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The combined predictive power of the atherogenic index of plasma and serum glycated albumin for cardiovascular events in postmenopausal patients with acute coronary syndrome after percutaneous coronary intervention

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Abstract

Background Glycated Albumin (GA) and atherogenic index of plasma (AIP) are two important biomarkers that respectively reflect lipid and glucose levels. Previous research has revealed their roles in cardiovascular diseases (CVD) and diabetes. However, their combined predictive ability in forecasting cardiovascular events (CVE) after percutaneous coronary intervention (PCI) among postmenopausal acute coronary syndrome (ACS) patients remains insufficiently studied.

Methods Based on the levels of AIP (AIP-L and AIP-H) and GA (GA-L and GA-H), four groups were used to categorize the patients. The CVE assessed included cardiac death, nonfatal myocardial infarction (MI) and nonfatal stroke. To evaluate the relationship between AIP, GA, and CVE, multivariate Cox regression analyses were performed.

Results 98 patients (7.5%) experienced CVE during follow-up. AIP and GA were revealed as strong independent predictors of CVE through multivariate analysis (AIP: HR 3.324, 95%CI 1.732–6.365, $P=0.004$; GA: HR 1.098, 95% CI 1.023–1.177, $P=0.009$). In comparison to those in the initial group (AIP-L and GA-L), the fourth group (AIP-H and GA-H) of patients exhibited the greatest CVE risk (HR 2.929, 95% CI 1.206–5.117, $P=0.018$). Derived from the model of baseline risk, the combination of AIP + GA significantly enhanced the AUC, meanwhile combining AIP and GA levels maximized prognostic accuracy in the baseline risk model.

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Conclusions This study found that the combined measurement of AIP and GA significantly enhanced the predictive capability for CVE following PCI in postmenopausal ACS patients. By integrating these two biomarkers, it became possible to more accurately identify high-risk individuals and provided clinicians with new predictive tools for postmenopausal ACS patients in risk assessment and management.

Keywords Acute coronary syndrome, Atherogenic index of plasma, Serum glycated albumin, Menopause, Percutaneous coronary intervention

Background

With global population aging and lifestyle changes, the incidence of diabetes, ischemic heart disease, and stroke is on the rise, posing a significant threat to human health [1]. Despite progress over the past 30 years, atherosclerotic cardiovascular disease (ASCVD) mortality rates are currently rising, with middle-aged women experiencing the fastest relative increase [2]. In this context, menopause, as a significant stage of female aging, becomes particularly important. It refers to the permanent cessation of menstruation due to the loss of ovarian function and has considerable impacts on women's social, reproductive, physiological, and psychological health [3]. Additionally, menopause brings significant metabolic and cardiovascular changes, resulting in a markedly increased risk of cardiovascular diseases (CVD) in menopausal women [4]. This trend may be partly attributed to the decline in estrogen levels in menopausal women, which weakens the protective cardiovascular effects [5]. Therefore, identifying biomarkers to predict and manage CVD risk in menopausal women has become particularly important. The atherogenic index of plasma (AIP), which reflects lipid levels and atherosclerosis risk, is gaining increasing attention. AIP has shown significant prognostic ability in traditional CVD patients and offers greater accuracy in predicting future cardiovascular events (CVE) [6]. Previous studies have suggested that in postmenopausal women, AIP may be a strong predictor of coronary artery disease (CAD) risk [7]. Furthermore, our preliminary research suggested that AIP may serve as an independent marker of CAD risk in menopausal Chinese Han women, potentially surpassing traditional lipid indicators [8], and our findings also indicated that AIP could predict CVE in patients with prediabetes complicated by unstable angina pectoris (UAP), highlighting its prognostic ability [9]. In addition, another important biomarker is glycated albumin (GA), essential to diabetes management. The clinical utility of GA measurement lies in its multifunctionality, serving both as an inflammatory mediator and as a marker for tracking high blood sugar and other diabetes complications [10]. In recent years, interest in GA has been steadily increasing, particularly in the field of diabetes monitoring, where it serves as a complementary biomarker to blood glucose and glycated hemoglobin A1c (HbA1c) [11]. Additionally, elevated serum GA levels can contribute to the formation of atherosclerotic plaques [12]. It was noteworthy that, in non-ST segment elevated myocardial infarction-acute coronary syndrome (NSTEMI-ACS) patients receiving percutaneous coronary intervention (PCI) treatment, GA was highly correlated with adverse outcomes, indicating in NSTEMI-ACS GA as a primary marker of adverse events [13]. In summary, AIP and GA are two important biomarkers in diabetes and CVD. While existing research has revealed their roles in these conditions, their combined predictive capability in forecasting CVE post-PCI in postmenopausal ACS patients remain insufficiently studied. Given the hormonal changes and increased susceptibility to lipid and glucose abnormalities in postmenopausal women, they face heightened risk of CVE following PCI. Building upon prior research, this study intended to investigate the combined predictive abilities of GA+AIP for postmenopausal ACS patients following PCI.

Methods

Study population

1305 postmenopausal patients were consecutively enrolled, who hospitalized at the Beijing Anzhen Hospital undergoing coronary angiography with the diagnosis with ACS and PCI treatment from January 2018 to December 2018. The criteria for exclusion were specified as: (1) heart failure, coronary artery bypass grafting (CABG) history, or cardiogenic shock; (2) incomplete clinical, laboratory or angiographic data; (3) PCI-related complications or failure; (4) in-hospital mortality or complications; (5) severe hepatic conditions and presence of other significant comorbidities; (6) extreme body mass index (BMI) and suspected familial hypertriglyceridemia; (7) estimated glomerular filtration rate (eGFR) below 30 defined as severe renal impairment. Depending on the median level of AIP, individuals were categorized into two groups (AIP-L group: <=0.0843, $n=653$; AIP-H group: >0.0843, $n=652$). Similarly, according to the median level of GA, two groups were formed from the patients (GA-L group: <=15.4%, $n=659$; GA-H group: >15.4%, $n=646$). Furthermore, 4 groups were stratified among the patients based on their AIP and GA levels: AIP-L+GA-L, AIP-H+GA-L, AIP-L+GA-H group, and AIP-H+GA-H. Strictly adhered to the principles of the Declaration of Helsinki, ethics committee approval was granted for this study from Beijing Anzhen Hospital.

All patients gave in written or oral form informed consent (Fig. 1).

Definitions and data collection

Data on patient demographics, smoking habits, detailed medical histories, and other pertinent medical information from electronic health records were methodically retrieved, which was comprised of past medical histories such as previous myocardial infarction (MI), hypertension, T2DM, previous PCI, hyperlipemia, and previous stroke. ACS referred to unstable ST-segment elevation myocardial infarction (STEMI), UAP, and NSTEMI, diagnosed according to established guidelines [14]. Through elevated blood glucose levels or self-reported use of oral hypoglycemic drugs (OAD) or insulin, categorized as casual blood glucose levels>=11.1 mmol/L, fasting blood glucose (FBG) levels>=7.0 mmol/L, or two-hour postprandial levels>11.1 mmol/L after a 75 g oral glucose tolerance test, T2DM was diagnosed [15]. Based on persistent blood pressure level>=140/90 mmHg, or the continuous medication usage of antihypertension, hypertension was diagnosed [16].

Fasting blood samples collected from veins were obtained for assessing high sensitivity C-reactive protein (hs-CRP), triglycerides (TG), eGFR, creatinine (Cr), total cholesterol (TC), GA, low-density lipoprotein cholesterol (LDL-C), FBG, high-density lipoprotein cholesterol (HDL-C), HbA1c, and uric acid using standardized laboratory techniques. With a two-dimensional modified Simpson's method, cardiac function was additionally assessed using the left ventricular ejection fraction (LVEF) measurement, offering critical insights into heart function. A calculator available online at http://syntaxscore.com/ was employed to determine the initial Synergy between PCI with TAXUS (a drug-eluting stent utilizing paclitaxel) and Cardiac Surgery (SYNTAX) score. Two independent reviewers analyzed the pre-procedural angiograms, unaware of the patients' initial clinical details and outcomes. A third evaluator was consulted to achieve consensus in cases where discrepancies arose between the two reviewers. This methodological choice was deemed crucial to ensure a robust and unbiased assessment of the initial synergy, as it allowed for a more comprehensive evaluation by integrating diverse

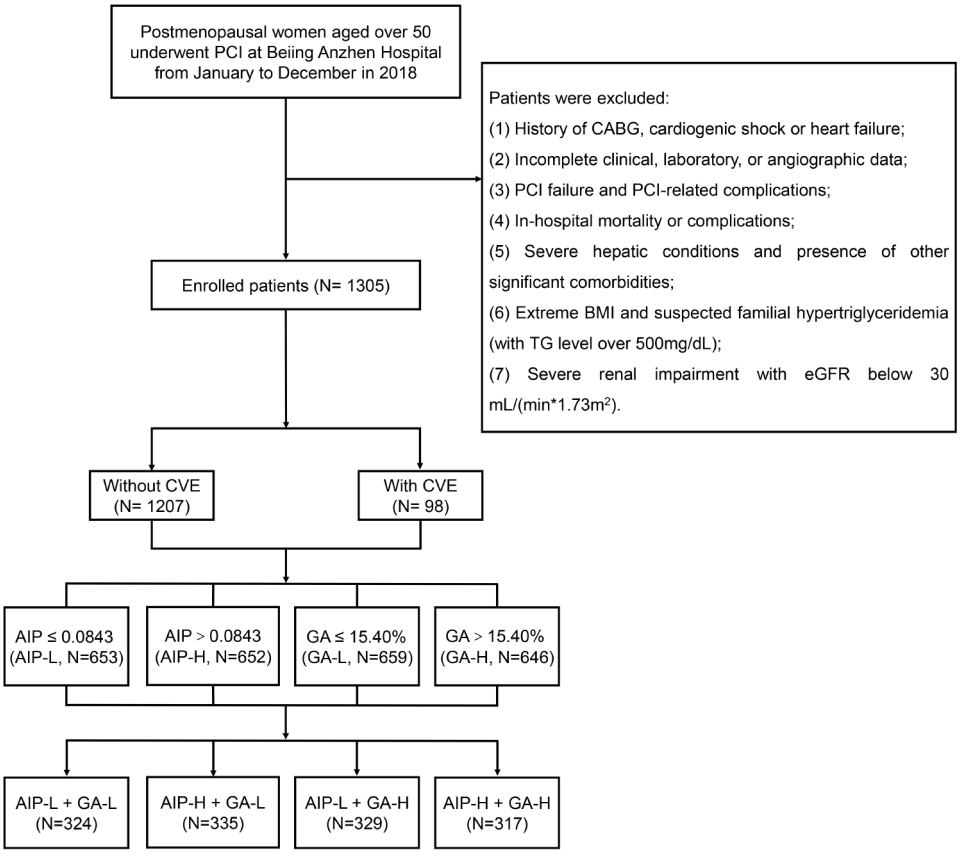

Fig. 1 Flow chart of the study population enrollment. PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BMI, body mass index; TG, triglycerides; eGFR, estimated glomerular filtration rate; CVE, cardiovascular events; AIP, atherogenic index of plasma; GA, glycated albumin; AIP-L + GA-L, lower AIP level + lower GA level; AIP-H + GA-L, higher AIP level + lower GA level; AIP-L + GA-H, lower AIP level + higher GA level; AIP-H + GA-H, higher AIP level + higher GA level

perspectives and expertise. All data were then recorded in the specialized digital database and underwent assessment of quality. AIP, introduced by Dobiásová and Frohlich in 2001, was calculated: AIP = $\log_{10}$ (TG/HDL-C) [17].

Endpoints and following up

At 1, 3, 6, and 12-months, evaluations of follow-up occurred after discharge, and then annually, either via clinic visits or phone calls. Skilled professionals recorded any outcomes in the follow-up period. In this investigation, the observational endpoint was the occurrence of CVE, which included cardiac death, nonfatal MI, and nonfatal stroke. Diagnoses of MI and stroke were made according to internationally recognized guidelines [14, 18]. All clinical endpoints were verified by reviewing medical records when necessary. During the period in each patient's follow-up, the first adverse event occurred was designated as the CVE.

Statistical analysis

Continuous variables were reported either as median with interquartile range or mean ± standard deviation. Depending upon the distribution of data, for continuous variables, differences in baseline characteristics between groups were analyzed utilizing the Mann-Whitney U test or t-test and the Fisher's exact test or chi-squared test expressed: counts with percentages for categorical variables. Based on the median of AIP and GA, the cumulative survival rates free of CVE were evaluated utilizing Kaplan-Meier analysis. This method was significant for estimating the survival function over time and allowed for the comparison of survival rates across different patient groups, effectively accounting for censored data, which enhanced the reliability of findings. Employing the log-rank test, differences between the lower and higher groups were evaluated. Both univariate and multivariate Cox regression analyses were used to assess the predictive values of AIP and GA for CVE. The univariate model evaluated the impact of each variable independently, while the multivariate model accounted for the simultaneous influence of multiple variables, allowing for a more comprehensive understanding of their independent effects on survival outcomes. The fully multivariate Cox regression model included variables such as age, BMI, current smoking, previous MI, previous stroke, previous PCI, T2DM, hypertension, hyperlipemia, LVEF, AIP, GA, TC, creatinine, LDL-C, hs-CRP, SYNTAX score, HbA1c and FBG. These variables were selected based on clinical expertise. TG and HDL-C were excluded as determinants of AIP. The 95% confidence interval (CI) and hazard ratio (HR) for CVE were calculated through treating AIP and GA as both a categorical and continuous variable. When treated as categorical, the lower median of AIP and GA served as the reference. As continuous variables, AIP and GA were normalized using the Z-score method to facilitate intuitive comparison of their predictive values, with HR examined per unit increase in normalized score. In addition, to ascertain the consistent predictive value of AIP and GA across different demographic characteristics and comorbidities, several subgroup analyses were conducted. Moreover, the continuous (linear or non-linear) relationship between AIP/GA and CVE risk was depicted using restricted cubic splines (RCS) based on the above adjusted Cox regression model. Through the application of receiver operating characteristic (ROC) analysis, the AIP and GA diagnostic effectiveness for predicting CVE was evaluated based on baseline risk model. Through using the Z-test, the area under the ROC curves (AUC) was calculated and then compared. Additionally, continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were assessed for determining the AIP and GA incremental value in risk stratification. Statistical analyses were conducted utilizing SPSS (version 23.0), MedCalc (version 20.0), and R software (version 4.3.1). Significance was determined at a two-tailed P-value < 0.05.

Results

Baseline information

The baseline analyses were presented in Tables 1, 2 and 3. 98 patients (7.50%) experienced CVE, which consisted of 16 (1.2%) cardiac death, 70 (5.4%) nonfatal MI, and 19 (1.5%) nonfatal strokes. Among the 1305 patients in this study, the average age was 64.92 ± 7.28 years.

Compared to without CVE, patients experiencing CVE exhibited a markedly higher prevalence of T2DM., previous PCI, hypertension, left main (LM) disease, and DES/DCB use. Additionally, individuals with CVE showed significant higher SBP, TG, AIP, GA, hs-CRP, FBG, HbA1c, and SYNTAX score. Meanwhile, significant lower HDL-C, LVEF, and diameter of stents were indicated in patients with CVE, who also had lower prevalence of one-vessel disease and complete revascularization. Furthermore, the rate of insulin and OAD use at discharge was significantly lower among non-CVE group.

Compared with patients in AIP-L + GA-L group, patients in AIP-H + GA-H group had a significant higher prevalence with hyperlipemia, T2DM, previous PCI, two-vessel disease, chronic total occlusion (CTO) disease, and diffuse lesion. Besides, patients with higher AIP and higher GA showed significant higher age, BMI, TG, TC, LDL-C, Cr, AIP, GA, hs-CRP, FBG, uric acid, HbA1c. Simultaneously, significant lower HDL-C, LVEF, eGFR, and diameter of stents were observed in AIP-H + GA-H group, which also had lower prevalence of one-vessel disease and complete revascularization. What's more, the

Table 1 Baseline characteristics of study patients with and without CVE

Variables	Total ($n=1305$)	Without CVE ($n=1207$)	With CVE ($n=98$)	*P* value
Demographics				
Age, years	64.92 ± 7.28	64.85 ± 7.26	65.79 ± 7.60	0.222
BMI, kg/m^2	25.44 ± 3.30	25.41 ± 3.31	25.87 ± 3.16	0.208
SBP, mmHg	133.08 ± 17.75	132.60 ± 17.35	139.06 ± 21.28	0.001
DBP, mmHg	74.98 ± 10.69	74.90 ± 10.56	75.94 ± 12.22	0.364
Current smoking, n (%)	46 (3.5)	42 (3.5)	4 (4.1)	0.979
Previous smoking, n (%)	21 (1.6)	20 (1.7)	1 (1.0)	0.949
Current drinking, n (%)	14 (1.1)	14 (1.2)	0 (0.0)	0.574
Previous drinking, n (%)	3 (0.2)	2 (0.2)	1 (1.0)	0.547
Family history of CVD, n (%)	94 (7.2)	87 (7.2)	7 (7.1)	1.000
Medical histories, n (%)				
Hypertension	915 (70.1)	828 (68.6)	87 (88.8)	< 0.001
Hyperlipemia	912 (69.9)	835 (69.2)	77 (78.6)	0.067
T2DM	455 (34.9)	400 (33.1)	55 (56.1)	< 0.001
Previous MI	109 (8.4)	100 (8.3)	9 (9.2)	0.905
Previous PCI	293 (22.5)	261 (21.6)	32 (32.7)	0.017
Previous stroke	65 (5.0)	60 (5.0)	5 (5.1)	1.000
Laboratory results				
TG, mmol/L	1.42 [1.04, 1.96]	1.39 [1.03, 1.93]	1.65 [1.17, 2.24]	0.001
TC, mmol/L	4.28 [3.67, 5.03]	4.27 [3.67, 5.04]	4.30 [3.70, 4.87]	0.758
HDL-C, mmol/L	1.17 [1.02, 1.36]	1.17 [1.03, 1.37]	1.05 [0.94, 1.25]	< 0.001
LDL-C, mmol/L	2.46 [1.94, 3.09]	2.46 [1.93, 3.11]	2.50 [2.06, 3.07]	0.800
LVEF, %	65.00 [60.00, 68.00]	65.00 [60.00, 68.00]	63.00 [59.00, 66.00]	0.010
eGFR, mL/min/1.73 m^2	92.19 [84.15, 98.32]	92.20 [84.54, 98.27]	91.75 [78.79, 98.66]	0.305
Cr, mmol/L	57.40 [50.90, 65.50]	57.50 [50.90, 65.05]	57.35 [51.68, 69.52]	0.332
AIP	0.08 [-0.09, 0.25]	0.08 [-0.10, 0.24]	0.19 [0.02, 0.37]	< 0.001
GA, n%	15.40 [14.10, 18.00]	15.40 [14.00, 17.70]	17.75 [14.75, 21.85]	< 0.001
hs-CRP, mg/L	1.42 [0.58, 3.49]	1.38 [0.57, 3.36]	2.12 [1.04, 4.25]	0.002
FBG, mmol/L	5.77 [5.16, 7.31]	5.73 [5.15, 7.18]	6.96 [5.44, 9.81]	< 0.001
Uric acid, μmol/L	302.30 [253.40, 353.10]	301.40 [252.30, 352.75]	313.40 [271.58, 364.10]	0.194
HbA1c, %	6.20 [5.80, 7.10]	6.20 [5.70, 7.00]	7.50 [6.25, 8.55]	< 0.001
Diagnosis on admission, n (%)				
UAP	1140 (87.4)	1061 (87.9)	79 (80.6)	0.054
NSTEMI	81 (6.2)	70 (5.8)	11 (11.2)	0.054
STEMI	84 (6.4)	76 (6.3)	8 (8.2)	0.610
Medications, n (%)				
DAPT	1304 (99.9)	1206 (99.9)	98 (100.0)	1.000
Statin	1293 (99.1)	1195 (99.0)	98 (100.0)	0.659
β-Blocker	820 (62.8)	749 (62.1)	71 (72.4)	0.052
ACEI/ARB	612 (46.9)	559 (46.3)	53 (54.1)	0.169
CCB	483 (37.0)	430 (35.6)	53 (54.1)	< 0.001
Antidiabetic drugs				
Insulin	131 (10.0)	113 (9.4)	18 (18.4)	0.007
OAD	302 (23.1)	263 (21.8)	39 (39.8)	< 0.001
Angiographic data				
LM disease, n (%)	67 (5.1)	57 (4.7)	10 (10.2)	0.033
One-vessel disease, n (%)	454 (34.8)	431 (35.7)	23 (23.5)	0.019
Two-vessel disease, n (%)	471 (36.1)	430 (35.6)	41 (41.8)	0.262
Three-vessel disease, n (%)	380 (29.1)	346 (28.7)	34 (34.7)	0.251
CTO disease, n (%)	225 (17.2)	203 (16.8)	22 (22.4)	0.201
Diffuse lesion, n (%)	478 (36.7)	434 (36.0)	44 (44.9)	0.099
Bifurcation lesion, n (%)	119 (9.1)	108 (9.0)	11 (11.2)	0.570
ISR disease, n (%)	94 (7.2)	80 (6.6)	14 (14.3)	0.009

Table 1 (continued)

Variables	Total ($n=1305$)	Without CVE ($n=1207$)	With CVE ($n=98$)	*P* value
SYNTAX score	11.00 [7.00, 16.00]	11.00 [7.00, 15.00]	13.00 [9.25, 17.88]	0.005
Procedural results				
Target vessel territory, n (%)				
LM	36 (2.8)	31 (2.6)	5 (5.1)	0.249
LAD	671 (51.4)	629 (52.1)	42 (42.9)	0.097
LCX	234 (17.9)	215 (17.8)	19 (19.4)	0.800
RCA	423 (32.4)	388 (32.1)	35 (35.7)	0.539
DES implantation, n (%)	1262 (96.7)	1173 (97.2)	89 (90.8)	0.002
DCB use, n (%)	55 (4.2)	46 (3.8)	9 (9.2)	0.022
IABP, n (%)	9 (0.7)	9 (0.7)	0 (0.0)	0.823
IVUS, n (%)	8 (0.6)	8 (0.7)	0 (0.0)	0.892
OCT, n (%)	9 (0.7)	9 (0.7)	0 (0.0)	0.823
Complete revascularization, n (%)	503 (38.5)	479 (39.7)	24 (24.5)	0.004
Number of stents	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	0.560
Diameter of stents, mm	2.75 [2.50, 3.00]	2.75 [2.50, 3.00]	2.50 [2.44, 3.00]	0.049
Length of stents, mm	23.00 [16.00, 30.00]	23.00 [16.00, 30.00]	23.00 [14.00, 32.00]	0.970

CVE, cardiovascular events; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular diseases; T2DM, type 2 diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; Cr, creatinine; AIP, atherogenic index of plasma; GA, glycated albumin; hs-CRP, high sensitivity C-reactive protein; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin A1c; UAP, unstable angina pectoris; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST segment elevated myocardial infarction; DAPT, Dual antiplatelet therapy; ACEI, angiotensin converting; enzyme inhibitor, ARB, angiotensin receptor blocker; CCB, calcium calcium entry blockers; OAD, oral hypoglycemic drugs; LM, left main; CTO, chronic total occlusion; ISR, in-stent restenosis; SYNTAX, Synergy between PCI with TAXUS and Cardiac Surgery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; DES, drug-eluting stent; DCB, drug-coated balloon; IABP, intra aortic balloon pump; IVUS, intravascular ultrasound; OCT, optical coherence tomography

rate of insulin and OAD use was lower in AIP-L+GA-L group.

Associations of AIP levels and CVE

In the univariate analysis, variables correlated with CVE included previous PCI, T2DM, hypertension, hyperlipemia, AIP, GA, hs-CRP, FBG, HbA1c, and SYNTAX score. As continuous variables for analysis, multivariate Cox regression indicated AIP and GA were independent predictors for CVE (AIP: HR 3.324, 95%CI 1.732–6.365, $P=0.004$; GA: HR 1.098, 95% CI 1.023–1.177, $P=0.009$) (Table 4).

Based on the median level of AIP (AIP-L: AIP<=0.0843, $n=653$; AIP-H: AIP>0.0843, $n=652$), individuals were partitioned into two groups. Depicted in Table 5, CVE rates in AIP-L and AIP-H were 5.4% and 9.7% with significant difference. The Kaplan-Meier survival analysis revealed a rise in CVE occurrences within the higher AIP group (Fig. 2A) (Log-rank $P=0.003$). Regarding individual adverse events, nonfatal MI increased with higher AIP (Fig. 3D) (Log-rank $P=0.027$), while cardiac death (Fig. 3A) and stroke (Fig. 3G) showed no differences in the two AIP groups. After adjusting for BMI, age, current smoking, previous MI, previous stroke, FBG, previous PCI, T2DM, hypertension, hyperlipemia, LDL-C, LVEF, AIP, GA, TC, creatinine, hs-CRP, HbA1c and SYNTAX score, multivariate Cox regression revealed group of AIP-H exhibited a higher CVE risk (HR 1.835, 95%CI 1.214–2.775, $P=0.004$)(Table 5). It was revealed AIP was correlated with the CVE risk positively by RCS curves (P for overall=0.018; Fig. 4A).

Associations of GA levels and CVE

Similarly, based on the median level of GA (GA-L: GA<=15.4%, $n=659$; GA-H: GA>15.4%, $n=646$), individuals were partitioned into two groups. Depicted in Table 5, the CVE rates in GA-L and GA-H were 4.7% and 10.3% with significant difference. Kaplan–Meier analysis revealed CVE increased with higher GA (Fig. 2B) (Log-rank $P<0.001$). Regarding individual adverse events, cardiac death (Fig. 3B), nonfatal MI (Fig. 3E), and stroke (Fig. 3H) increased with higher GA levels (cardiac death: Log-rank $P=0.011$; nonfatal MI: Log-rank $P=0.010$; stroke: Log-rank $P=0.010$). The adjusted HR for higher GA was 2.828 (95% CI 1.491–3.494, $P<0.001$). RCS curves indicated GA was associated with CVE risk positively (P for overall<0.001; Fig. 4B).

Inter-relationship of AIP, GA levels and CVE

To evaluate the interaction between AIP, GA, and CVE, Four groups were stratified among the patients based on levels of AIP and GA: AIP-L+GA-L group ($n=324$), AIP-H+GA-L group, ($n=335$), AIP-L+GA-H group ($n=329$), and AIP-H+GA -H group, ($n=317$). The CVE rates in these groups were 2.8%, 6.6%, 7.9%, and 12.9%, with significant difference (Table 3). When compared with the AIP-L+GA-L group, the AIP-H+GA -L, AIP-L+GA-H, and AIP-H+GA -H groups had 2.004-,

Table 2 Baseline clinical characteristics of patients stratified by the AIP and GA

Variables	AIP-L + GA-L (*n* = 324)	AIP-H + GA-L (*n* = 329)	AIP-L + GA-H (*n* = 335)	AIP-H + GA-H (*n* = 317)	*P* value
Demographics					
Age, years	65.02 ± 7.71	63.84 ± 7.15	65.85 ± 7.08	64.99 ± 7.07	0.005
BMI, kg/m^2	25.25 ± 3.51	25.78 ± 3.15	25.01 ± 3.38	25.73 ± 3.09	0.007
SBP, mmHg	132.11 ± 17.82	131.53 ± 17.49	134.49 ± 18.01	134.23 ± 17.56	0.080
DBP, mmHg	74.86 ± 11.40	75.99 ± 10.45	73.90 ± 10.08	75.16 ± 10.76	0.098
Current smoking, n (%)	10 (3.1)	14 (4.2)	9 (2.7)	13 (4.1)	0.678
Previous smoking, n (%)	2 (0.6)	5 (1.5)	4 (1.2)	10 (3.2)	0.067
Current drinking, n (%)	6 (1.9)	3 (0.9)	2 (0.6)	3 (0.9)	0.445
Previous drinking, n (%)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.6)	0.284
Family history of CVD, n (%)	22 (6.8)	21 (6.3)	23 (7.0)	28 (8.8)	0.614
Medical histories, n (%)					
Hypertension	215 (66.4)	238 (71.0)	232 (70.5)	230 (72.6)	0.355
Hyperlipemia	219 (67.6)	233 (69.6)	216 (65.7)	244 (77.0)	0.011
T2DM	22 (6.8)	23 (6.9)	206 (62.6)	204 (64.4)	< 0.001
Previous MI	25 (7.7)	24 (7.2)	22 (6.7)	38 (12.0)	0.059
Previous PCI	58 (17.9)	55 (16.4)	90 (27.4)	90 (28.4)	< 0.001
Previous stroke	14 (4.3)	15 (4.5)	15 (4.6)	21 (6.6)	0.492
Laboratory results					
TG, mmol/L	1.07 [0.88, 1.27]	1.97 [1.63, 2.54]	1.01 [0.79, 1.19]	1.91 [1.61, 2.64]	< 0.001
TC, mmol/L	4.24 [3.65, 4.90]	4.41 [3.79, 5.14]	4.07 [3.53, 4.83]	4.39 [3.76, 5.12]	< 0.001
HDL-C, mmol/L	1.32 [1.16, 1.50]	1.06 [0.94, 1.20]	1.28 [1.15, 1.49]	1.05 [0.91, 1.17]	< 0.001
LDL-C, mmol/L	2.44 [1.88, 3.12]	2.59 [2.04, 3.15]	2.29 [1.86, 2.95]	2.51 [1.95, 3.09]	0.003
LVEF, %	65.00 [62.00, 69.00]	65.00 [60.00, 68.00]	65.00 [60.00, 68.00]	65.00 [60.00, 67.00]	0.011
eGFR, mL/min/1.73 m^2	94.11 [87.48, 99.74]	92.44 [84.65, 98.21]	91.55 [83.67, 98.17]	90.74 [78.79, 96.95]	< 0.001
Cr, mmol/L	55.80 [49.38, 62.32]	57.70 [50.95, 65.70]	57.40 [50.40, 65.60]	59.50 [53.20, 68.00]	< 0.001
AIP	-0.08 [-0.19, 0.02]	0.25 [0.16, 0.38]	-0.10 [-0.22, -0.01]	0.25 [0.15, 0.41]	< 0.001
GA, %	14.30 [13.50, 14.80]	13.90 [13.20, 14.50]	18.00 [16.20, 21.20]	18.00 [16.30, 21.50]	< 0.001
hs-CRP, mg/L	1.15 [0.49, 2.88]	1.56 [0.65, 3.79]	1.23 [0.50, 2.90]	1.79 [0.76, 3.99]	< 0.001
FBG, mmol/L	5.33 [4.97, 5.82]	5.38 [5.03, 5.92]	6.70 [5.52, 8.51]	7.10 [5.97, 9.27]	< 0.001
Uric acid, μmol/L	286.60 [246.15, 330.35]	321.60 [281.60, 368.90]	277.20 [235.30, 333.20]	317.40 [263.90, 368.10]	< 0.001
HbA1c, %	5.80 [5.50, 6.10]	5.90 [5.60, 6.20]	7.00 [6.20, 8.00]	7.30 [6.50, 8.25]	< 0.001
Diagnosis on admission, n (%)					
UAP	287 (88.6)	289 (87.8)	289 (86.3)	275 (86.8)	0.808
NSTEMI	14 (4.3)	19 (5.7)	24 (7.3)	24 (7.6)	0.281
STEMI	23 (7.1)	27 (8.1)	16 (4.9)	18 (5.7)	0.340
Medications, n (%)					
DAPT	324 (100.0)	334 (99.7)	329 (100.0)	317 (100.0)	0.408
Statin	321 (99.1)	330 (98.5)	327 (99.4)	315 (99.4)	0.605
β-Blocker	187 (57.7)	216 (64.5)	210 (63.8)	207 (65.3)	0.173
ACEI/ARB	139 (42.9)	159 (47.5)	149 (45.3)	165 (52.1)	0.120
CCB	100 (30.9)	131 (39.1)	126 (38.3)	126 (39.7)	0.068
Antidiabetic drugs					
Insulin	8 (2.5)	5 (1.5)	61 (18.5)	57 (18.0)	< 0.001
OAD	18 (5.6)	16 (4.8)	137 (41.6)	131 (41.3)	< 0.001
Angiographic data					
LM disease, n (%)	12 (3.7)	18 (5.4)	17 (5.2)	20 (6.3)	0.513
One-vessel disease, n (%)	136 (42.0)	134 (40.0)	99 (30.1)	85 (26.8)	< 0.001
Two-vessel disease, n (%)	106 (32.7)	100 (29.9)	134 (40.7)	131 (41.3)	0.003
Three-vessel disease, n (%)	82 (25.3)	101 (30.1)	96 (29.2)	101 (31.9)	0.307
CTO disease, n (%)	43 (13.3)	59 (17.6)	51 (15.5)	72 (22.7)	0.012
Diffuse lesion, n (%)	101 (31.2)	115 (34.4)	141 (42.9)	121 (38.2)	0.014
Bifurcation lesion, n (%)	28 (8.6)	36 (10.8)	27 (8.2)	28 (8.8)	0.669

Table 2 (continued)

Variables	AIP-L + GA-L (*n* = 324)	AIP-H + GA-L (*n* = 329)	AIP-L + GA-H (*n* = 335)	AIP-H + GA-H (*n* = 317)	*P* value
ISR disease, n (%)	16 (4.9)	22 (6.6)	30 (9.1)	26 (8.2)	0.175
SYNTAX score	10.00 [7.00, 14.25]	11.00 [7.00, 16.00]	11.00 [7.00, 16.00]	11.50 [7.00, 16.00]	0.250
Procedural results					
Target vessel territory, n (%)					
LM	10 (3.1)	8 (2.4)	8 (2.4)	10 (3.2)	0.892
LAD	181 (55.9)	154 (46.8)	170 (50.7)	166 (52.4)	0.136
LCX	58 (17.9)	68 (20.7)	54 (16.1)	54 (17.0)	0.458
RCA	91 (28.1)	111 (33.7)	118 (35.2)	103 (32.5)	0.237
DES implantation, n (%)	315 (97.2)	319 (97.0)	323 (96.4)	305 (96.2)	0.881
DCB use, n (%)	11 (3.4)	13 (3.9)	13 (4.0)	18 (5.7)	0.499
IABP, n (%)	3 (0.9)	0 (0.0)	5 (1.5)	1 (0.3)	0.088
IVUS, n (%)	0 (0.0)	1 (0.3)	3 (0.9)	4 (1.3)	0.157
OCT, n (%)	3 (0.9)	3 (0.9)	2 (0.6)	1 (0.3)	0.765
Complete revascularization, n (%)	146 (45.1)	140 (41.8)	105 (31.9)	112 (35.3)	0.002
Number of stents	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	0.988
Diameter of stents, mm	2.75 [2.50, 3.00]	2.75 [2.50, 3.00]	2.75 [2.50, 3.00]	2.75 [2.50, 3.00]	0.002
Length of stents, mm	23.00 [18.00, 29.00]	23.00 [16.00, 30.00]	23.00 [16.00, 30.00]	22.00 [15.00, 30.00]	0.892

CVE, cardiovascular events; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular diseases; T2DM, type 2 diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; Cr, creatinine; AIP, atherogenic index of plasma; GA, glycated albumin; hs-CRP, high sensitivity C-reactive protein; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin A1c; UAP, unstable angina pectoris; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST segment elevated myocardial infarction; DAPT, Dual antiplatelet therapy; ACEI, angiotensin converting; enzyme inhibitor, ARB, angiotensin receptor blocker; CCB, calcium calcium entry blockers; OAD, oral hypoglycemic drugs; LM, left main; CTO, chronic total occlusion; ISR, in-stent restenosis; SYNTAX, Synergy between PCI with TAXUS and Cardiac Surgery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; DES, drug-eluting stent; DCB, drug-coated balloon; IABP, intra aortic balloon pump; IVUS, intravascular ultrasound; OCT, optical coherence tomography

Table 3 Comparison of endpoint events stratified by the AIP and GA

Variables *n* (%)	Total	AIP-L + GA-L (*n* = 324)	AIP-H + GA-L (*n* = 329)	AIP-L + GA-H (*n* = 335)	AIP-H + GA-H (*n* = 317)	*P* value
CVE	98 (7.5)	9 (2.8)	22 (6.6)	26 (7.9)	41 (12.9)	< 0.001
Cardiac death	16 (1.2)	1 (0.3)	2 (0.6)	4 (1.2)	9 (2.8)	0.017
Nonfatal MI	70 (5.4)	8 (2.5)	17 (5.1)	18 (5.5)	27 (8.5)	0.009
Nonfatal stroke	19 (1.5)	1 (0.3)	3 (0.9)	5 (1.5)	10 (3.2)	0.018

AIP, atherogenic index of plasma; GA, glycated albumin; AIP-L + GA-L, lower AIP level + lower GA level; AIP-H + GA-L, higher AIP level + lower GA level; AIP-L + GA-H, lower AIP level + higher GA level; AIP-H + GA-H, higher AIP level + higher GA level; MI, myocardial infarction

2.375-, and 4.915-fold higher CVE risks. After factors adjusted, the AIP-H + GA -L, AIP-L + GA-H, and AIP-H + GA-H groups had 2.318-, 2.719-, and 2.929-fold higher CVE risks [HR (95% CI): 2.318 (0.940–3.834), *P* = 0.068; 2.719 (1.145–4.452), *P* = 0.023; 2.929 (1.206–5.117), *P* = 0.018] (Table 5). As illustrated in Fig. 2C, it was shown CVE was highest in G4 among the 4 groups by Kaplan–Meier survival analysis. As for individual adverse events, cardiac death (Fig. 3C), nonfatal MI (Fig. 3F), and stroke (Fig. 3I) was highest in the G4 group among the four groups (cardiac death: Log-rank *P* = 0.016; nonfatal MI: Log-rank *P* = 0.008; stroke: Log-rank *P* = 0.017).

The predictive significance of AIP and GA for CVE in subgroup analysis

After adjusting for multiple factors including covariates performed in adjusted Cox regression model aside from what utilized in stratification, both AIP and GA were significant predictors of CVE across various subgroups. The association between AIP and GA with CVE, stratified by age, BMI, hypertension, T2DM, current smoking, LDL-C, LVEF, hyperlipemia, HbA1c, and type of ACS, was illustrated in Fig. 5.

Incremental effect of the AIP, GA and AIP + GA for predicting CVE

The inclusion of both AIP and GA significantly enhanced the AUC derived from the model of baseline risk, including age, BMI, current smoking, previous MI, previous stroke, hs-CRP, FBG, previous PCI, T2DM, hypertension, LDL-C, hyperlipemia, LVEF, TC, creatinine, HbA1c and SYNTAX score (Table 6; Fig. 6C) (AUC: baseline risk model 0.689 vs. baseline risk model + AIP + GA, 0.738, P for comparison = 0.009). Notwithstanding, the

Table 4 Univariate and multivariate Cox regression analysis for CVE

Variables	Univariate HR	95%CI	*P* value	Multivariate HR	95%CI	*P* value
Age	1.017	0.990–1.045	0.220	1.024	0.986–1.063	0.224
BMI	1.042	0.979–1.108	0.194	0.978	0.903–1.059	0.584
Current smoking	1.218	0.448–3.315	0.699	1.473	0.444–4.883	0.527
Previous MI	1.109	0.559–2.202	0.766	0.789	0.320–1.942	0.606
Previous stroke	1.055	0.429–2.594	0.908	0.928	0.280–3.077	0.903
Previous PCI	1.694	1.110–2.583	0.014	1.920	1.089–3.387	0.024
T2DM	2.496	1.675–3.719	< 0.001	0.862	0.424–1.752	0.682
Hypertension	1.509	1.074–3.569	< 0.001	1.724	1.209–3.137	0.016
Hyperlipemia	1.650	1.018–2.673	0.042	1.056	0.584–1.908	0.858
LVEF	0.970	0.944–1.006	0.120	0.971	0.934–1.009	0.133
AIP	2.920	1.323–5.417	< 0.001	3.324	1.732–6.365	0.004
GA	1.097	1.061–1.134	< 0.001	1.098	1.023–1.177	0.009
TC	0.971	0.796–1.186	0.776	0.869	0.426–1.772	0.699
LDL-C	1.004	0.796–1.266	0.975	1.368	0.599–3.123	0.456
hs-CRP	1.050	1.013–1.089	0.008	1.029	0.974–1.086	0.308
Creatinine	1.013	0.998–1.028	0.097	1.012	0.993–1.032	0.217
FBG	1.136	1.084–1.189	< 0.001	1.049	0.953–1.155	0.326
HbA1c	1.392	1.252–1.546	< 0.001	1.159	0.872–1.539	0.309
SYNTAX score	1.047	1.017–1.077	0.002	1.017	0.978–1.057	0.396

CVE, cardiovascular events; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; T2DM, type 2 diabetes mellitus; LVEF, left ventricular ejection fraction; AIP, atherogenic index of plasma; GA, glycated albumin; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin A1c; SYNTAX, Synergy between PCI with TAXUS and Cardiac Surgery

Table 5 Associations of AIP and GA categories with CVE

Variable	Events, *n*/Total	Unadjusted model HR (95%CI)	*P* value	Adjusted model HR (95%CI)	*P* value
AIP			0.003		< 0.001
Low	35/653 (5.4)	Reference		Reference	
High	63/652 (9.7)	1.835 (1.214–2.775)	0.004	1.592 (1.014-2.500)	0.043
GA			< 0.001		
Low	31/659 (4.7)	Reference		Reference	< 0.001
High	67/646 (10.3)	2.828 (1.491–3.494)	< 0.001	2.253 (1.471–3.452)	< 0.001
Combined categories			< 0.001		< 0.001
AIP-L + GA-L	9/324 (2.8)	References		References	
AIP-H + GA-L	22/329 (6.6)	2.004 (1.361–4.196)	0.006	2.318 (0.940–3.834)	0.068
AIP-L + GA-H	26/335 (7.9)	2.375 (1.093–5.517)	0.029	2.719 (1.145–4.452)	0.023
AIP-H + GA-H	41/317 (12.9)	4.915 (2.389–6.112)	< 0.001	2.929 (1.206–5.117)	0.018

CVE, cardiovascular events; AIP, atherogenic index of plasma; GA, glycated albumin; HR, hazard ratio; CI, confidence interval; AIP-L + GA-L, lower AIP level + lower GA level; AIP-H + GA-L, higher AIP level + lower GA level; AIP-L + GA-H, lower AIP level + higher GA level; AIP-H + GA-H, higher AIP level + higher GA level

independent inclusion of AIP and GA did not substantially improve the AUC of the initial risk model (Table 6; Fig. 6A, B). Moreover, the combined use of AIP and GA markedly enhanced reclassification and discrimination capabilities exceeding those of the model of baseline risk, demonstrating a category-free NRI of 0.359 and an IDI of 0.048, surpassing the individual contributions of AIP or GA alone (Table 7).

Discussion

Main findings

This study pioneered the investigation into the combined predictive efficacy of the AIP and serum GA for CVE in postmenopausal patients with ACS after PCI. Our findings revealed that both GA and AIP, when combined, serve as significant independent predictors of CVE in this specific patient population. The main findings included that: (1) multivariate Cox regression demonstrated both AIP and GA levels independently predicted CVE; (2) cumulative CVE was highest in the AIP-H+GA-H group among the four groups, and after controlling for potential variables, compared to AIP-L+GA-L group, the AIP-H+GA-H groups had 2.929-fold higher risks of CVE; (3) after adjusting for multiple factors, both AIP and GA were significant predictors of CVE across various subgroups; (4) the combination of AIP and GA

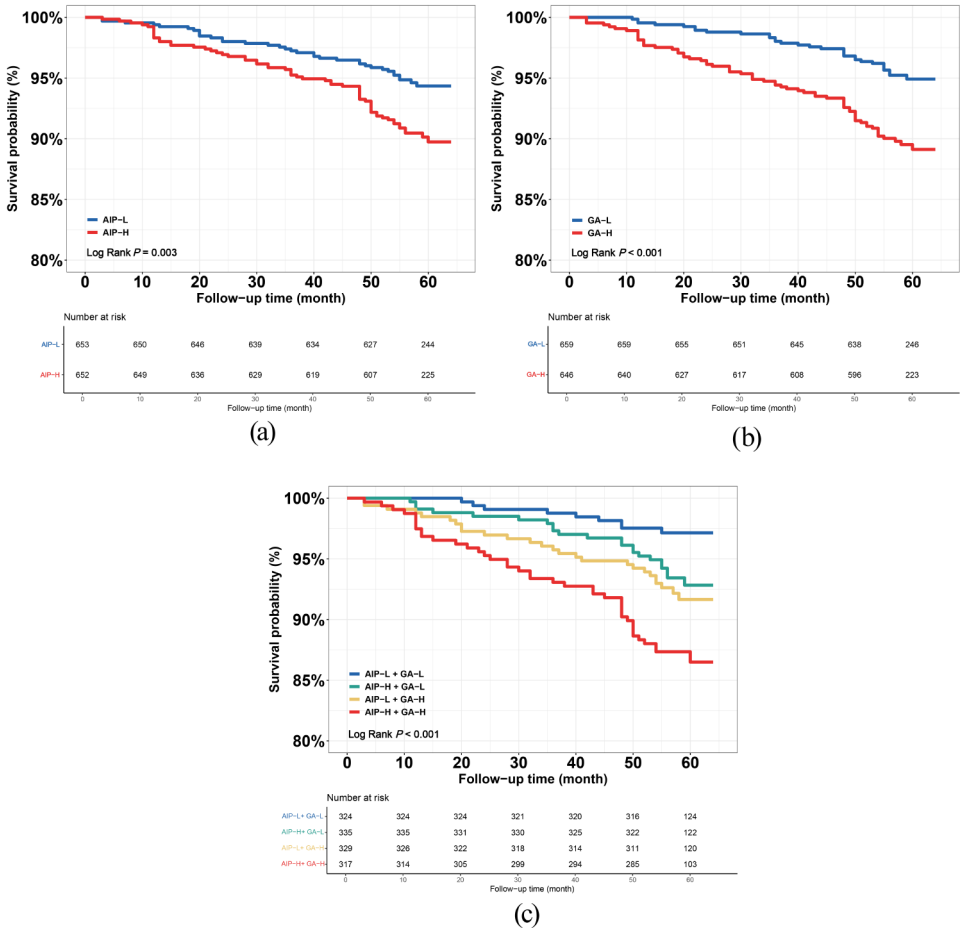

Fig. 2 The event-free survival rate in AIP , GA, and combined groups for CVE. (**A**) Kaplan-Meier curves of AIP for CVE; (**B**) Kaplan-Meier curves of GA for CVE; (**C**) Kaplan-Meier curves of AIP + GA for CVE. AIP, atherogenic index of plasma; GA, glycated albumin; AIP-L + GA-L, lower AIP level + lower GA level; AIP-H + GA-L, higher AIP level + lower GA level; AIP-L + GA-H, lower AIP level + higher GA level; AIP-H + GA-H, higher AIP level + higher GA level

significantly enhanced the AUC derived from the baseline risk model, meanwhile combining AIP and GA levels maximized prognostic accuracy in the baseline risk model. The results underscored the critical importance of considering both lipid and glucose abnormalities, especially in the context of hormonal changes that might heighten cardiovascular risk.

The roles of AIP and GA in atherosclerosis

Atherosclerosis is a systemic and inflammatory disease, where inflammation at the site of atherosclerotic plaques plays a crucial pathophysiological role in acute plaque rupture. Dyslipidemia is one of the most important components of this event chain and exerts a significant influence on the development of coronary atherosclerosis [19]. AIP served as a surrogate for small, dense LDL particles. An elevation in AIP levels indicated a higher likelihood of oxidized particles forming foam cells, leading to an increase in oxidized apolipoprotein B and LDL-C. AIP values maintained at a high level indicated sustained high TG levels and/or relatively low HDL-C levels. Following an increase in TG levels, they competed with glucose for entry into cells, reducing the quantity and activity of insulin receptors on adipocytes, thus preventing insulin from binding to its receptors [20]. Additionally, high TG levels led to an increase in free fatty acids and the formation of toxic lipids, which altered insulin signaling and caused excessive secretion of glucagon [21]. However, low levels of HDL-C decreased cholesterol efflux, leading to the accumulation of cholesterol in pancreatic beta cells, which in turn caused beta cell dysfunction, impaired insulin secretion, elevated blood glucose, and beta cell apoptosis [22, 23]. These potential mechanisms provided a pathophysiological explanation for the association between AIP and atherosclerosis. Moreover, elevated AIP values were directly associated with endothelial dysfunction through promotion of lipid peroxidation, resulting in excessive expression of activation of oxygen free radicals and adhesion molecules. These factors collectively contribute to heightened atherogenicity [24]. In addition to AIP, GA was also a crucial biomarker. It reflected short-term (2 to 4 weeks) glycemic control and may provide

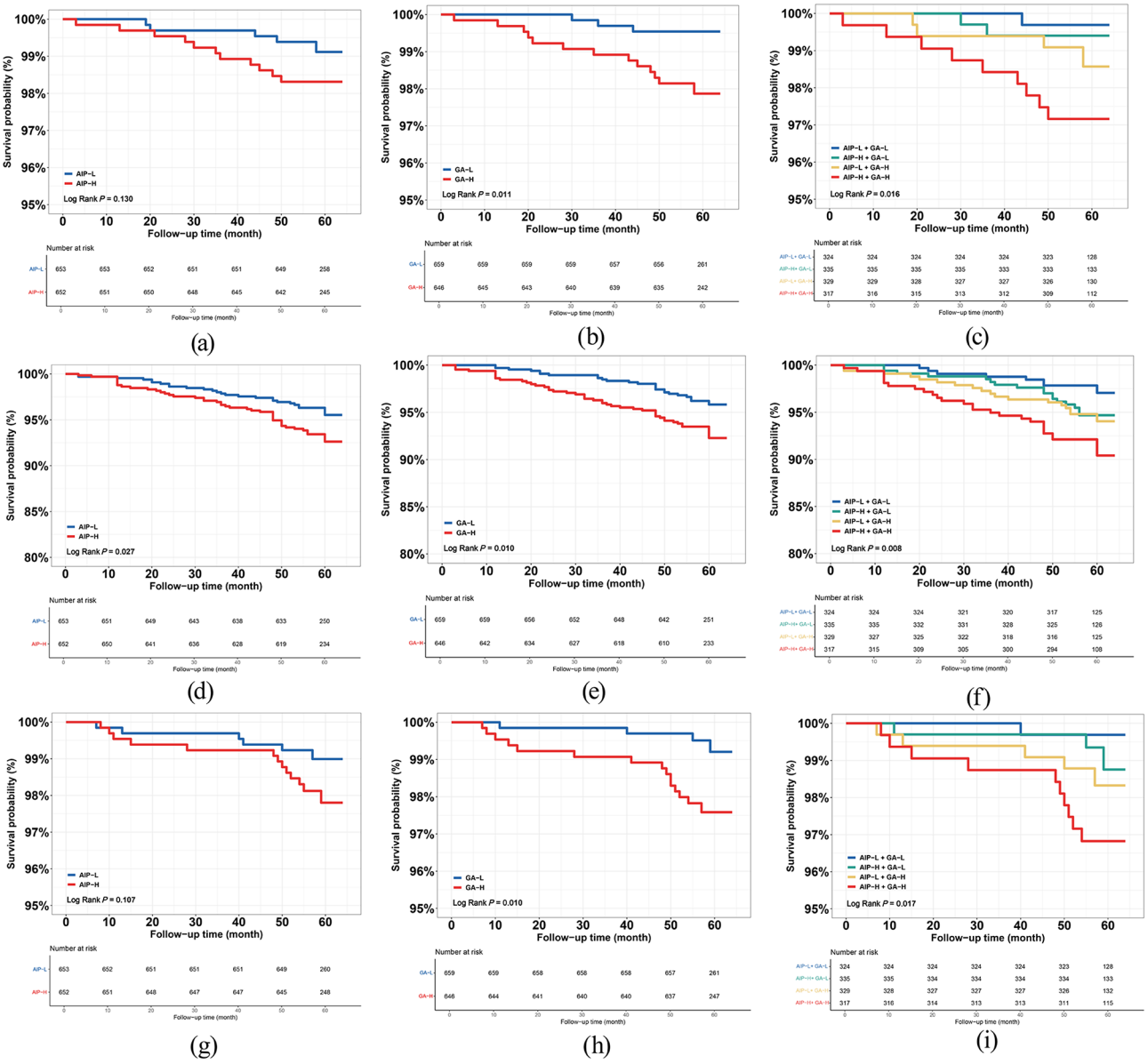

Fig. 3 The event-free survival rate in AIP, GA, and combined groups for the individual adverse events. (**A**) Kaplan-Meier curves of AIP for cardiac death; (**B**) Kaplan-Meier curves of GA for cardiac death; (**C**) Kaplan-Meier curves of AIP + GA for cardiac death; (**D**) Kaplan-Meier curves of AIP for nonfatal MI; (**E**) Kaplan-Meier curves of GA for nonfatal MI; (**F**) Kaplan-Meier curves of AIP + GA for nonfatal MI; (**G**) Kaplan-Meier curves of AIP for nonfatal stroke; (**H**) Kaplan-Meier curves of GA for nonfatal stroke; (**I**) Kaplan-Meier curves of AIP + GA for nonfatal stroke. MI, myocardial infarction; AIP, atherogenic index of plasma; GA, glycated albumin; AIP-L + GA-L, lower AIP level + lower GA level; AIP-H + GA-L, higher AIP level + lower GA level; AIP-L + GA-H, lower AIP level + higher GA level; AIP-H + GA-H, higher AIP level + higher GA level

supplementary information to HbA1c in identifying individuals at risk for diabetes or its complications [25]. Advanced glycation end products (AGE) on albumin played a potential role in atherosclerosis by impairing endoplasmic reticulum function associated with macrophage cholesterol efflux. This process promoted diabetic atherosclerosis through glycation levels in albumin within the body [26]. Additionally, Machado-Lima et al. has found that receptor for AGE (RAGE)-mediated AGE-albumin has detrimental effects on cholesterol efflux in macrophages [27], and Minanni et al. pointed out reducing AGE in albumin can improve cholesterol efflux [28]. Furthermore, Gomes et al. have demonstrated AGE directly contributed to albumin's involvement in atherosclerosis development in dyslipidemic mice. and showed that this effect was independent of the presence of diabetes and partially involves inducing lipid peroxidation and inflammation to modulate the renin-angiotensin system [29]. In the glycation form, albumin not only exhibited changes in its physiological functions but also acquired

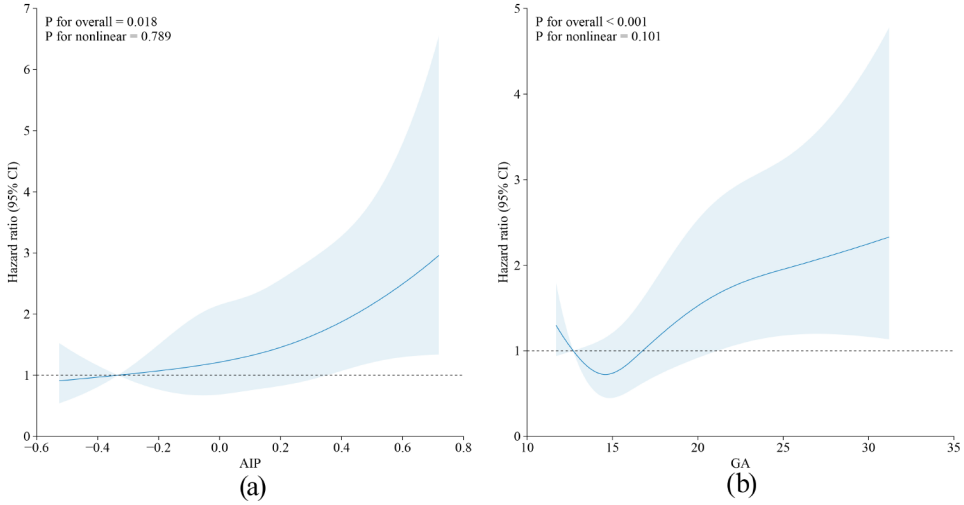

Fig. 4 Restricted cubic spline curves for the association of AIP and GA with the risk of CVE in the adjusted model. (**A**) RCS of AIP for the risk of CVE; (**B**) RCS of GA for the risk of CVE. AIP, atherogenic index of plasma; GA, glycated albumin; CVE, cardiovascular events; RCS, restricted cubic spline. Adjusted model included: age, BMI, current smoking, previous MI, previous stroke, previous PCI, T2DM, hypertension, hyperlipemia, LVEF, TC, creatinine, LDL-C, hs-CRP, SYNTAX score, HbA1c and FBG

Variable	Count	Percent	Forest Plot (AIP)	HR(95% CI)	*P* value	*P* for interaction	Forest Plot (GA)	HR(95% CI)	*P* value	*P* for interaction
Overall	1305	100		1.77(1.17 to 2.68)	0.007			1.69(1.04 to 2.75)	0.034	
Age						0.201				0.656
<65	641	49.1		1.67(1.06 to 2.43)	0.008			1.62(1.02 to 2.54)	0.027	
>=65	664	50.9		2.31(1.25 to 3.47)	0.028			2.05(1.42 to 2.94)	0.045	
BMI						0.865				0.430
<28	1059	81.1		1.79(1.04 to 2.80)	0.012			1.48(1.06 to 2.04)	0.015	
>= 28	246	18.9		1.93(1.24 to 3.05)	0.024			1.96(1.39 to 2.57)	0.047	
Hypertension						0.891				0.143
No	390	29.9		1.88(1.15 to 2.65)	0.031			1.81(1.20 to 2.36)	0.017	
Yes	915	70.1		1.76(1.14 to 2.74)	0.012			1.90(1.13 to 2.88)	0.016	
T2DM						0.985				0.298
No	850	65.1		1.69(1.09 to 2.63)	0.039			1.83(1.36 to 2.34)	0.042	
Yes	455	34.9		1.92(1.05 to 3.05)	0.033			1.95(1.32 to 2.58)	0.019	
Current Smoking						0.053				0.633
No	1259	96.5		1.88(1.03 to 2.64)	0.002			1.60(1.07 to 2.43)	0.046	
Yes	46	3.5		1.94(1.26 to 2.97)	0.025			1.75(1.14 to 2.55)	0.023	
LDL−C						0.569				0.673
<1.8	240	18.4		2.41(1.29 to 3.30)	0.037			1.64(1.14 to 2.11)	0.039	
>= 1.8	1065	81.6		1.68(1.06 to 2.66)	0.028			1.70(1.12 to 2.29)	0.045	
LVEF						0.063				0.883
>=50	1248	95.6		1.71(1.10 to 2.51)	0.002			1.87(1.13 to 2.71)	0.040	
<50	57	4.4		1.96(1.27 to 3.02)	0.040			1.71(1.04 to 2.53)	0.035	
Hyperlipemia						0.745				0.301
No	393	30.1		1.62(1.02 to 2.77)	0.027			1.77(1.26 to 2.27)	0.036	
Yes	912	69.9		1.80(1.12 to 2.88)	0.015			2.04(1.47 to 2.54)	0.012	
HbA1c						0.631				0.887
<7	943	72.3		1.85(1.15 to 2.76)	0.014			1.86(1.26 to 2.27)	0.026	
>= 7	362	27.7		2.01(1.14 to 3.26)	0.016			1.75(1.17 to 2.45)	0.039	
Diagnosis on admission						0.706				0.236
UAP	1140	87.4		1.71(1.08 to 2.71)	0.023			2.36(1.44 to 2.85)	0.001	
STEMI	84	6.4		2.56(1.48 to 3.43)	0.024			2.45(1.81 to 2.96)	0.046	
NSTEMI	81	6.2		1.99(1.19 to 3.07)	0.009			1.99(1.27 to 2.69)	0.049	

Fig. 5 Forest plot illustrating the association of the AIP and GA with the risk of CVE stratified by different subgroups. AIP, atherogenic index of plasma; GA, glycated albumin; CVE, cardiovascular events; BMI, body mass index; T2DM, type 2 diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; UAP, unstable angina pectoris; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST segment elevated myocardial infarction. Adjusted model included: previous MI, previous stroke, previous PCI, TC, creatinine, hs-CRP, SYNTAX score, and FBG

pathological phenotypes. High levels of GA could lead to irreversible damage in various organs and tissues, making it a major target for diabetic complications [30, 31]. Additionally, GA could activate and aggregate platelets, upregulating the expression of adhesion molecules involved in atherosclerotic plaque formation and promoting oxidative processes [32, 33]. As a primary mechanism through which GA exerted its damaging effects, the activation of RAGE subsequently participated in the activation of the production of pro-inflammatory cytokines and growth factors, cell apoptosis, oxidative stress, and pro-thrombotic activity, all of which were pathologically associated with elevated levels of AGE and GA [34, 35]. Hence, assessing the possible impact of AIP and GA as predictive biomarkers may hold substantial clinical relevance for risk assessment in ACS patients. Given their association with atherosclerotic processes, these biomarkers could aid in identifying patients at elevated

Table 6 C-statistics for discrimination ability of various models

	AUC	95%CI	*P* value	Z value	*P* for comparison
Baseline risk model	0.689	0.663–0.715	< 0.001	Reference	Reference
+ AIP	0.719	0.693–0.744	< 0.001	1.896	0.058
+ GA	0.706	0.680–0.732	< 0.001	1.562	0.118
+ AIP + GA	0.738	0.712–0.762	< 0.001	2.621	0.009

AUC, area under the curve; CI, confidence interval; AIP, atherogenic index of plasma; GA, glycated albumin. Adjusted model included: age, BMI, current smoking, previous MI, previous stroke, previous PCI, T2DM, hypertension, hyperlipemia, LVEF, TC, creatinine, LDL-C, hs-CRP, SYNTAX score, HbA1c and FBG

CVE risk, thereby guiding more personalized and effective therapeutic interventions.

The association of AIP and GA with CVE

Based on CHARLS database, a study investigating the connection between AIP and cardiovascular metabolic diseases in mid-aged and elderly populations indicated that dynamic monitoring of AIP is critically important for preventing and managing cardiovascular metabolic diseases, including diabetes, CAD, and stroke [36]. Furthermore, both heightened baseline AIP levels and prolonged AIP levels were associated with an increased risk of MI [37], and the risk of Moreover, a distinct positive association existed between AIP and the in-stent restenosis (ISR) risk in ACS patients [38]. In studies concerning AIP and stroke, both longitudinally updated mean AIP and baseline levels were correlated with stroke and ischemic stroke risks [39]. Regarding studies on AIP in women and menopausal women, AIP was markedly linked to carotid artery plaques in CAD patients, with the stronger

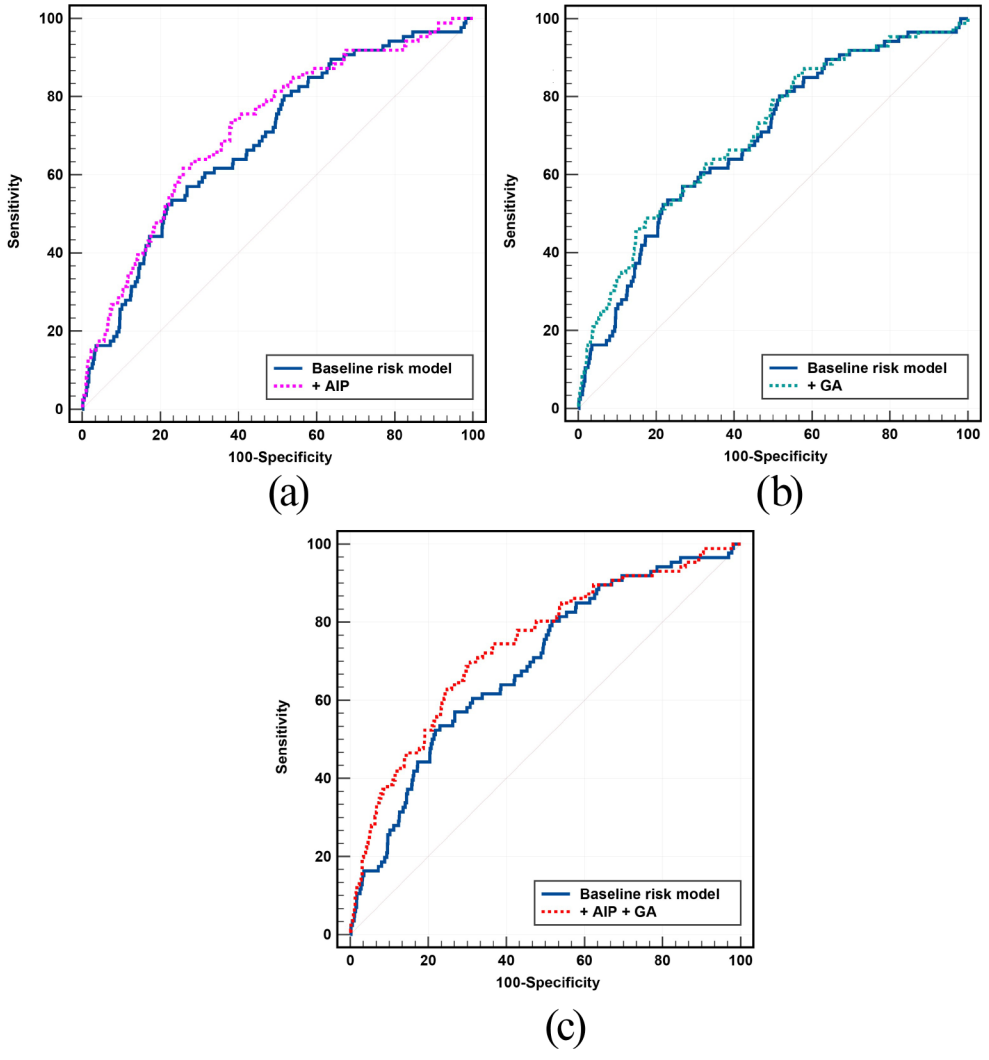

Fig. 6 C-statistics evaluating incremental effect of AIP, GA or AIP + GA beyond baseline risk model. AIP, atherogenic index of plasma; GA, glycated albumin; CVE, cardiovascular events. Baseline risk model included: age, BMI, current smoking, previous MI, previous stroke, previous PCI, T2DM, hypertension, hyperlipemia, LVEF, TC, creatinine, LDL-C, hs-CRP, SYNTAX score, HbA1c and FBG

Table 7 Category-free NRI and IDI for the incremental predictive values of various models

	NRI Index	95% CI	*P* value	IDI Index	95% CI	7*P* value
Baseline risk model	-	-	Reference	-	-	Reference
+ AIP	0.228	0.124–0.381	< 0.001	0.019	0.012–0.066	< 0.001
+ GA	0.276	0.107–0.350	< 0.001	0.024	0.012–0.060	< 0.001
+ AIP + GA	0.359	0.159–0.427	< 0.001	0.048	0.018–0.062	< 0.001

NRI, net reclassification improvement; IDI, integrated discrimination improvement; CI, confidence interval; AIP, atherogenic index of plasma; GA, glycated albumin. Adjusted model included: age, BMI, current smoking, previous MI, previous stroke, previous PCI, T2DM, hypertension, hyperlipemia, LVEF, TC, creatinine, LDL-C, hs-CRP, SYNTAX score, HbA1c and FBG

correlation observed in women compared to men [40]. In a study involving 340 healthy women, AIP was identified as a potential biomarker for early diagnosis of CVE [41]. AIP was linked to all-cause mortality risk independently among elderly women with arterial hypertension, regardless of age, smoking habits, statin therapy, or comorbidities [42]. Meanwhile, there was limited data on the association between GA and CVD risk, and previous studies have been constrained by cross-sectional designs or small prospective studies with limited CVE numbers [43]. Recently, there was increasing research interest in GA. One study found that serum GA was a new predictive marker for forecasting prolonged outcomes in T2DM complicated by stable CAD [44]. Additionally, elevated GA levels were notably linked to the CVD occurrence and its species, even in populations with normal HbA1c levels or without diabetes [45]. Importantly, in low-risk ACS patients undergoing PCI, elevated serum GA levels were correlated with adverse mid-term outcomes particularly among those combined concomitant diabetes [46]. In this study, our findings revealed that elevated AIP and GA, whether assessed continuously or categorically, were correlated with a higher CVE risk. Importantly, this correlation remained significant even after controlling for conventional risk factors. Regarding the imbalance in patient distribution between those without CVE and those with CVE, this imbalance was significant, as it may affect the generalizability of the findings and the statistical power of the analyses. While the data were analyzed by stratifying AIP and GA levels and conducting both univariate and multivariate Cox regression analyses, the presence or absence of CVE was only included in the baseline table. This distribution did not have a substantial impact on the final grouping results.

These findings highlighted that AIP and GA was a robust predictor of CVE independently among postmenopausal patients with ACS undergoing PCI. Moreover, it was indicated a significant correlation between AIP, GA, and CVE by RCS curves. Due to their potential relationship, this study stratified the cohort into 4 groups in compliance with median levels of AIP/GA. Findings demonstrated that patients with elevated levels of both biomarkers had notably increased CVE risks compared to those with lower levels of AIP and GA. What's more, regarding C-statistics and IDI, attaching both AIP/GA to the built model for CVE provided significant incremental value compared to adding either biomarker alone (AIP or GA). This discovery highlighted the benefit of concurrently assessing both biomarkers for precise CVE prediction. As far as we knew, this study represented the initial investigation into the joint prognostic role of AIP and GA in postmenopausal ACS patients undergoing PCI, revealing their combined impact. It was worth noting that factors such as lifestyle behaviors including diet, physical activity, and medication adherence could significantly impact the relationships observed between AIP, GA, and CVE. Although this study did not include sensitivity analyses to specifically address these unmeasured confounders, acknowledging the potential influence of these unmeasured confounders was essential for a comprehensive interpretation of the findings. Future research should consider these factors to enhance the robustness of the conclusions and provide clearer insights into the role of AIP and GA in cardiovascular risk assessment.

The correlation of AIP and GA with T2DM

In the Chinese population aged 45 and older, AIP exhibited a positive connection with the prediabetes and T2DM risk [47]. Additionally, a quantitative study exploring the exact connection between AIP and the prediabetes risk among a large sample population found a linear positive correlation [48]. Meanwhile, GA as a marker reflecting glycemic control, provided crucial information on cardiovascular risk in diabetic patients. Currently, there was no international consensus or recommendation on the clinical application of GA, but mounting evidence supported its use in clinical practice. Therefore, GA was increasingly considered a novel short-term biomarker for diabetes [49]. Previous research has consistently demonstrated a robust correlation between glycated albumin and microvascular conditions, similar in magnitude to that of HbA1c [50]. Due to hormonal changes, postmenopausal women were more prone to lipid abnormalities and glucose fluctuations, further increasing their risk of CVE after PCI. Considering AIP and GA together, where AIP revealed lipid abnormalities and GA provided information on glycemic control, their combined application can more accurately predict CVD risk. This

integrated approach can aid in developing more effective treatment and management strategies to improve patient outcomes.

In clinical settings, the findings regarding the combined predictive value of AIP and GA can be implemented by incorporating these biomarkers into routine cardiovascular risk assessment protocols. This stratification allowed healthcare professionals to assess cardiovascular risk more effectively and tailor prevention strategies accordingly. For instance, patients in the AIP-H and GA-H group were identified as high-risk and could have benefited from more intensive monitoring and early interventions, such as lifestyle modifications or targeted pharmacotherapy. Conversely, those in the AIP-L and GA-L group might have required less aggressive management. The integration of AIP and GA measurements into routine practice could have enhanced risk assessment and improved patient outcomes through personalized treatment approaches.

Strengths and limitations

This study's strength lied in being the first to specifically assess the combined predictive capabilities of AIP and GA for CVE. AIP focused on lipid metabolism, while GA assessed glycemic control. Their combined application can more accurately reflect the overall cardiovascular risk. Therefore, integrating AIP and GA in clinical practice helped in better predicting and managing CVE risks, thereby improving outcomes. This study also had several limitations. Firstly, GA and AIP were assessed using baseline data, which precluded the evaluation of their longitudinal relationships with CVE risk over time. This limitation highlighted the importance of incorporating dynamic data in future studies, as changes in AIP and GA levels over time could have provided deeper insights into their prognostic value and improved risk stratification for CVE. Secondly, potential influences from long-term use of OAD, insulin, antihypertensive, and lipid-lowering medications on lipid and glucose levels could not be omitted. Thirdly, despite adjusting for numerous confounding factors, residual confounding effects, for example dietary habit, cannot be completely ruled out, so causal relationships cannot be established. Fourthly, being a single-center study conducted in a Chinese population, the results of this study may not be generalizable to wider populations, and there might be hospital admission bias. Meanwhile, this study was conducted on Chinese postmenopausal women, which limited the generalizability of the findings to other populations. Future research should aim to include more diverse populations to validate the results and assess their applicability across different demographics. Moreover, further forward-looking, multicenter randomized controlled, large-sample trials could enhance the reliability of our conclusions. Subsequent research should consider these factors to improve the precision and credibility of the findings.

Conclusions

This study found that the combined measurement of AIP and GA can significantly improve the ability to predict CVE after PCI in postmenopausal patients with ACS. The combination of AIP and GA provided a more comprehensive prognosis assessment.

Abbreviations

ASCVD	Atherosclerotic cardiovascular diseases
CVD	Cardiovascular diseases
AIP	Atherogenic index of plasma
CVE	Cardiovascular events
CAD	Coronary artery disease
UAP	Unstable angina pectoris
GA	Glycated albumin
HbA1c	Glycosylated hemoglobin A1c
T2DM	Type 2 diabetes mellitus
NSTEMI	Non-ST segment elevated myocardial infarction
ACS	Acute coronary syndrome
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass grafting
BMI	Body mass index
eGFR	Estimated glomerular filtration rate
MI	Myocardial infarction
STEMI	ST-segment elevation myocardial infarction
OAD	Oral hypoglycemic drugs
TC	Total cholesterol
TG	Triglycerides
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
Cr	Creatinine
hs-CRP	High sensitivity C-reactive protein
FBG	Fasting blood glucose
LVEF	Left ventricular ejection fraction
SYNTAX	Synergy between PCI with TAXUS and Cardiac Surgery
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
CI	Confidence interval
HR	Hazard ratio
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
AUC	Area under the curve
NRI	Net reclassification improvement
IDI	Integrated discrimination improvement
LM	Left main
LAD	Left anterior descending artery
CTO	Chronic total occlusion
AGE	Advanced glycation end product
RAGE	Receptor for advanced glycation end product
ISR	In-stent restenosis

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Author contributions

XXF, QYG and YJZ participated in the study design. XXF, QYG, YL, JQY, SWY, and ZMZ participated in data collection. XXF, JQY and YL performed the statistical analysis. XXF drafted the article. All the authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol strictly adhered to the Declaration of Helsinki. All laboratory tests in this study were reviewed by the Ethics Review Board of the Beijing Anzhen Hospital. All patients signed an informed consent form.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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