	0.480(0.343–0.673)	**< 0.001**
DL	0.004	0.131	0.001	1.004(0.777–1.298)	0.976
MVL	0.402	0.137	8.640	1.495(1.143–1.955)	**0.003**
RASi	0.198	0.089	5.014	1.219(1.025–1.450)	**0.025**
β-blocker	0.304	0.091	11.116	1.355(1.134–1.621)	**0.001**
CCB	0.007	0.100	0.006	1.008(0.828–1.226)	0.940
Antiplatelet	-0.188	0.214	0.770	0.829(0.545–1.260)	0.380
Statins	-0.166	0.147	1.278	0.847(0.635–1.130)	0.258
Clopidogrel or Tiagrelor	-0.384	0.083	21.714	0.681(0.579-0.800)	**< 0.001**
Hypertension	0.057	0.100	0.322	1.059(0.870–1.289)	0.570

Abbreviations: MACEs, The major adverse cardiovascular events; HGI, Hemoglobin glycation index; UA, Uric acid; TG, Triglyceride; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; MVL, multibranch vascular lesions; RASi, renin-angiotensin system inhibitors; CCB, Calcium channel blocker; Note: The boldfaced *p*-Values are statistically different

Table 7 Multivariate COX regression analysis in MACCEs

Variable	B	SE	Wald	HR(95%CI)	*P* value
HGI (low vs. medium)	0.132	0.098	1.799	1.141(0.941–1.383)	0.180
HGI (high vs. medium)	0.157	0.095	2.729	1.170(0.971–1.410)	0.099
Sex	-0.089	0.101	0.779	0.915(0.750–1.115)	0.378
Age	0.013	0.004	12.909	1.013(1.006–1.020)	**P< 0.001**
Smoker	-0.108	0.102	1.124	0.898(0.735–1.096)	0.289
Alcohol	0.129	0.106	1.465	1.138(0.923–1.402)	0.226
Family history	-0.041	0.110	0.144	0.959(0.774–1.189)	0.705
Creatinine	0.000	0.000	0.061	1.000(1.000–1.000)	0.805
Uric acid	0.000	0.000	0.018	1.000(1.000–1.000)	0.893
TG	-0.030	0.031	0.903	0.971(0.913–1.032)	0.342
TC	0.005	0.110	0.002	1.005(0.810–1.246)	0.966
HDL	-0.511	0.158	10.509	0.600(0.440–0.817)	**0.001**
LDL	0.049	0.124	0.157	1.050(0.823–1.340)	0.692
MVD	0.402	0.129	9.652	1.495(1.160–1.927)	**0.002**
RASi	0.155	0.084	3.408	1.167(0.991–1.375)	0.065
β-blocker	0.229	0.085	7.224	1.257(1.064–1.486)	**0.007**
CCB	0.054	0.094	0.337	1.056(0.879–1.269)	0.561
Antiplatelet	-0.129	0.209	0.380	0.879(0.584–1.324)	0.537
Statins	-0.217	0.137	2.524	0.805(0.615–1.052)	0.112
Clopidogrel or Tiagrelor	-0.368	0.078	22.215	0.692(0.594–0.806)	**< 0.001**
Hypertension	0.072	0.095	0.567	1.074(0.891–1.295)	0.451

Abbreviations: MACCEs, The major adverse cardiovascular and cerebrovascular events. HGI, Hemoglobin glycation index; UA, Uric acid; TG, Triglyceride; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; MVD, multibranch vascular disease; RASi, renin-angiotensin system inhibitors; CCB, Calcium channel blocker; Note: The boldfaced p-Values are statistically different

it is susceptible to a number of factors and varies with actual average blood glucose [10]. HGI is a metric used to quantify inter-individual variability in Hb1Ac and mean blood glucose (MBG) [12]. Currently, HGI has been shown to be associated with vasculopathy in diabetic patients. Higher HGI can increase the risk of retinal [20], neuropathy [18], and renal [21]microangiopathy in diabetic patients [22], as well as increase the hazard in carotid atherosclerosis [23]and CAD macrovascular [24]lesions. The mechanism by which high HGI levels are associated with increased risk of MACEs in patients with CAD may be connected with advanced glycation end-products (AGEs) [25]. High HGI could stand for an increased intracellular non-enzymatic glycation rate that might influence AGEs generation [26].The AGEs could promote CAD by reducing vascular elasticity and myocardial flexibility, decreasing NO production and thus leading to impaired vasodilation, decreasing LDL uptake with subsequent increase in foam cell formation, promoting endothelial dysfunction through mediation of oxidative stress and exacerbation of inflammatory response [27].Other studied also reported that the high HGI was associated with obesity, dyslipidemia, inflammation, which were the risk factors of CAD [28, 29]. In turn, obesity has been linked with chronic inflammation [30]. Moreover, AGEs production increases during acute and chronic inflammation [25]. Thus high HGI, AGEs, and inflammation form a cycle reinforcing each other. Futhermore, high HGI was negatively associated with telomere attrition mediated by TNFα, independent of HbA1c [31], as has been recently reported. Our study with a large sample size verified the relation between HGI and ACM reported previously by Cheng [14]. Nevertheless, our study also clarified the relation between HGI and CM, MACE, and MACCE. Our findings have important clinical impact on the refinement of risk stratification and residual risk estimation in the high-risk patients with CAD. This could involve closer follow-up of the CAD patients with low or high HGI levels, tighter control of common cardiovascular risk factors in these patients, intensification of treatment or usage of alternative agents.

This study has several limitations: Firstly, as a single-center, large sample observational study, there was a possibility of selection bias in our study and a causal relationship between clinical outcomes and HGI in patients with CAD cannot be established. Secondly, although we adjusted for several important confounders, there are possibly unknown confounding factors that could have affected our results. We did not perform subgroup analysis in our study, a fact that renders the effect of HGI on adverse outcomes in different subgroups of CAD patients uncertain. Thirdly, we used a single FPG, rather than an average glucose, to calculate the predicted Hb1Ac.Therefore, the predicted Hb1Ac results may be affected. Fourthly, in this study, we mainly focused on CAD patients and involved patients with or without diabetes, so, the observed association of HGI with adverse outcomes may not apply to other group of patients. Additionally, our study population consisted of Chinese patients and thus, the results may differ in other ethnic groups. Fifthly, our analysis included both SCAD and ACS patients, so there is the possibility that stress hyperglycemia, observed mainly in ACS patients, might have partially confounded the final findings. Lastly, the data on anti-glucose lowering medication taken were not recorded and therefore, they were not accounted for in our multivariate models. The need for further multicenter prospective studies to confirm the current findings is justified.

Conclusion

In our study, we found that either higher HGI or lower HGI was an independent predictor for adverse clinical outcomes in patients with CAD. Our findings have meaningful clinical impact in risk stratification.

Acknowledgements

The authors are grateful to the Department of Cardiology at the First Affiliated Hospital of Xinjiang University for their help and expertise in conducting this study.

Author contributions

ZYW, FPL and YYZ designed the study and wrote the manuscript. XX performed the data analyses. TTW, XGH, YP, CJD, YXL, XCH, WTG, and HXC collected the data. ZYW, FPL, and YYZ revised the manuscript. XX supervised the study. All authors read and approved the final manuscript.

Funding

This study was funded by the Natural Science Foundation of Xinjiang Uygur Autonomous Region, the Outstanding Youth Fund (2022D01E70), the 2023 Tianchi Talent Science and Technology Innovation Leading Talent Project, Tianshan Talent Science and Technology Innovation Leading Talent Project (2022TSYCLJ0029).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The ethics committee of the First Affiliated Hospital of Xinjiang Medical University approved this research. All patients provided informed consent to participate.

Consent to publish

All authors agree to the publication of this work.

Competing interests

The authors declare no competing interests.

Received: 16 June 2024 / Accepted: 22 September 2024
Published online: 04 October 2024

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