Prognostic Implication of Serum Glycated Albumin for Patients With Non-ST-segment Elevation Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

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Abstract

Background: It has been demonstrated that glycated albumin (GA) is significantly associated with diabetes complications and mortality. However, among patients diagnosed with non-ST-elevation acute coronary syndrome (NSTE-ACS) administered percutaneous coronary intervention (PCI), the predictive value of GA for poor prognosis is unclear.

Methods: This study eventually included 2247 NSTE-ACS patients in Beijing Anzhen Hospital, Capital Medical University in January-December 2015 who received PCI. All patients were followed up until death or for 48 months post-discharge. The primary endpoint was major adverse cardio-cerebral events (MACCEs), including all-cause death, non-fatal myocardial infarction, ischemia-induced revascularization and non-fatal ischemic stroke.

Results: In total, 547 (24.3%) MACCEs were recorded during the follow-up period. Upon adjusting for potential confounders, GA remained an important risk predictor of MACCEs (hazard ratio [HR]=1.051, 95% confidence interval [CI] 1.026-1.077; P<0.001). GA addition significantly enhanced the predictive ability of the traditional risk model (Harrell's C-index, GA vs. Baseline model, 0.691 vs. 0.678, comparison P=0.001; continuous net reclassification improvement (continuous-NRI)=0.099, P=0.027; integrated discrimination improvement (IDI)=0.008, P=0.020).

Conclusion: GA is highly correlated with poor prognosis in NSTE-ACS patients undergoing PCI, suggesting that it may be a major predictive factor of adverse events among these individuals.

Introduction

Type 2 diabetes mellitus (T2DM) independently and significantly predicts atherosclerotic cardiovascular disease (ASCVD), and increases ASCVD risk by about 2 times [1]. Patients with T2DM also suffer from many risk factors, including dyslipidemia and hypertension, which further increase the risk of ASCVD [2]. Fasting blood glucose (FBG) levels and glycosylated hemoglobin (HbA1c) amounts are widely considered important indicators of blood glucose control. Studies have confirmed that HbA1c can predict coronary artery disease (CAD) severity as well as adverse prognosis [3-5]. Among non-diabetic patients hospitalized with acute coronary syndrome (ACS), FBG ≥10 mmol/l could predict one-year mortality [6]. Elevated FBG levels significantly increase 6-month mortality in patients with ACS [7]. However, the constant change of FBG levels over time makes it difficult to accurately predict the risk of disease. Similarly, HbA1c has many limitations in short-term regulation of blood glucose as well as in individuals with large blood glucose fluctuations, chronic kidney disease and/or liver cirrhosis and hemoglobin lesions [8].

In recent years, glycated albumin (GA) has attracted widespread attention for being unaffected by food intake and red blood cell lifespan. GA generally reflects the status of blood sugar control in 2-4 weeks. In cases for whom FBG and HbA1c have the above limitations and cannot accurately reflect the patient's blood glucose levels, GA would be a good surrogate indicator [9]. At present, GA has been confirmed to be closely related to coronary heart disease, ischemic stroke, heart failure, cardiovascular death and other diseases [10]. HbA1c, GA and FBG levels are positively correlated with carotid artery intima-media thickness, which is widely considered an early sign of atherosclerosis [11]. More interestingly, it was shown serum GA represents a better marker compared with HbA1c for evaluating the presence of CAD, assessing CAD severity and predicting major adverse cardiovascular events [12].

However, the prognostic value of GA in individuals with non-ST-elevation acute coronary syndrome (NSTE-ACS) administered percutaneous coronary intervention (PCI) is largely undefined. In addition, studies comparing the predictive values of FBG, HbA1c and GA in poor cardiovascular prognosis are lacking. Therefore, the current work aimed to assess GA for its predictive value for poor outcomes in NSTE-ACS patients after PCI.

Materials And Methods

Patients

This single-center, observational trial continuously included NSTE-ACS cases administered PCI from Jan. to Dec. 2015 in Beijing Anzhen Hospital, Capital Medical University. Diagnostic criteria for NSTE-ACS (including non-ST-segment elevation myocardial infarction [NSTEMI] and unstable angina [UA]) were based on relevant guidelines [13]. Exclusion criteria were: (1) <18 years of age; (2) lack of baseline or follow-up data; (3) definite or plausible type 1 diabetes mellitus (T1DM); (4) previous coronary artery bypass grafting (CABG), cardiogenic shock, acute decompensated heat failure, chronic infectious disease or malignancy; (5) hyperthyroidism or hypothyroidism; (6) kidney damage (estimated glomerular filtration rate [eGFR] below 30 mL/(min×1.73 m^2) or kidney replacement treatment, severe liver dysfunction (alanine or aspartate transaminase amounts ≥ 5 times the upper reference limits); (7) PCI failure, PCI-associated complications or in-hospital death. Finally, totally 2247 individuals were included in this study (Figure 1).

Data collection and definitions

Patient baseline data were obtained from the electronic medical information recording system of Beijing Anzhen Hospital. Hypertension was defined as systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP≥90 mmHg after repeated measurements on different days [14]. Criteria for diabetes were blood glucose levels ≥11.1 mM, FBG≥7.0 mM, and/or 2-h blood glucose after oral glucose tolerance test ≥11.1 mM [15-16]. Dyslipidemia referred to fasting total cholesterol (TC) levels >200 mg/dL, low-density lipoprotein cholesterol (LDL-C) >130 mg/dL, triglyceride (TG) levels >150 mg/dL, high-density lipoprotein cholesterol (HDL-C) <40 mg/dL and/or long-term administration of lipid-lowering agents. Stroke referred to cerebral infarction or transient ischemic attack. The following conditions were considered peripheral arterial diseases (PADs): non-coronary aortic and arterial-related vascular disease with exercise-associated continuous claudication, decreased or absent pulsation and lumen stenosis of more than 50%.

Echocardiograms were verified by 2 ultrasound specialists. Coronary angiography, percutaneous coronary intervention and perioperative management were based on current guidelines[17]. Chronic total occlusion (CTO) was reflected by complete coronary artery occlusion, with Thrombolysis in Myocardial Infarction Flow grade 0 for ≥3 months [18]. Complete revascularization was reflected by PCI or bypass of the totality of epicardial vessels with a diameter above 1.5 mm and a luminal reduction above 50% in angiographic views [19].

Follow-up and study endpoint

After discharge from the hospital, all patients were followed up until death or 48 months after discharge. The primary endpoint was major adverse cardio-cerebral events (MACCEs), including all-cause death, non-fatal MI, non-fatal ischemic stroke and ischemia-induced revascularization. MI was reflected by increased cardiac troponin or creatine kinase levels surpassing the upper limits of the reference ranges, with ischemia signs and/or ECG findings suggesting myocardial ischemia. Stroke definition involved signs of neurological damage, caused by ischemic lesions confirmed by computed tomography or magnetic resonance imaging. Ischemia-induced revascularization was reflected by revascularization in target and/or non-target vessels due to recurring or persistent ischemic symptoms, including PCI and CABG.

Statistical analysis

Cases were assigned to 2 groups based on median GA (lower GA [GA < 14.4], higher GA [GA ≥ 14.4]). Normally distributed continuous variates are mean±standard deviation, and were compared by two-sample independent t test. Continuous variates with skewed distribution were represented by median and 25th and 75th percentiles, and compared by the Mann-Whitney U test. Nominal variates were described by numbers and percentages, and compared by the Chi-square, continuity-corrected chi-square or Fisher's exact test.

The Kaplan-Meier method was utilized for describing event rates at follow-up and plotting time-to-event curves in both groups, which were compared by the log rank test. The univariable Cox proportional hazards model was used for preliminary assessment of factors associated with MACCEs. Variates with significant associations with MACCEs and those that may be meaningful based on clinical experience were included in five multivariate models. Variates with potential collinearity were not included in the multivariate analysis. GA was tested as nominal and continuous variables, respectively. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to describe the associations. In multivariable Cox proportional hazard analysis, five models were established for evaluating GA's predictive value in MACCEs: Model 1, adjustment for age, gender and body mass index (BMI); Model 2, adjustment for Model 1 variables and smoking history, hypertension, diabetes and previously diagnosed MI and PCI; Model 3, adjustment for Model 2 variables and TG, TC, eGFR, high-sensitivity C-reactive protein (hs-CRP), HDL-C, left ventricular ejection fraction (LVEF); Model 4, adjustment for Model 3 variables and oral hypoglycemic agent (OHA) and insulin prescriptions at discharge; Model 5, adjustment for Model 4 variables and left main artery lesion (LM), multi-vessel lesion, complete revascularization and drug-eluting stent (DES) amount. According to Model 5, a restrictive cubic spline curve was established to illustrate the dose-response association of GA with MACCEs. Except for variables used for stratification, stratified analysis adjusted for Model 5 variables. Interactions were examined by the likelihood ratio test.

Harrell's C-index, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used for investigating the additive effects of GA on the predictive abilities of traditional cardiovascular disease risk factors in MACCEs.

SPSS v26.0 and R v3.6.3 were used for data analysis. Two-tailed P<0.05 was deemed statistically significant.

Results

Baseline patient features

Totally 2247 patients were included, with an average age of 60.1±9.0, and the proportion of males was 71.9% (n=1616). Patients were assigned to 2 groups based on median GA. Demographic data, clinical features, laboratory results, and medical and procedural details are shown in Table 1 and Table 2. In the high GA group, participants were older and had a lower proportion of men compared with the low GA group. Participants with high GA levels had higher heart rate, systolic blood pressure and incidence rates of hypertension and diabetes, and lower rates of smoking and drinking history. Higher rates of previous PCI and previous stroke were observed in individuals with high GA. For laboratory examinations, participants with high GA had lower levels of TC, LDL-C, creatinine and uric acid, while FBG and HbA1c amounts were elevated. Regarding medication at admission, patients with higher GA received a higher proportion of OHA and insulin treatments, and a lower proportion of statins. In terms of discharge medications, participants with high GA were prescribed angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), OHA and insulin at a higher rate. Regarding coronary angiography and PCI, in the GA high group, the

proportions of multivessel lesion and in-stent restenosis were higher. Participants with high GA had more target vessels of left circumflex artery (LCX) and right coronary artery (RCA) treated, more DES implanted, and a lower proportion of complete revascularization.

Predictive value of GA for MACCE

After 48 months of follow-up, 547 (24.3%) cases of MACCEs were recorded, including 36 (1.6%) all-cause death, 112 (5.0%) non-fatal myocardial infarction (MI), 45 (2.0%) non-fatal stroke and 354 (15.8%) ischemia-driven revascularization cases. The incidence rates of MACCEs (*P*<0.001), all-cause death (*P*=0.006), non-fatal MI (*P*=0.001) and ischemia-driven revascularization (*P*<0.001) were significantly higher in the high GA group compared with the low GA group. However, the incidence rates of non-fatal stroke were comparable in both groups (Table 3).

Kaplan-Meier analysis was performed for evaluating the time-dependent cumulative incidence of MACCEs collectively and individually in both groups in the general, diabetic and non-diabetic populations. In the general population, the cumulative incidence of MACCEs was increased significantly in the high GA group in comparison with the low GA group (Figure 2A, log-rank P<0.001). Similar results were obtained in diabetic (Figure 2B, log-rank P=0.011) and non-diabetic (Figure 2C, log-rank P<0.001) populations.

Furthermore, five multivariate models were established for assessing the predictive performances of GA for MACCEs. Univariate Cox proportional hazards analysis was used to initially define the potential determinants of the primary endpoint (Supplemental Table 1). According to univariate analysis (P<0.05) and clinical importance, variables were included in the multivariate models (shown in Methods). After adjusting for variates in the five models, whether GA was considered a categorical or continuous variable, it showed significant independent prognostic value in all models (Table 4).

After adjusting for variates in Model 5, the dose-response relationship between GA level and MACCEs was illustrated by drawing restricted cubic spline curve (Figure 3). It was found that MACCE risk increased with GA level (*P* for overall association <0.001), suggesting that GA had a linear relationship with MACCE risk. This was further confirmed in the non-linear correlation test (*P* for nonlinear association <0.001).

Subgroup analysis further confirmed the predictive value of GA for MACCEs. In the subgroups of gender (male or female), age (<65 or ≥65 years), BMI (<28 or ≥28 kg/m^2), smoking history (no or yes), hypertension (no or yes), OHA at admission (no or yes), and insulin at admission (no or yes), there were no differences in the predictive power of GA in MACCEs (all *P* for interaction >0.05). It is worth noting that the predictive value of GA seemed to be higher in non-diabetic patients [HR (95%CI) diabetes no 1.167 (1.017-1.087) vs. diabetes yes 1.047 (1.019-1.075), *P* for interaction=0.006] (Figure 4).

GA increases the predictive values of other factors for MACCEs

In the baseline model comprising the currently known cardiovascular risk factors (gender, age, BMI, smoking history, family history of CAD, hypertension, diabetes, NSTEMI, eGFR, TC, LVEF, LM disease and multi-vessel disease), addition of GA markedly enhanced the ability of the model to predict risk (Harrell's C-index: GA vs. Baseline model, 0.691 vs. 0.678, *P*=0.001). The reclassification and discrimination abilities were significantly improved in comparison with the baseline risk model after addition of GA (Continuous-NRI=0.099, *P*=0.027; IDI=0.008, *P*=0.020). In Harrell's C-index, NRI and IDI analysis, addition of FBG (Harrell's C-index: FBG, 0.687 vs. baseline risk model, 0.678, *P*=0.001;

Continuous NRI: 0.092, P=0.040; IDI: 0.005, P=0.040) and HbA1c (Harrell's C-index: HbA1c, 0.689 vs. baseline risk model, 0.678, *P*=0.002; Continuous NRI: 0.060, P=0.053; IDI: 0.007, P=0.020) also significantly improved the risk prediction ability of the baseline model. Although GA was not better than FBG and HbA1c in improving the predictive ability of the baseline model, it was not inferior to the latter two either.

Discussion

The present work firstly assessed the predictive value of GA for poor prognosis in NSTE-ACS patients after PCI. We found that the incidence of MACCEs was markedly elevated in individuals with high GA levels in comparison with the low GA group. Upon adjustment for confounding factors, GA increase was still an important and independent predictor of poor prognosis in the study population. Adding GA to the model comprising traditional risk factors significantly improved its ability to predict the risk of poor prognosis.

About 40 years ago, researchers firstly found elevated GA levels in the serum of diabetic patients [20]. Then, with studies assessing GA test methods and comparative assessment of GA and HbA1c, GA has gradually been used as a marker of diabetes in clinical practice [21-23]. Glycated serum albumin has 85 glycosylation sites, while HbA1c has only one [24]. According to previous reports, the glycosylation rate of GA is approximately 4.5 times that of HbA1c [25]. In addition, the GA test is cheaper and faster than HbA1c assessment [26]. More importantly, the half-life of GA is only 12-21 days, and GA testing can provide information about blood sugar control for about 2-3 weeks [27-29]. Therefore, when short-term assessment of blood glucose status is required, e.g., for the adjustment of hypoglycemic therapy during hospitalization, GA is better than HbA1c. Moreover, in patients with T1DM and T2DM administered hypoglycemic therapy, the change in GA at 4 weeks is the same as that of HbA1c at 12 weeks [30]. In addition, GA can not only reflect short-term average blood glucose, but also indicate blood glucose fluctuations. Compared with HbA1c, GA has more obvious advantages with rapid changes in blood sugar or rapid deterioration of blood glucose [31], such as in fulminant type I diabetes. GA can also monitor postprandial blood glucose's swimming fluctuations and hypoglycemia as well as other pathologic factors [32, 33].

Many studies have also explored the value of GA in ASCVD. Based on Atherosclerosis Risk in Communities (ARIC) Study in 1990-1992, Selvin et al. followed up 11104 patients for 20 years, and found that GA was associated with vascular outcomes and mortality in the community, and these associations were similar to those observed for HbA1c [10]. In patients receiving PCI, Yang et al. tested serum GA in 576 type 2 diabetes and stable CAD cases who were implanted with a sirolimus-eluting stent. After two years of follow-up and adjustment for possible confounding factors, serum GA level (HR=1.22, 95%CI 1.16–1.28; HR=1.15, 95%CI 1.11–1.19, respectively; both p<0.001) still independently predicted the primary (cardiac death, non-fatal myocardial infarction and non-fatal stroke) and secondary (occurrence of clinically driven repeat revascularization) outcomes [34]. In addition, studies have also confirmed that GA level increase is highly correlated with the severity of coronary artery damage in T2DM and CAD cases [35, 36], as well as impaired collateral growth in patients with CTO [37]. Combined with the above studies, our results further clarify the predictive value of elevated GA for poor prognosis in NSTE-ACS patients undergoing PCI, and the results were consistent with previous conclusions. Multivariate and subgroup analyses in this study showed that GA is significant and robust as a predictor of adverse cardiovascular and cerebrovascular events. Interestingly, however, GA showed higher predictive value in the non-diabetic subgroup compared with the diabetic subgroup. Currently, HbA1c has been demonstrated to be an independent predictor of CAD odds and severity in non-diabetic individuals [38]. However, there is no relevant research examining GA for its predictive value in the prognosis of poor cardiovascular and cerebrovascular diseases in non-diabetic populations. Considering that GA and HbA1c have similar predictive values in the prognosis of cardiovascular diseases, it seems to be worthy of further study. On the

other hand, although addition of GA improves the ability of traditional risk models to predict poor prognosis, GA did not show more advantages than FBG and HbA1c in this study.

Regarding the mechanism-level explanation of GA's predictive value for poor prognosis in atherosclerotic cardiovascular disease, inflammation has attracted widespread attention. In cultured rat vascular smooth muscle cells (VSMCs), GA can induce proliferation and migration as well as the expression of the pro-inflammatory cytokine IL-6 at the mRNA level [39]. The presence of GA is harmful to endothelial cells, which become more pro-coagulant, promoting inflammation [40]. This damage to endothelial cells can lead to oxidative stress, which in turn leads to inflammation [41]. Kolluru et al. also confirmed the above conclusions [42]. GA's ability to predict poor prognosis in atherosclerotic cardiovascular disease may also have other mechanisms. Du and collaborators confirmed elevated serum GA amounts are associated with negative coronary artery remodeling in type 2 diabetes cases [43]. In addition, Rubenstein et al. found that the presence of GA enhances platelet aggregation, with the degree of glycation enhancing platelet activation [44]. Yamada et al. found that GA is highly correlated with peripheral vascular calcification in type 2 diabetic hemodialysis [45]. In summary, the role of GA in cardiovascular atherosclerosis may involve multiple pathophysiological processes.

There were limitations in this study. First, this was a single-center, retrospective, observational trial, which might reduce the effectiveness and power of these research findings. Therefore, more in-depth prospective, multi-center studies are required to further verify the current findings. Secondly, some patients received anti-diabetic treatment before admission, which may have affected the actual level of GA. Thirdly, factors such as age, obesity, inflammation, etc. may impact GA levels in this work. Fourthly, this study only included Chinese patients, and the generalizability of the findings to other ethnicities requires further investigation.

Conclusions

In NSTE-ACS patients administered PCI, GA level is significantly correlated with high risk of adverse cardio-cerebral events. Addition of GA significantly improves the ability of traditional risk models to predict poor prognosis. This conclusion needs further prospective, large-scale studies for confirmation.

Abbreviations

T2DM: type 2 Diabetes mellitus; ASCVD: atherosclerotic cardiovascular disease; FBG: Fasting blood glucose; HbA1c: glycosylated hemoglobin; CAD: coronary artery disease; ACS: acute coronary syndrome; GA: glycated albumin; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; PCI: percutaneous coronary intervention; NSTEMI: non-ST-segment elevation myocardial infarction; UA: unstable angina; T1DM: type 1 diabetes mellitus; CABG: coronary artery bypass grafting; eGFR: estimated glomerular filtration rate; BP: blood pressure; TC total cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; PAD: peripheral arterial disease; CTO: chronic total occlusion; MACCE: major adverse cardio-cerebral event; HR: hazard ratio; CI: confidence interval; BMI: body mass index; hs-CRP: high-sensitivity C-reactive protein; LVEF: left ventricular ejection fraction; OHA: oral hypoglycemic agents; LM: left main artery; DES: drug-eluting stent; NRI: net reclassification improvement; IDI: integrated discrimination improvement; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; LCX: left circumflex artery; RCA: right coronary artery; MI: myocardial infarction; ARIC: Atherosclerosis Risk in Communities; VSMC: vascular smooth muscle cell;

Declarations

Ethics approval and consent to participate

This research protocol was approved by the Clinical Research Ethics Committee of Beijing Anzhen Hospital, Capital Medical University. Although the study design was retrospective, participants provided written or verbal informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have declared that no competing interests exist.

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Authors’ contributions

CL and QZ made substantial contributions to study design, data collection, data analysis and manuscript writing. YJZ and XLL made substantial contributions to study design and intellectual direction. XTM, YJC, YS, DZ made contributions to data collection and analysis. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline demographic, clinical and laboratory characteristics of the study population

	Total population (n = 2247)	Lower GA (< 14.4; n = 1133)	Higher GA (≥ 14.4; n = 1114)	*P* value
Age, years	60.1±9.0	58.2±9.2	62.0±8.3	< 0.001
Gender, male, n (%)	1616 (71.9)	864 (76.3)	752 (67.5)	< 0.001
BMI, kg/m^2	26.1±3.2	26.2±3.2	26.0±3.2	0.323
Heart rate, bpm	69.7±10.2	68.9±9.6	70.6±10.6	< 0.001
SBP, mmHg	130.2±16.5	128.9±15.9	131.6±16.9	< 0.001
DBP, mmHg	77.0±9.8	77.3±9.3	76.7±10.2	0.162
Smoking history, n (%)	1280 (57.0)	714 (63.0)	566 (50.8)	< 0.001
Drinking history, n (%)	526 (23.4)	300 (26.5)	226 (20.3)	0.001
Family history of CAD, n (%)	233 (10.4)	120 (10.6)	113 (10.1)	0.728
Medical history, n (%)				
Diabetes	774 (34.4)	101 (4.5)	673 (30.0)	< 0.001
Hypertension	1397 (62.2)	671 (59.2)	726 (65.2)	0.004
Hyperlipidemia	1932 (86.0)	979 (86.4)	953 (85.5)	0.557
Previous MI	473 (21.1)	220 (19.4)	253 (22.7)	0.056
Previous PCI	376 (16.7)	161 (14.2)	215 (19.3)	0.001
Previous stroke	259 (11.5)	113 (10.0)	146 (13.1)	0.020
Previous PAD	79 (3.5)	36 (3.2)	43 (3.9)	0.380
Clinical diagnosis, n (%)				
UA	1873 (83.4)	951 (83.9)	922 (82.8)	
NSTEMI	374 (16.6)	182 (16.1)	192 (17.2)	
Laboratory examinations				
TG, mmol/L	1.7±0.9	1.7±0.9	1.7±0.9	0.126
TC, mmol/L	4.1±1.0	4.2±1.0	4.1±1.0	0.029
LDL-C, mmol/L	2.5±0.9	2.5±0.9	2.5±0.8	0.022
HDL-C, mmol/L	1.0±0.2	1.0±0.2	1.0±0.2	0.261
hs-CRP, mg/L	3.5±6.0	3.3±5.9	3.8±6.2	0.048
Creatinine, μmol/L	75.8±16.5	76.9±16.7	74.7±16.3	0.001
eGFR, mL/(min × 1.73m^2)	93.6±20.0	93.7±19.5	93.5±20.5	0.790
Uric acid, μmol/L	344.1±80.4	358.6±79.5	329.5±78.6	0.001
FBG, mmol/L	6.1±1.9	5.3±0.9	6.9±2.3	< 0.001

HbA1c, %	6.3±1.2	5.7±0.5	6.9±1.4	0.001
LVEF, %	64.0±6.7	63.9±7.0	64.0±6.5	0.625

GA glycated albumin, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CAD* coronary artery disease, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PAD* peripheral artery disease, *UA* unstable angina, *NSTEMI* non-ST-segment elevation myocardial infarction, *TG* triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *eGFR* estimated glomerular filtration rate, *FBG* fasting blood glucose, *HbA1c* glycosylated hemoglobin A1c, *LVEF* left ventricular ejection fraction

Table 2. Therapeutic, angiographic, and procedural characteristics of the study population

	Total population (n = 2247)	Lower GA (< 14.4 n = 1133)	Higher GA (≥ 14.4; n = 1114)	*P* value
Medication at admission, n (%)				
ACEI/ARB	500 (22.3)	246 (21.7)	254 (22.8)	0.535
DAPT	677 (30.1)	348 (30.7)	329 (29.5)	0.542
Aspirin	1192 (53.0)	598 (52.8)	594 (53.3)	0.797
P2Y12 inhibitors	718 (32.0)	371 (32.7)	347 (31.1)	0.417
β-Blocker	496 (22.1)	251 (22.2)	245 (22.0)	0.927
Statins	691 (30.8)	370 (32.7)	321 (28.8)	0.048
OHA	400 (17.8)	56 (4.9)	344 (30.9)	< 0.001
Insulin	218 (9.7)	13 (1.1)	205 (18.4)	< 0.001
Medication at discharge, n (%)				
ACEI/ARB	1558 (69.3)	758 (66.9)	800 (71.8)	0.012
DAPT	2245 (99.9)	1133(100.0)	1112 (99.8)	0.154
Aspirin	2246 (100.0)	1133 (100.0)	1113(99.9)	0.313
P2Y12 inhibitors	2247 (100.0)	1133 (100.0)	1114 (100.0)	-
β-Blocker	2045 (91.0)	1024 (90.4)	1021 (91.7)	0.292
Statins	2195 (97.7)	1101 (97.2)	1094 (98.2)	0.105
OHA	396 (17.6)	56 (4.9)	340 (30.5)	< 0.001
Insulin	211 (9.4)	12 (1.1)	199 (17.9)	< 0.001
Angiographic data, n (%)				
LM lesion	102 (4.5)	45 (4.0)	57 (5.1)	0.192
Multi-vessel lesion	1498 (66.7)	655 (57.8)	843 (75.7)	< 0.001
In-stent restenosis	124 (5.5)	47 (4.1)	77 (6.9)	0.004
Chronic total occlusion lesion	295 (13.1)	136 (12.0)	159 (14.3)	0.111
Procedural information				
Target vessel territory, n (%)				
LM	60 (2.7)	31 (2.7)	29 (2.6)	0.845
LAD	1464 (65.2)	738 (65.1)	726 (65.2)	0.987
LCX	784 (34.9)	364 (32.1)	420 (37.7)	0.006
RCA	952 (42.4)	434 (38.3)	518 (46.5)	<0.001
Complete revascularization, n (%)	1323 (58.9)	746 (65.8)	577 (51.8)	< 0.001

Number of DES	2.0±1.3	1.9±1.3	2.0±1.3	0.022

GA glycated albumin, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *DAPT* dual antiplatelet therapy, *OHA* oral hypoglycemic agents, *LM* left main artery, *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery, *DES* drug-eluting stent

Table 3. Incidence of primary endpoint and each component according to the median of GA

	Total population (n = 2247)	Lower GA (≤ 14.4; n = 1133)	Higher GA (> 14.4; n = 1114)	*P* value
MACCE, n (%)	547 (24.3)	205 (18.1)	342 (30.7)	< 0.001
All-cause death, n (%)	36 (1.6)	10 (0.9)	26 (2.3)	0.006
Non-fatal MI, n (%)	112 (5.0)	40 (3.5)	72 (6.5)	0.001
Non-fatal ischemic stroke, n (%)	45 (2.0)	22 (1.9)	23 (2.1)	0.835
Ischemia-driven revascularization, n (%)	354 (15.8)	133 (11.7)	221 (19.8)	< 0.001

GA glycated albumin, *MACCE* major adverse cardio-cerebral events, *MI* myocardial infarction

Table 4. Predictive value of GA for the risk of MACCE

	As nominal variate[a]		As continuous variate[b]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Unadjusted	1.826 (1.536-2.171)	< 0.001	1.072 (1.054-1.091)	< 0.001
Model 1	1.639 (1.374-1.956)	< 0.001	1.065 (1.046-1.083)	< 0.001
Model 2	1.517 (1.232-1.869)	< 0.001	1.061 (1.037-1.086)	< 0.001
Model 3	1.647 (1.334-2.034)	< 0.001	1.061 (1.036-1.087)	< 0.001
Model 4	1.638 (1.326-2.024)	< 0.001	1.060 (1.034-1.086)	< 0.001
Model 5	1.565 (1.267-1.933)	< 0.001	1.051 (1.026-1.077)	< 0.001

Model 1: adjusted for age, gender, BMI

Model 2: adjusted for variates in Model 1 and smoking history, hypertension, diabetes, previous MI, previous PCI,

Model 3: adjusted for variates in Model 2 and TG, TC, eGFR, hs-CRP, HDL-C, LVEF

Model 4: adjusted for variates in Model 3 and OHA at discharge, insulin at discharge

Model 5: adjusted for variates in Model 4 and left main artery lesion, multi-vessel lesion, complete revascularization, number of DES

[a]The HR was evaluated regarding the lower median of GA as reference

[b]The HR was evaluated by per 1-unit increase of GA

HR hazard ratio, *CI* confidence interval

Table 5. Incremental effects of GA, FBG, and HbA1c on risk stratification for the MACCE beyond existing risk factors

	Harrell's C-index			Continuous-NRI			IDI		
	Estimation	95% CI	P for comparison	Estimation	95% CI	*P* value	Estimation	95% CI	*P* value
Baseline model	0.678	0.657-0.700	-	-	-	-	-	-	-
+ GA	0.691	0.669-0.712	0.001	0.099	0.028-0.143	0.027	0.008	0.002-0.018	0.020
+FBG	0.687	0.666-0.709	0.001	0.092	0.003-0.138	0.040	0.005	0.000-0.012	0.040
+ HbA1c	0.689	0.668-0.710	0.002	0.060	0.000-0.119	0.053	0.007	0.001-0.015	0.020

NRI net reclassification improvement, *IDI* integrated discrimination improvement, *CI* confidence interval

GA glycated albumin, *FBG* fasting blood glucose, *HbA1c* glycosylated hemoglobin A1c

Figures

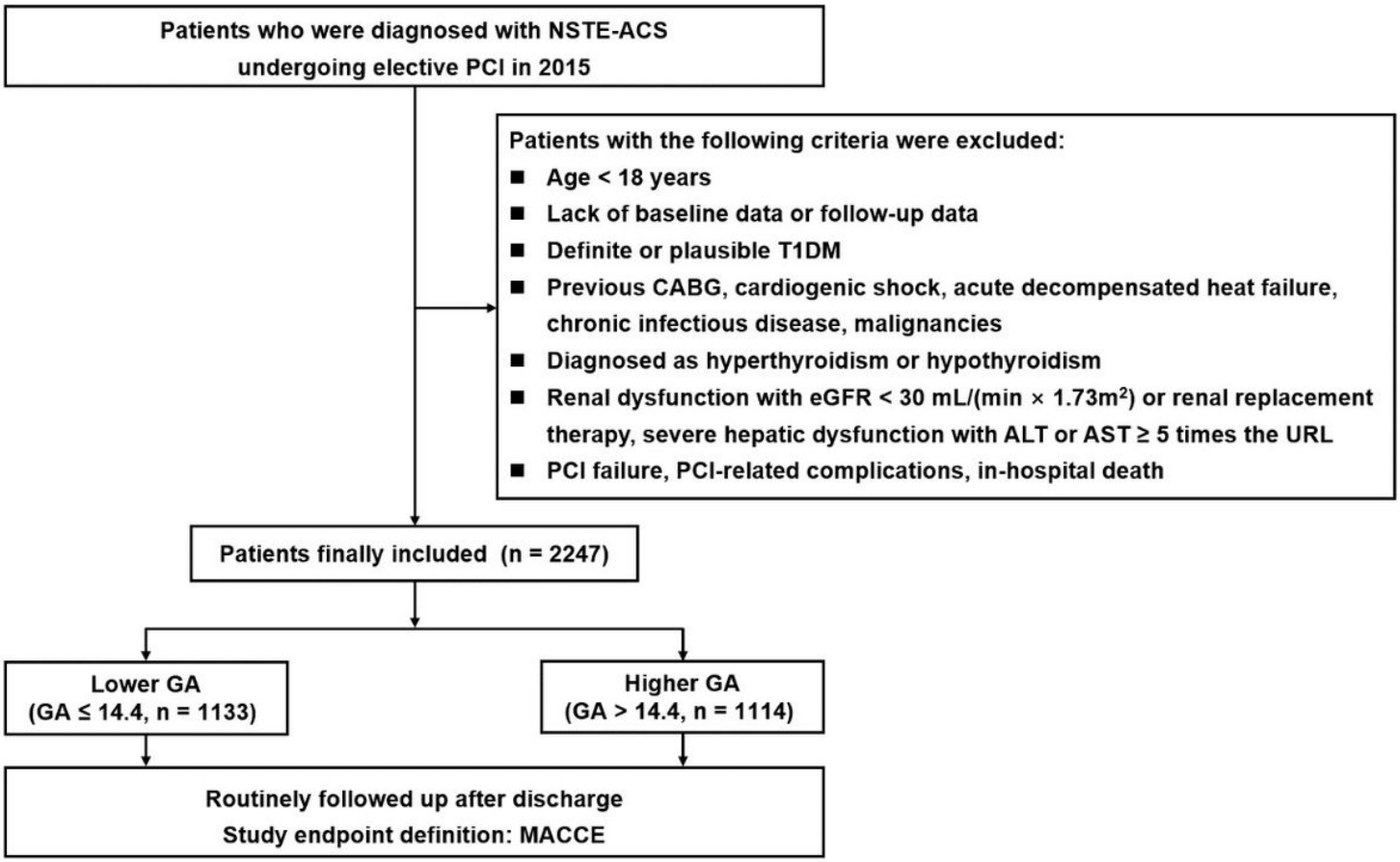

Figure 1

Flow diagram for the enrollment of study population. NSTE-ACS non-ST-segment elevation acute coronary syndrome, PCI percutaneous coronary intervention, T1DM Type 1 Diabetes mellitus, CABG coronary artery bypass grafting, eGFR estimated glomerular filtration rate, ALT alanine transaminase, AST aspartate transaminase, URL upper reference limit, GA glycated albumin, MACCE major adverse cardio-cerebral events

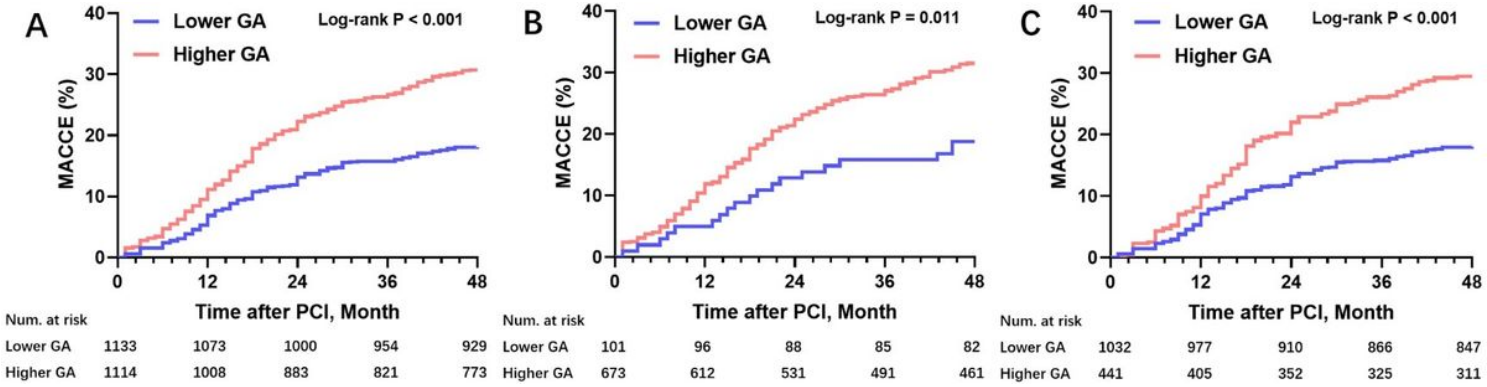

Figure 2

Kaplan-Meier survival curves according to the median of GA. A Kaplan-Meier survival curves for the primary endpoint in the entire population; B Kaplan-Meier survival curves for the primary endpoint in the patients with diabetes; C Kaplan-Meier survival curves for the primary endpoint in the patients without diabetes. GA glycated albumin, MACCE major adverse cardio-cerebral events

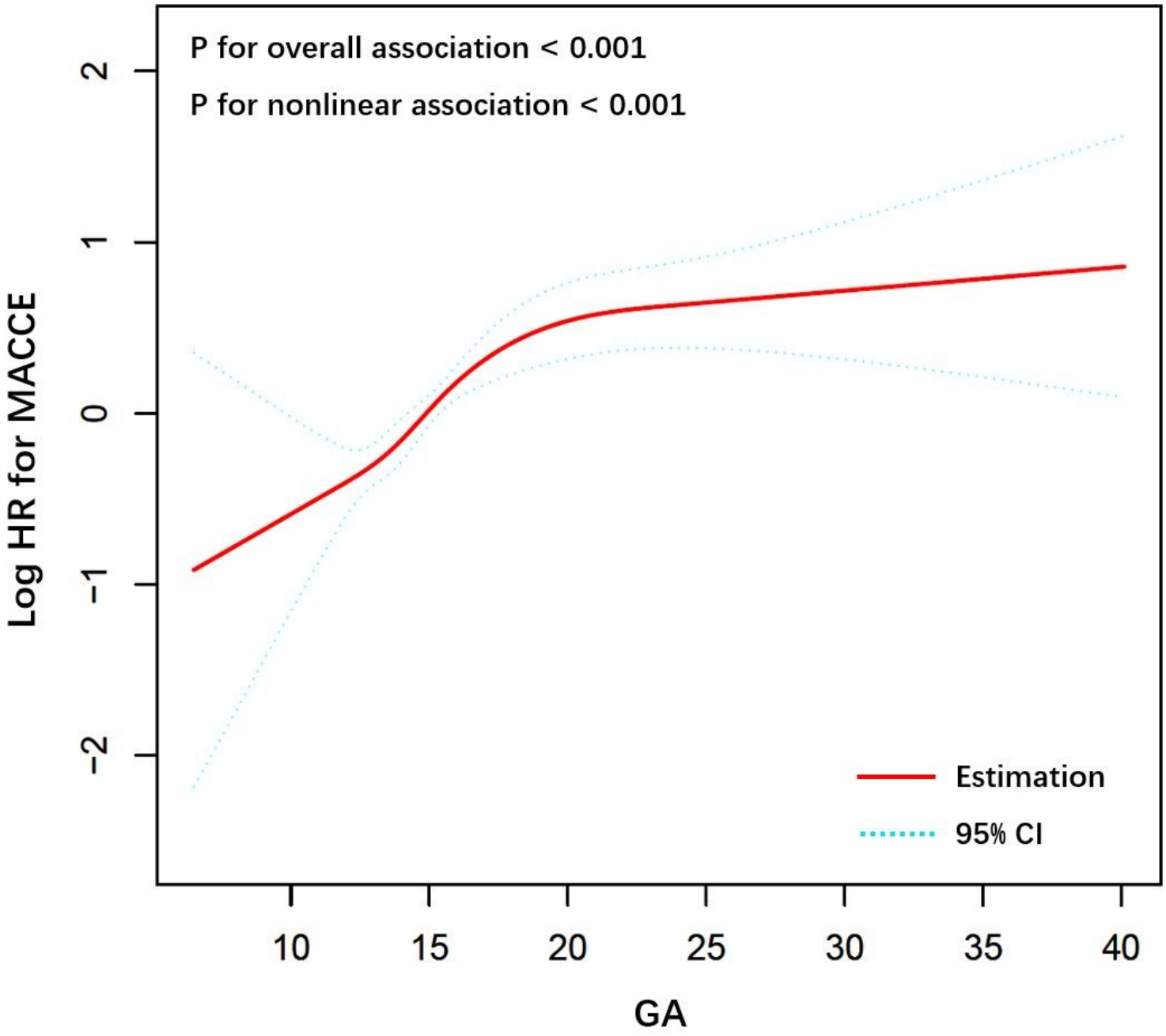

Figure 3

Restricted cubic smoothing for the risk of the primary endpoint according to the GA. The analysis was adjusted for Model 5. HR was evaluated by per 1-unit increase of GA. GA glycated albumin, MACCE major adverse cardio-cerebral events

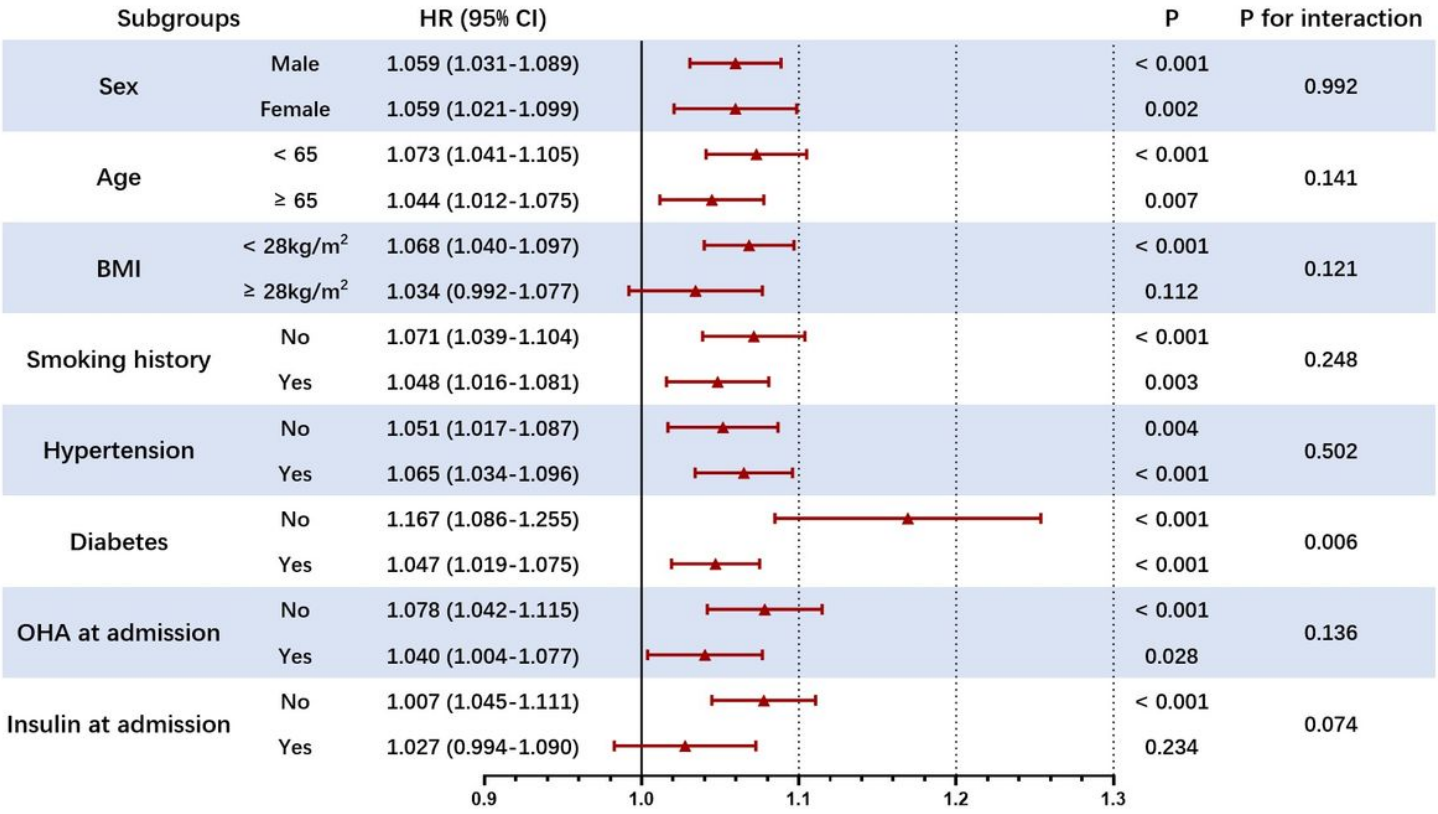

Figure 4

Subgroup analysis evaluating the robustness of GA in predicting the risk of the primary endpoint. The analysis was adjusted for Model 5 except for variates applied for grouping. HR was evaluated by per 1-unit increase of GA. BMI body mass index, OHA oral hypoglycemic agents

Supplementary Files

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