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Prognostic value of serum glycated albumin in acute coronary syndrome patients without standard modifiable cardiovascular risk factors

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Abstract

Background Glycated albumin (GA) has been demonstrated to be associated with adverse outcomes in patients with acute coronary syndrome (ACS). However, as a specific subgroup of ACS, a significant proportion of patients with ACS without standard modifiable cardiovascular risk factors (SMuRFs) are currently being identified. The prognostic value of serum GA for adverse events in such patients remains unexplored. This study aims to evaluate the prognostic value of GA in predicting adverse outcomes in patients with ACS without SMuRFs.

Methods This retrospective study involved 1,140 consecutive patients who were diagnosed with ACS without SMuRFs at the Beijing Anzhen Hospital between May 2018 and December 2020 and underwent coronary angiography. Each patient was followed up for a period of 35–66 months after discharge. The primary endpoint of this study was major adverse cardiovascular and cerebrovascular events (MACCEs) that included all-cause mortality, non-fatal myocardial infarction, non-fatal ischemic stroke, and ischemia-driven revascularization.

Results The average age of the study participants was 59.55 ± 10.98 years, and men accounted for 61.8%. The average GA level was 14.37 ± 2.42. The median follow-up duration was 48.3 months, during which 220 cases (19.3%) experienced MACCEs. In the fully adjusted model, with GA as a continuous variable, the hazard ratio (HR) for MACCEs in the high GA group was 1.069 (95% confidence interval (CI): 1.008, 1.133), the HR for ischemia-driven revascularization was 1.095 (95% CI: 1.021, 1.175), and the HR for all-cause mortality was 1.155 (95% CI: 1.021, 1.306), all with P values less than 0.05. Similarly, when GA was considered as a categorical variable, in the fully adjusted model, GA was associated with MACCEs, ischemia-driven revascularization, and all-cause mortality, with P values all less than 0.05. The restricted cubic spline curve showed that the relationship between GA and MACCEs was linear (p for non-linear = 0.079; p for overall association = 0.026). Furthermore, GA levels were correlated with poor prognosis in the subgroups of patients.

Conclusion Serum GA might be an independent predictor of all-cause death and ischemia-driven revascularization in patients with ACS without SMuRFs.

Keywords Serum glycated albumin, Standard modifiable cardiovascular risk factors, Acute coronary syndrome, Prognosis

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Background

Currently, within the realm of cardiovascular disease research, standard modifiable cardiovascular risk factors, known as SMuRFs, are composed of hypertension, diabetes, hypercholesterolemia, and smoking [1–3]. These risk factors play a pivotal role in the pathogenesis of acute coronary syndrome (ACS) and serve as the focal points for the primary and secondary prevention of cardiovascular disease. However, in recent years, the ACS population without SMuRFs (SMuRF-less) has garnered increasing attention and concern due to their higher mortality and complication rates than ACS patients with at least one risk factor [4–7]. Several studies conducted in Australia have investigated ST-segment elevation myocardial infarction (STEMI) patients without standard modifiable cardiovascular risk factors, revealing a significant increase in this patient proportion over approximately a decade [8, 9]. Furthermore, a global meta-analysis comprised of 15 studies with a total of 1,285,722 ACS patients revealed that the SMuRF-less cohort accounted for 11.56% of patients experiencing their first ACS event and were more likely to present with STEMI ($p=0.007$), with a noted increase in the proportion of patients with SMuRF-less ACS [10]. In conclusion, these studies indicated a significant and rapid increase in the proportion of such patients. Investigating the unique pathogenic mechanisms and risk factors of these patients to improve their prognosis is a focal point for future research.

Glycated albumin (GA) is the predominant circulating Amadori-type glycated protein in the body [11]. As a biomarker for blood glucose control, GA shares similarities with glycated hemoglobin A1c (HbA1c) in terms of (1) measurement units, (2) independence from food intake, (3) reflection of past blood glucose control, and (4) being a standardized marker. Unlike HbA1c, GA is not affected by the lifespan of red blood cells and reflects blood glucose control for 2–3 weeks. Therefore, GA is superior to HbA1c when a short-term assessment of blood glucose status is required, such as during hospitalization for the adjustment of hypoglycemic treatment. Additionally, GA can serve as an inflammatory marker [12], potentially acting as one of the biomarkers for atherosclerotic cardiovascular disease (ASCVD), an inflammatory disease. Current research evidence suggests that GA is closely associated with the risk of developing coronary heart disease, heart failure, and cardiogenic death [13]. However, the prognostic value of GA for patients with SMuRF-less ACS remains unclear based on current studies. Thus, the present work aims to evaluate the predictive value of GA for adverse outcomes in patients with SMuRF-less ACS.

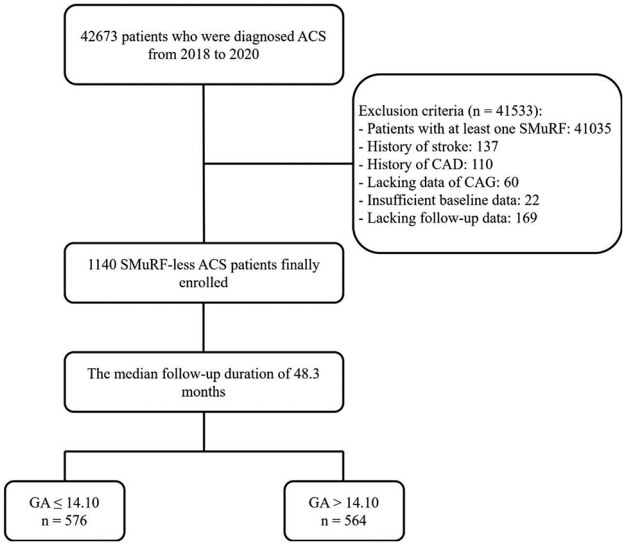

Fig. 1 Study flow chart of inclusion and exclusion criteria of the study population. GA, glycated albumin; ACS, acute coronary syndrome; SMuRFs, standard modifiable cardiovascular risk factors; CAG, coronary angiography; CAD, coronary artery disease

Methods

Study population

This study was a single-center retrospective study that consisted of patients diagnosed with ACS who were treated at the Beijing Anzhen Hospital affiliated with Capital Medical University from May 2018 to December 2020. The exclusion criteria were as follows: incomplete baseline and follow-up data, previous history of stroke or coronary heart disease, or the presence of at least one standard cardiovascular risk factor (hypertension, diabetes, hypercholesterolemia, or a history of smoking, collectively termed SMuRFs). Consequently, a cohort of 1,140 consecutive patients diagnosed with SMuRF-less ACS was included in this research. Figure 1 illustrates the selection process. The design of this study adhered to the Declaration of Helsinki and received approval from the Ethics Committee of the Beijing Anzhen Hospital.

Definition of SMuRFs

SMuRFs include hypertension, diabetes, hypercholesterolemia, and smoking [1, 2]. Patients with hypertension were defined as those with a previous diagnosis, use of hypertension medications, or having hypertension listed in the medical records as the secondary discharge diagnosis (based on a mean systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg recorded from at least two readings obtained on separate days). Diabetes was defined to a previous diagnosis of diabetes, previous administration of diabetes medications, an HbA1c concentration of ≥6.5% during this admission, or having diabetes listed in the medical records as the secondary discharge diagnosis. An individual with hypercholesterolemia during the index admission was defined as having a prior medical diagnosis of hypercholesterolemia, receiving previous or ongoing treatment for

hypercholesterolemia, or having low-density lipoprotein cholesterol (LDL-c) ≥ 3.4 mmol/L or a total cholesterol (TC) level of ≥ 5.2 mmol/L [14]. Smoking status included past or current smoking. Due to the neurohormonal responses to myocardial infarction (MI) in the acute phase, both the fasting blood glucose (FBG) and the acute phase blood pressure were not incorporated in the definitions [1]. Medical records, hospital findings, and self-reported disease conditions during admission served as the basis for the definition of SMuRFs.

Data collection

The laboratory test included the FBG, lipid profiles, high-sensitivity C-reactive protein (hs-CRP), creatinine, serum albumin (SA), and other biochemical markers, all of which were assessed at baseline. The GA levels were determined enzymatically after a fasting period of 8–12 h, with immediate blood sample transportation to the testing center's laboratory. The GA value was expressed as a percentage of the total albumin concentration. Additionally, demographic and clinical data, including vital signs, age, sex, height, weight, medical history, and smoking status, were collected from the electronic medical record database of the Beijing Anzhen Hospital.

Two qualified professionals independently evaluated the results of the coronary angiography (CAG) and echocardiography examinations. Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) were conducted following current guidelines [15, 16]. Medication details at the time of discharge were recorded.

Follow-up and study endpoint

Routinely, patients were followed up every 6 months after discharge by professional clinical follow-up personnel via telephone interviews. The maximum follow-up period was 66 months, with an average follow-up duration of 48.3 months. The primary endpoint was the occurrence of major adverse cardiovascular and cerebrovascular events (MACCEs) that included all-cause mortality, non-fatal MI, non-fatal ischemic stroke, and ischemia-driven revascularization. MI was diagnosed based on the fourth universal definition [17], while ischemic stroke was confirmed by clinical manifestations of neurological impairment and imaging evidence from computed tomography scans or magnetic resonance imaging. Ischemia-driven revascularization was determined by interventions, including the PCI and CABG, performed in response to the patient's recurrent or persistent ischemic symptoms, targeting either the affected vessels or non-target vessels.

Statistical analysis

Patients were stratified into two groups based on the median level of GA, the low group (GA ≤ 14.10%) and the high group (GA > 14.10%), to observe differences between the cohorts. Subsequently, the incidence of MACCEs between the two groups was compared. Measurement data that followed a normal distribution are reported as the mean ± standard deviation (SD). A student's t-test was used if the variances were equal. Otherwise, the rank-sum test was used. Non-normally distributed measurement data are presented as medians with interquartile ranges (IQRs). Categorical variables are expressed as percentages and were compared using the chi-square test or Fisher's exact test. The log-rank test based on the Kaplan-Meier method for describing event rates during follow-up was used to compare the time-to-event curves of diverse GA levels.

This study used a univariate Cox regression analysis to identify variables associated with MACCEs and its components. Following this, the study used Cox proportional hazards models to investigate the association between GA and all-cause mortality, ischemia-driven revascularization, and MACCEs. Variables with potential collinearity were excluded from the multivariate analysis. GA was assessed both as a categorical variable and as a continuous variable. After adjusting for independent risk factors and potential confounding clinical variables identified in the initial univariate Cox regression analysis, we established three regression models. Model 1 was a partially adjusted model that controlled for age, sex, and body mass index (BMI). Model 2 included all variables from Model 1, as well as systolic blood pressure (SBP), diastolic blood pressure (DBP), left ventricular ejection fraction (LVEF), creatinine, high-density lipoprotein cholesterol (HDL-c), LDL-c, triglycerides (TG), hs-CRP, and uric acid (UA). Model 3 encompassed all variables from Model 2 and the left main coronary artery (LM), left anterior descending artery (LAD), left circumflex artery (LCX), right coronary artery (RCA), multivessel disease, intervention, non-ST elevation acute coronary syndrome (NSTE-ACS), and discharge medications.

Additionally, the restricted cubic spline curve was plotted following Model 3 to examine the dose-response relationship between GA and the primary endpoint. To examine the potential effect of risk-factor control (LDL-c and blood pressure) and other variables (age, sex, BMI, SA, multi-vessel disease status, and diagnosis) on the link of GA to the prognosis, subgroup analyses were conducted. The hazard ratios (HRs), 95% confidence intervals (CIs), p-values, and p-values for interactions are shown in the graphs.

The statistical analyses were conducted using SPSS (IBM SPSS, version 26, Chicago, Illinois) as well as R statistical software (version 4.3.2). A two-sided P-value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

Table 1 presents demographic data, clinical characteristics, laboratory results, and treatment information. The study included 1,140 patients with SMuRF-less ACS, with an average age of 59.55±10.98 years, and 61.8% (n=704) of the cohort were male. Patients were divided into two groups based on the median value of GA. Compared with the low GA group, the high GA group consisted of older patients, a higher proportion of women, and had lower BMIs and LVEF (all p<0.05). Additionally, laboratory tests revealed that the high GA group had lower levels of TG and UA but higher levels of HDL-c and FBG than the low GA group (all p<0.05). No statistical differences were observed between the two groups regarding coronary angiography characteristics, treatment choices upon admission, or discharge medications (all p>0.05).

GA and endpoints

During a median follow-up of 48.3 months (IQR: 37.0–56.3), a total of 220 cases (19.3%) experienced MACCEs, comprising 56 cases (4.9%) of all-cause mortality, 15 cases (1.3%) of non-fatal MI, 14 cases (1.2%) of non-fatal ischemic stroke, and 135 cases (11.8%) of ischemia-driven revascularization. As shown in Table 2, the high GA group had a significantly higher incidence of MACCEs (p<0.001), all-cause mortality (p<0.001), and ischemia-driven revascularization (p=0.003) than the low GA group. However, there were no statistically significant differences between the two groups regarding non-fatal MI and non-fatal ischemic stroke (all p>0.05).

Prognostic value of GA for MACCEs

An initial univariate Cox proportional hazards analysis was conducted to preliminarily identify potential determinants associated with all-cause mortality, ischemia-driven revascularization, and MACCEs (Supplementary Files 1: Tables S1 and S2). Subsequently, variables were incorporated into the multivariate models based on the results of the univariate Cox analysis (p<0.05) and clinical significance. Three multivariate models were established to evaluate the predictive performance of GA on the three endpoint events. As shown in Table S3, in the fully adjusted multivariate model (Model 3), each 1-unit increase in GA was associated with an HR of 1.155 for all-cause mortality (95% CI: 1.021, 1.306) (p=0.022). When GA was considered as a categorical variable, in Model 3, the high GA group had an HR of 3.448 for all-cause mortality (95% CI: 1.429, 8.319) (p=0.006). Table S4 shows the multivariate adjusted model for ischemia-driven revascularization. GA, whether as a categorical or continuous variable, demonstrated significant independent prognostic value across all models. Similarly, Table 3 shows the multivariate adjusted model for MACCEs, where in the fully adjusted model (Model 3), GA, regardless of being a categorical or continuous variable, showed a significant independent prognostic value.

A Kaplan-Meier survival analysis was used to assess the incidence of MACCEs and its components during the follow-up period. The cumulative risk of all-cause mortality (Fig. 2A, log-rank p<0.0001), ischemia-driven revascularization (Fig. 2D, log-rank p=0.0042), and MACCEs (Fig. 2E, log-rank p<0.0001) significantly increased progressively with higher serum GA levels (from low to high GA levels). No statistically significant differences were observed in the cumulative incidence of non-fatal MI (Fig. 2B, log-rank p=0.89) and non-fatal ischemic stroke (Fig. 2C, log-rank p=0.29).

After adjusting for variables in Model 3, we plotted the restricted cubic spline curve to illustrate the dose-response relationship between the GA levels and MACCEs risk (Fig. 3). It was observed that the risk of MACCEs increased with rising GA levels (overall association p=0.026), and there was a linear relationship between GA and the incidence of MACCEs (non-linearity p-value>0.05).

Despite the absence of SMuRFs in this population, the extent to which the control of risk factors influences prognosis warrants further investigation. To further substantiate the predictive value of GA for MACCEs, we conducted a subgroup analysis (Fig. 4). The predictive ability of GA for MACCEs showed no difference across subgroups defined by age (≤65 or >65 years), sex (male or female), BMI (≤24.0 or >24.0 kg/m^2), LDL-c control (≤1.80 or >1.80 mmol/L), blood pressure control (≤130/80 or >130/80 mmHg), SA (≤42.0 or >42.0 g/L), and multivessel disease (yes or no) (all P values for the interactions were >0.05).

GA and residual risk

To investigate the relationship between GA and adverse events with residual inflammatory risk assessed by hs-CRP and residual cholesterol risk assessed by LDL-c, we divided hs-CRP and LDL-c into tertiles to study the differences in GA and MACCEs across different levels of residual risk. As shown in Table S5, a statistically significant difference was observed only in the hs-CRP group (p<0.05). Furthermore, both GA and MACCEs were highest in the group with the highest hs-CRP levels (Tertile 3).

Discussion

To the best of our knowledge, this study is the first investigation into the prognostic value of GA in the ACS population without SMuRFs, such as hypertension, diabetes, hypercholesterolemia, and smoking. The findings of this research revealed that compared with the low GA group, the high GA group exhibited a significantly elevated

Table 1 Baseline demographics and clinical characteristics of the study patients

	Total population (*n* = 1140)	**Lower GA (≤ 14.10%, *n* = 576)**	**Higher GA (> 14.10%, *n* = 564)**	***P* value**
Demographics				
Age, years	59.55 ± 10.98	56.37 ± 11.00	62.80 ± 10.00	**< 0.001**
Sex, male, n (%)	704 (61.8)	379 (65.8)	325 (57.6)	**0.005**
BMI, kg/m^2	25.01 ± 3.24	25.37 ± 3.33	24.64 ± 3.10	**< 0.001**
Heart rate, bpm	69.67 ± 12.42	69.44 ± 11.58	69.90 ± 13.23	0.535
SBP, mmHg	125.78 ± 15.43	125.12 ± 14.82	126.46 ± 16.01	0.142
DBP, mmHg	75.89 ± 10.48	76.44 ± 10.33	75.33 ± 10.61	0.072
Clinical diagnosis, n (%)				
UAP	830 (72.8)	426 (74.0)	404 (71.6)	0.377
NSTEMI	147 (12.9)	76 (13.2)	71 (12.6)	0.760
STEMI	163 (14.3)	74 (12.8)	89 (15.8)	0.157
Echocardiographic findings				
LVEF, %	61.59 ± 8.21	62.20 ± 7.42	61.01 ± 8.87	**0.023**
Laboratory test				
Creatinine, umol/L	69.62 ± 29.36	68.84 ± 14.27	70.42 ± 39.14	0.385
TC, mmol/L	3.96 ± 0.68	3.97 ± 0.67	3.95 ± 0.68	0.710
TG, mmol/L	1.47 ± 0.86	1.54 ± 0.82	1.39 ± 0.91	**0.003**
LDL-c, mmol/L	2.28 ± 0.58	2.29 ± 0.58	2.26 ± 0.58	0.412
HDL-c, mmol/L	1.15 ± 0.28	1.13 ± 0.27	1.17 ± 0.30	**0.006**
FBG, mmol/L	5.78 ± 1.59	5.44 ± 1.05	6.13 ± 1.93	**< 0.001**
SA, g/L	42.70 ± 3.68	42.68 ± 3.23	42.73 ± 4.07	0.822
UA, umol/L	328.31 ± 84.60	337.50 ± 88.85	319.05 ± 79.10	**< 0.001**
hs-CRP, mg/L	1.20[0.53, 3.17]	1.20[0.56, 3.00]	1.20[0.48, 3.56]	0.808
CK, U/L	82.00[57.00, 121.25]	81.00[58.00, 116.00]	83.00[57.00, 126.00]	0.403
GA, %	14.37 ± 2.42	12.91 ± 0.85	15.87 ± 2.59	**< 0.001**
Angiography, n (%)				
Left main	64 (5.6)	33 (5.7)	31 (5.5)	0.864
Left anterior descending	830 (72.8)	425 (73.8)	405 (71.8)	0.453
Circumflex	416 (36.5)	209 (36.3)	207 (36.7)	0.884
Right coronary artery	460 (40.4)	225 (39.1)	235 (41.7)	0.370
Single-vessel disease	599 (52.5)	302 (52.4)	297 (52.7)	0.938
Multi-vessel disease	474 (41.6)	239 (41.5)	235 (41.7)	0.953
Treatment, n (%)				
Revascularization	846 (74.2)	436 (75.7)	410 (72.7)	0.247
PCI	765 (67.1)	395 (68.6)	370 (65.6)	0.285
CABG	81 (7.1)	41 (7.1)	40 (7.1)	0.986
Medication	294 (25.8)	140 (24.3)	154 (27.3)	0.247
Discharge medication, n (%)				
Aspirin	1086 (95.3)	553 (96.0)	533 (94.5)	0.232
P_2Y_{12} inhibitors	992 (87.0)	509 (88.4)	483 (85.6)	0.170
Statins	1095 (96.1)	548 (95.1)	547 (97.0)	0.109
ACEI/ARBs	114 (10.0)	50 (8.7)	64 (11.3)	0.133
Beta blockers	668 (58.6)	331 (57.5)	337 (59.8)	0.433

GA glycated albumin, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, LVEF left ventricular ejection fraction, UAP unstable angina, NSTEMI non-ST-segment elevation myocardial infarction, STEMI ST-segment elevation myocardial infarction, TC total cholesterol, TG triglyceride, LDL-c low-density lipoprotein cholesterol, HDL-c high-density lipoprotein cholesterol, FBG fasting blood glucose, SA serum albumin, UA uric acid, hs-CRP high-sensitivity C-reactive protein, CK creatine kinase, PCI percutaneous coronary intervention, CABG coronary artery bypass grafting, ACEI angiotensin-converting enzyme inhibitors, ARBs angiotensin receptor blockers

incidence of all-cause mortality, ischemia-driven revascularization, and MACCEs. After adjusting for potential confounding factors, an increase in GA remained a significant and independent predictor of all-cause mortality, ischemia-driven revascularization, and MACCEs, whether as a continuous or categorical variable.

Serum GA is formed through the glycation of various proteins, including human serum albumin, a process that

Table 2 Clinical outcomes according to GA levels

	Total population (*n* = 1140)	Lower GA (*n* = 576)	Higher GA (*n* = 564)	*P* value
MACCEs, n (%)	220 (19.3)	78 (13.5)	142 (25.2)	**< 0.001**
All-cause mortality, n (%)	56 (4.9)	13 (2.3)	43 (7.6)	**< 0.001**
Non-fatal MI, n (%)	15 (1.3)	8 (1.4)	7 (1.2)	0.827
Non-fatal ischemic stroke, n (%)	14 (1.2)	5 (0.9)	9 (1.6)	0.265
Ischemia-driven revascularization, n (%)	135 (11.8)	52 (9.0)	83 (14.7)	**0.003**

GA glycated albumin, MACCEs major adverse cardiovascular and cerebrovascular events, MI myocardial infarction

Table 3 Multivariable Cox regression analyses for the association between GA and MACCEs

	As continuous variate[a]		As nominal variate[b]	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Unadjusted	1.080 (1.042, 1.119)	**< 0.001**	1.884 (1.429, 2.484)	**< 0.001**
Model 1	1.080 (1.034, 1.128)	**0.001**	1.762 (1.309, 2.373)	**< 0.001**
Model 2	1.057 (0.998, 1.120)	0.057	1.599 (1.116, 2.292)	**0.011**
Model 3	1.069 (1.008, 1.133)	**0.027**	1.656 (1.154, 2.376)	**0.006**

Model 1: adjusted for age, sex, and BMI

Model 2: adjusted for Model 1 + SBP, DBP, LVEF, creatinine, TG, HDL-c, LDL-c, hs-CRP and UA

Model 3: adjusted for Model 2 + LM, LAD, LCX, RCA, Multi-vessel, operational intervention, NSTE-ACS, and discharge medication

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

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

HR hazard ratio, CI confidence interval

involves the non-enzymatic addition of reducing sugars and/or their reactive degradation products to the amino groups of proteins [18]. Like glycated hemoglobin, GA serves as a biomarker for blood glucose control. However, unlike glycated hemoglobin, GA reflects blood glucose control for 2–3 weeks prior to testing and is not influenced by food intake or red blood cell lifespan, though it is affected by albumin metabolism [19]. Furthermore, previous study has identified an increased risk of adverse events during hospitalization for STEMI patients with hypoalbuminemia [20]. In our study, a subgroup analysis based on the median revealed a statistically significant difference in the impact of GA on MACCEs among individuals with albumin levels > 42.0 g/L ($p = 0.028$). However, there was no interaction between SA levels and GA (p for interaction > 0.05). Multiple studies have shown that GA can provide supplemental and valuable information for blood glucose control compared with measured HbA1c levels [19, 21]; hence, its clinical importance is increasingly recognized.

Previous research has found serum GA levels to be associated with all-cause mortality [22, 23]. Regarding the relationship between GA and ASCVD, many studies have identified a correlation between GA and poor prognosis in populations with coronary heart disease [24–27]. Additionally, GA has been found to aid in the early identification of the onset of coronary heart disease and is related to its progression [11, 26, 28, 29]. In the general population, GA is associated with arterial stiffness regardless of the glucose tolerance status [30], and it also reflects the risk of subclinical atherosclerosis in middle-aged and elderly Chinese individuals with impaired glucose regulation [31]. Shen et al. showed a link between elevated serum GA levels in diabetic patients with stable angina and chronic total occlusion and a reduction in coronary collateral circulation [32]. Elevated GA levels in patients with heart failure correlate positively with the severity of the disease [33]. Taken together, these studies demonstrate a close association between GA and cardiovascular diseases. Our research findings suggested a correlation between GA and adverse outcomes in a specific ACS subpopulation and were consistent with prior studies.

The study population consisted of patients with SMuRF-less ACS, a distinct subset of the ACS population found to be free of SMuRFs, such as hypertension, diabetes, hypercholesterolemia, and smoking at the time of onset [1]. However, Mazhar et al. showed that patients with clinical coronary atherosclerosis who lacked SMuRFs exhibited a similar plaque progression rate to those with SMuRFs [34], suggesting the presence of certain unknown pathogenic factors in this patient population.

Liu et al. found that among NSTE-ACS patients undergoing PCI treatment, GA was an independent predictor of adverse cardiovascular and cerebrovascular events, both as continuous and categorical variables ($p < 0.001$), after adjusting for confounding factors. Moreover, in subgroup analyses, GA's predictive value was higher in the non-diabetic subgroup than in the diabetic subgroup [27]. A study involving 2,965 Japanese community residents aged ≥ 40 years, with a median follow-up of 10.2 years, confirmed that elevated GA levels were significantly associated with the occurrence of cardiovascular diseases, even in a general population without diabetes [28]. This suggests that in populations without diabetes, an increase in serum GA levels is closely related to the development of cardiovascular diseases. This indirectly indicates that GA may be an important pathogenic target in the SMuRFs-less ACS population.

Over the past few decades, studies have shown that ASCVD is an inflammatory disease [35, 36], and anti-inflammatory treatments can significantly reduce the recurrence rate of cardiovascular events in populations with coronary heart disease [37]. Previous research has found that acute myocardial infarction patients without SMuRFs often have concomitant autoimmune/inflammatory diseases [38]. This suggests that although the

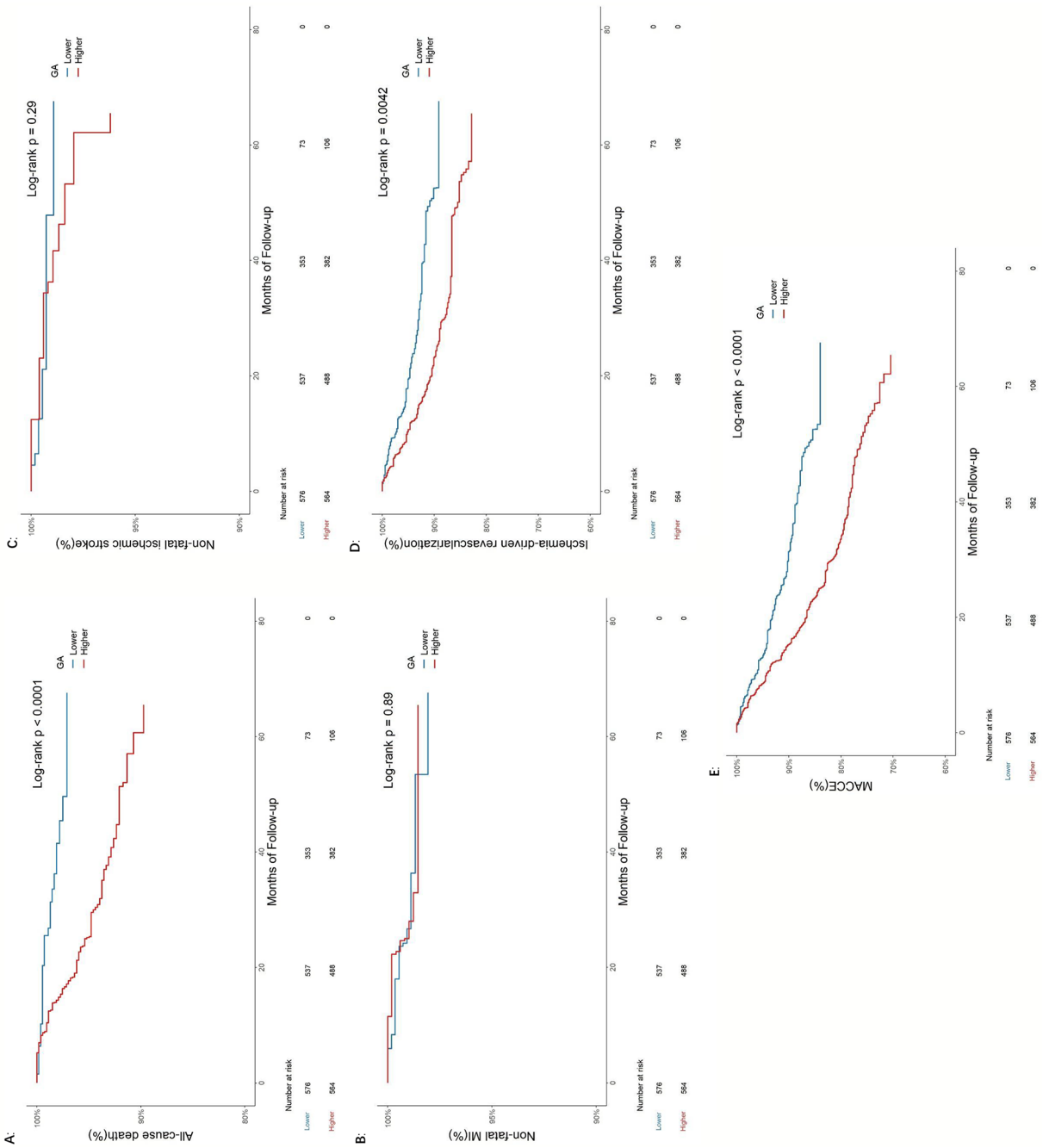

Fig. 2 Kaplan-Meier survival curves according to the median of GA. **A** Kaplan-Meier survival curve of all-cause death; **B** Kaplan-Meier survival curve of non-fatal MI; **C** Kaplan-Meier survival curve of non-fatal ischemic stroke; **D** Kaplan-Meier survival curve of ischemia-driven revascularization; **E** Kaplan-Meier survival curve of MACCEs. GA glycated albumin, MACCEs major adverse cardiovascular and cerebrovascular events, MI myocardial infarction

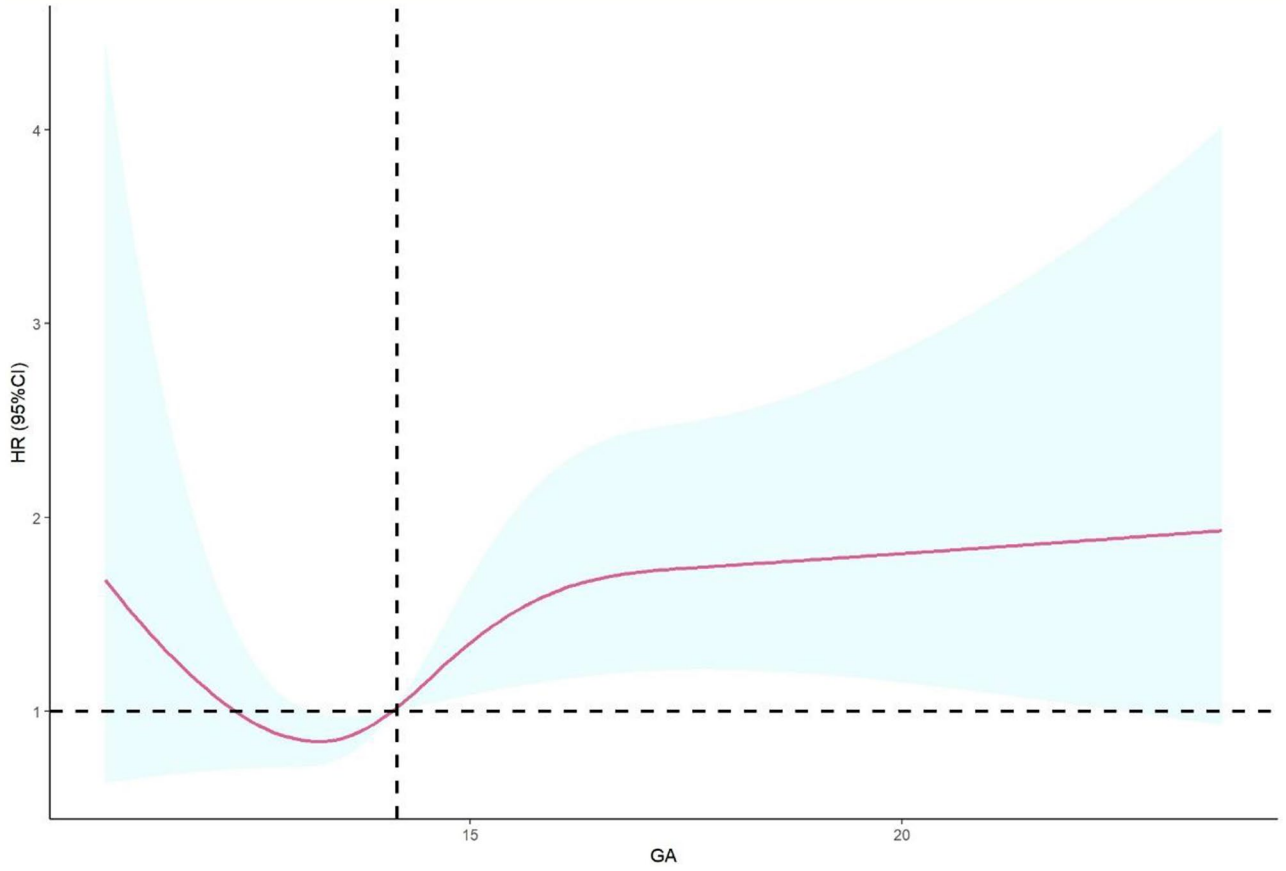

Fig. 3 The restricted cubic spline curve for the association of GA with MACCEs. The analysis was adjusted for Model 3. HR was evaluated by per 1-unit increase of GA. GA glycated albumin, HR hazard ratio, CI confidence interval

SMuRF-less ACS population lacks standard cardiovascular risk factors, inflammatory factors within their bodies may be a key element that triggers their condition. GA can form in a non-diabetic environment and be induced by inflammatory responses. Additionally, GA can induce endothelial dysfunction in macrophages and produce pro-inflammatory effects by increasing reactive oxygen species [39]. Hattori et al. discovered that GA can stimulate the growth and migration of vascular smooth muscle cells (VSMCs). Furthermore, GA promotes the proliferation and migration of VSMCs by inducing inflammatory mediators in the vascular wall, such as the pro-inflammatory cytokine interleukin (IL)-6, thereby playing a role in atherosclerosis [40]. This might be one of the reasons for the high ischemia-driven revascularization rate observed in our study population. The clinical application of GA measurement may lie in its multifunctionality as an inflammatory mediator and as a marker for tracking glucose abnormalities. Further understanding of GA's role in glucose and inflammatory diseases could make it an independent biomarker of inflammation [12].

In this study, the blood glucose control indicator GA is linked with the SMuRF-less ACS population for the first time, and this information will further aid in exploring the pathogenesis and pathophysiology of this group to provide more precise medical management. GA may have the potential to become a routine examination to assess the prognosis of such patients in the future, but this requires further confirmation using large-scale prospective studies.

Limitation

This study has some non-negligible limitations. First, as a single-center, retrospective, observational trial, the nature of the research may diminish the validity and statistical power of the findings. Therefore, more in-depth prospective, multicenter, and multi-ethnic population studies are required to further validate the current results. Second, the study only included GA levels measured at the time of hospital admission, without further dynamic observations and monitoring of GA levels after patient discharge. Third, since our study primarily focused on whether patients experienced MACCEs during the follow-up period, subsequent hematological examinations and measurements, such as blood pressure, were not conducted, making it impossible to determine

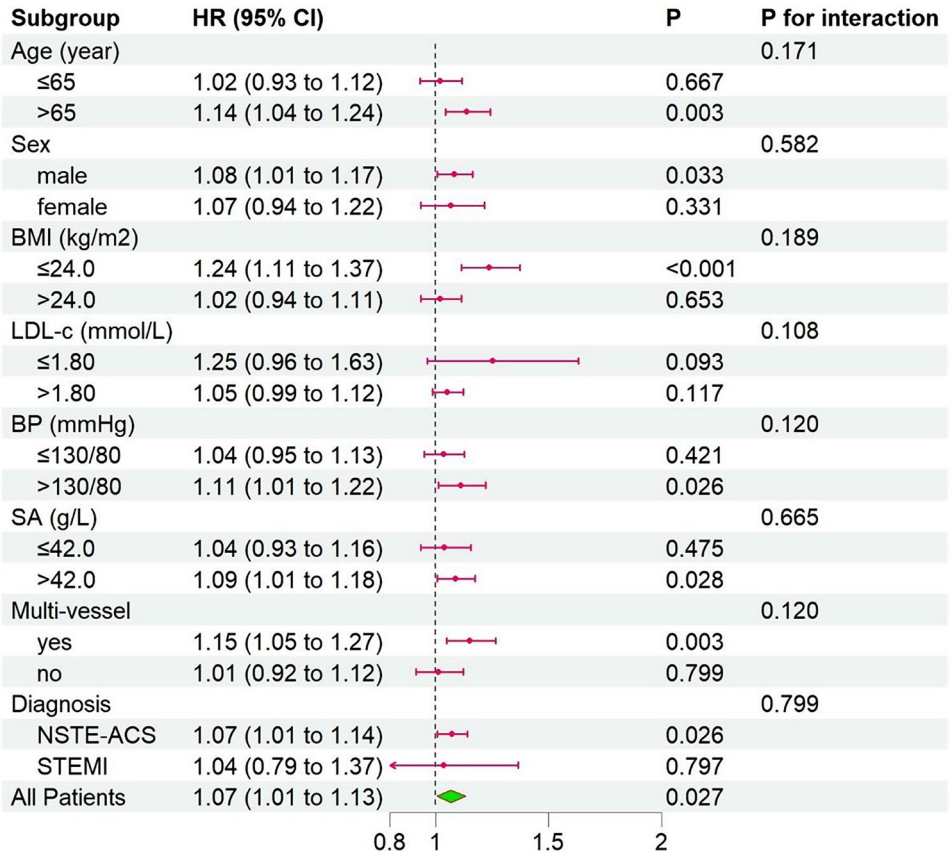

Fig. 4 Forest plot of MACCEs according to different subgroups. Adjusted model included age, sex, body mass index, systolic blood pressure, diastolic blood pressure, LVEF, creatinine, HDL-c, LDL-c, TG, hs-CRP, uric acid, LM, LAD, LCX, RCA, Multi-vessel lesion, operational intervention, NSTE-ACS, aspirin, P_2Y_{12} inhibitors, statins, ACEI/ARBs, Beta blockers. HR was evaluated by per 1-unit increase of GA. MACCEs major adverse cardiovascular and cerebrovascular events, BMI body mass index, LDL-c low-density lipoprotein cholesterol, BP blood pressure, SA serum albumin, NSTE-ACS non-ST-segment elevation acute coronary syndrome; STEMI ST-segment elevation myocardial infarction, HR hazard ratio, CI confidence interval

whether patients developed SMuRFs. Fourth, the study only included Chinese patients, and the generalizability of the results to other ethnicities requires further investigation.

Conclusion

Serum GA has been demonstrated to be an independent predictor of all-cause death and ischemia-driven revascularization in the SMuRF-less ACS population. Further exploration into the role of GA in the inflammatory processes of ACS could establish it as an independent biomarker correlated with prognosis. This conclusion warrants confirmation through additional prospective, multicenter, and multiethnic studies.

Abbreviations

ASCVD	Atherosclerotic cardiovascular disease
SMuRFs	Standard modifiable cardiovascular risk factors
ACS	Acute coronary syndrome
GA	Glycated albumin
TC	Total cholesterol
LDL-c	Low-density lipoprotein cholesterol
BMI	Body mass index
LVEF	Left ventricular ejection fraction
UAP	Unstable angina pectoris
NSTEMI	Non-ST-segment elevation myocardial infarction
NSTE-ACS	Non-ST-segment elevation acute coronary syndrome
STEMI	ST-segment elevation myocardial infarction
CAG	Coronary angiography
MACCEs	Major adverse cardiovascular and cerebrovascular events
MI	Myocardial infarction
HR	Hazard ratio
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
HDL-c	High-density lipoprotein cholesterol
UA	Uric acid
LM	Left main coronary artery
LAD	Left anterior descending artery
LCX	Left circumflex artery
RCA	Right coronary artery
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass graft
CI	Confidence interval
TG	Triglyceride
SA	Serum albumin
FBG	Fasting blood glucose
hs-CRP	High-sensitivity C-reactive protein
CK	Creatine kinase
ACEI	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin receptor blockers
VSMCs	Vascular smooth muscle cells
SD	Standard deviation
IQR	Interquartile range

Supplementary Information

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Supplementary Material 1: Additional file 1: **Table S1.** Unadjusted Cox regression analysis investigating predictors of all-cause mortality and ischemia-driven revascularization. **Table S2.** Unadjusted Cox regression analysis investigating predictors of MACCEs. **Table S3**. Multivariable Cox regression analyses for the association between GA and all-cause mortality. **Table S4.** Multivariable Cox regression analyses for the association between GA and ischemia-driven revascularization. **Table S5.** Predictive value of baseline high-sensitivity CRP and LDL-c for MACCEs

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Author contributions
XMZ: designed the study, analyzed the data and wrote the article; YD and QYG: substantively revised the manuscript. All authors contributed to collecting and analyzing the data. All the authors have read and approved the final manuscript.

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Data availability
The datasets used/or analyzed during the current study are available from the corresponding author on reasonable request.

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.

Competing interests
The authors declare no competing interests.

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