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Coronary artery calcification burden, atherogenic index of plasma, and risk of adverse cardiovascular events in the general population: evidence from a mediation analysis

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Abstract

Background Dyslipidemia and abnormal cholesterol metabolism are closely related to coronary artery calcification (CAC) and are also critical factors in cardiovascular disease death. In recent years, the atherogenic index of plasma (AIP) has been widely used to evaluate vascular sclerosis. This study aimed to investigate the potential association of AIP between CAC and major adverse cardiovascular events (MACEs).

Methods This study included 1,121 participants whose CACs were measured by multislice spiral CT. Participants' CAC Agatston score, CAC mass, CAC volume, and number of vessels with CACs were assessed. AIP is defined as the base 10 logarithm of the ratio of triglyceride (TG) concentration to high-density lipoprotein-cholesterol (HDL-C) concentration. We investigated the multivariate-adjusted associations between AIP, CAC, and MACEs. The mediating role of the AIP in CAC and MACEs was subsequently discussed.

Results During a median follow-up of 31 months, 74 MACEs were identified. For each additional unit of log-converted CAC, the MACE risk increased by 48% (HR 1.48 [95% CI 1.32–1.65]). For each additional unit of the AIP (multiplied by 10), the MACEs risk increased by 19%. Causal mediation analysis revealed that the AIP played a partial mediating role between CAC (CAC Agatston score, CAC mass) and MACEs, and the mediating proportions were 8.16% and 16.5%, respectively. However, the mediating effect of CAC volume tended to be nonsignificant ($P=0.137$).

Conclusions An increased AIP can be a risk factor for CAC and MACEs. Biomarkers based on lipid ratios are a readily available and low-cost strategy for identifying MACEs and mediating the association between CAC and MACEs. These findings provide a new perspective on CAC treatment, early diagnosis, and prevention of MACEs.

Keywords Cardiovascular diseases, Coronary artery calcification, Atherogenic index of plasma, Mediation analysis

Introduction

Coronary artery calcification (CAC) is considered a indicator for assessing atherosclerosis, quantifiable through the Agatston method [1]. According to the 2019 ACC/AHA Guidelines for Primary Prevention, the measurement of CAC has been upgraded to a Level IIa recommendation, becoming a reliable tool for personalized cardiovascular disease (CVD) risk management [2, 3]. Traditional prediction tools for CVD risk, such as the

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pooled cohort equation (PCE), rely on conventional risk factors such as age, which may lead to misclassification in risk assessment. The CAC score can help reclassify patients' risk and provide more accurate treatment decision support [4, 5].

In recent years, in addition to the traditional Agatston score, other measurement indicators of CAC, such as the CAC mass, volume, number and distribution area of lesions, have been used and may further improve the accuracy of cardiovascular disease risk prediction via linear quantification [6–8]. However, research on the role of these CAC measurement indicators in evaluating major adverse cardiovascular events (MACEs) is still relatively limited.

Many easily measured biomarkers have been crucial in predicting vascular calcification and cardiovascular disease risk. Triglycerides (TG), total cholesterol (TC), and other plasma lipid profiles have been used by clinicians to assess the risk of CVD [9, 10]. Lipid metabolism disorders are linked to the development of atherosclerosis-related diseases and have become critical therapeutic targets. In 2001, Dobiásová M and colleagues proposed the plasma Atherosclerosis Index (AIP), calculated based on TG levels and high-density lipoprotein cholesterol (HDL-C) levels to assess the pathological degree of vascular sclerosis [11]. Compared with measuring either index alone, the AIP showed greater predictive power for atherosclerosis and cardiovascular events. Moreover, this index is positively correlated with the cholesterol esterification rate, lipoprotein particle size, and residual lipoprotein [12]. AIP has gradually become a key indicator in the field of lipidology, and increased AIP is associated with an increased risk of cardiovascular disease [13–15].Although there is a close interaction between lipids and vascular calcification, research on the relationship between AIP and CAC burden is still limited. In addition, the moderating relationship between AIP in CAC and MACEs risk has not been reported. Therefore, this study aimed to explore the differences in AIP among patients with different CAC loads and analyse the role of the AIP in mediating CAC and MACEs. By investigating the potential relationship between AIP, CAC positive burden and MACE risk, this study provides valuable insights into the underlying mechanisms and offers new targets for early diagnosis and intervention of cardiovascular diseases.

Materials and methods

Study participants

The participants included 4,128 participants who underwent coronary CT angiography at the Affiliated Hospital of Jiangsu University between May 2019 and March 2022. Participants with missing CAC scores, poor imaging, a previous and index hospitalization for percutaneous coronary angioplasty, severe kidney disease, malignancy, blood disease, autoimmune disease, history of coronary stenting, mental illness, missing covariates, and follow-up failure were excluded. Finally, the study included 1,121 participants. This study was approved by the Ethics Committee of the Affiliated Hospital of Jiangsu University (Registration Number: KY2021K1226). Figure S1 shows the study design.

Coronary artery calcium measurements

CAC was measured via a multidetector CT scanner (GE Revolution CT 256, USA). The CAC Agatston score is calculated via a standardized method. The total calcification score was determined by adding the left main artery (LMA), left anterior descending (LAD), left circumflex (LCX), and right coronary (RCA) scores. According to the CT values of the labelled areas, 130–199 HU was assigned 1 point, 200–299 HU was assigned 2 points, 300–399 HU was assigned 3 points, and > 400 HU was assigned 4 points. Multiplied by calcification area (mm^2), the individual scores of each coronary artery segment in each section were added together. The sum of the volume scores of all cross-sectional images is the coronary CAC volume score. Similar to the previous methods for measuring CAC mass [16], the CAC mass was calibrated through a quantitative model of calcification and CAC, and the CAC mass was obtained.

Definition of AIP

As previously reported, the AIP is determined by taking the base-10 logarithm of the TG levels ratio to the molar concentration of HDL-C, represented mathematically as log(TG/HDL-C) [11]. The participants were subsequently grouped based on the quartiles of AIP (Q1 ≤ -0.111; Q2-0.110–0.073; Q3 0.074–0.253; and Q4 > 0.253).

Assessment of covariates

The demographic characteristics and medical history of the participants, including sex, age, height, weight, smoking status, hypertension status, and diabetes status, were recorded. The medication history of the participants, including the use of statins, aspirin, and antihypertensive drugs, was recorded in the personal questionnaire survey. Body mass index (BMI) is assessed based on height and weight (kg/m^2). BMI ≥ 28 kg/m^2 is recognized as obesity [17]. Participants who have smoked over 100 cigarettes will be considered as having a smoking history during their lifetime. For biochemical analysis, all participants underwent venous blood collection of approximately 3 ml after fasting for 10–12 h, and all blood samples were sent to the central laboratory for biochemical analysis, including HDL-C, TC, low-density lipoprotein

cholesterol (LDL-C), serum creatinine (Scr), blood urea nitrogen (BUN), and hemoglobin.

Endpoints and follow-up

The study was followed up with electronic medical records or telephone calls until March 2023. The endpoint was MACEs, including nonfatal myocardial infarction (MI) [18], stroke, target revascularization [19], and all-cause death, which occurred as one or more combined events. Trained researchers recorded all outcome events over the phone until the end of the follow-up.

Statistical analysis

Descriptive statistics are presented as the mean ± standard deviation (SD), median (interquartile range), or frequency (percentage). The baseline characteristics of the CAC group (CAC = 0, 0–99, ≥ 100) and the AIP quartile group were considered. Due to the apparent distribution skew in CAC, the data were logarithmically transformed to base ten before analysis. They were mathematically derived to log(x + 1). Cox proportional hazards regression model was used to test the hazard ratio between CAC burden and MACEs. The model considered age (continuous), sex (male or female), BMI (< 28 or ≥ 28), smoking status (no or yes), hypertension (no or yes), diabetes (no or yes), aspirin (no or yes), statins (no or yes), antihypertensive drugs (no or yes), LDL-C (continuous), TC (continuous), Scr (continuous), BUN (continuous), and hemoglobin (continuous). Similarly, the model was evaluated for the hazard ratio between AIP and MACEs.

Using multivariable Cox regression models, the category-free net reclassification improvement (NRI) was calculated as an exploratory metric to quantitatively assess and compare the predictive abilities of the CAC Agatston score, CAC mass, and CAC volume. The category-free NRI offers a continuous risk scale-based measurement, reflecting the enhancement in classification rates achieved by one model compared with another. More specifically, Model 1 was adjusted for age, sex, BMI, smoking status, hypertension, diabetes, aspirin usage, statin usage, antihypertensive drug usage, LDL-C, TC, Scr, BUN, and hemoglobin. The extension of Model 1 involves incorporating either the CAC Agatston score (Model 2), CAC mass (Model 3), or CAC volume (Model 4) to evaluate their respective predictive contributions. Before the model was entered, Kaplan–Meier event–free survival curves related to CAC were compared via the log-rank test.

The variance inflation factor (VIF) evaluates covariates to avoid multiple multicollinearity [20]. A VIF value < 5 indicates that there is no severe multicollinearity. Restricted cubic splines (RCS) were used to evaluate the relationship between AIP and CAC burden, as well as MACEs.

Then, this study analyzed the mediating function between AIP(mediating variable), CAC(exposure), and MACEs(outcome). In simple terms, this approach involves two regression models: one for modeling the mediating variable and another for modeling the outcome variable [21]. Adopting the bootstrap method to calculate the indirect effect and its significance improved the stability of the indirect effect estimation. The model was adjusted for covariates as described previously. Finally, this study evaluated the mediating effect of CAC (exposure factor) through the components of the AIP (including HDL-C and TG as mediating factors) on the relationship with MACEs (outcome variables). R 3.6.4 software was used for all statistical analyses. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

Finally, this study included 1121 participants, 46.9% of whom were women, with an average age of 62.9 (SD 12.5) years (Table 1). Overall, 572 (51%) participants had a baseline CAC of 0; 244 (21.8%) participants had a CAC of 1–100; and 305 (27.2%) participants had a CAC of ≥ 100. The participants with a high CAC burden were more likely to have high hypertension, diabetes, and lower hemoglobin, TC, HDL-C, and LDL-C levels; more likely to have higher Scr, BUN, TG, and AIP values; and more likely to take antihypertensive drugs, statins, and aspirin. Table 2 shows grouping by quartile of AIP, and the same trend of CAC burden was observed. With increased CAC burden, the LAD CAC, LCX CAC, LMA CAC, and RCA CAC burden increased. CAC quality and CAC volume also increased, and the cumulative number of calcified vessels also increased significantly (Table S1).

Correlation between CAC and AIP in patients

Furthermore, we assessed the correlation between the AIP and calcification. Figure S2 shows that the CAC Agatson, CAC mass, and CAC volume all increase with increasing AIP quartile. Figure 1 shows the distribution of calcification features and AIP density grouped by sex, and the results revealed a strong positive correlation between calcification features. The correlation between the AIP and calcification features was greater in the female population.

Associations between CAC and MACEs in patients

During a median follow-up of 31 months (interquartile range (IQR), 27–35 months), 74 MACEs were identified, including 26 all-cause death events, 25 nonfatal myocardial infarction events, 18 cerebral infarction events, and

Table 1 Baseline characteristics of the study population

Characteristics	Total *n* = 1121	CAC = 0 *n* = 572	0 < CAC < 100 *n* = 244	CAC ≥ 100 *n* = 305	*P*
Age (years)	62.9 ± 12.5	59.4 ± 12.2	64.5 ± 12.2	68.2 ± 11.0	< 0.001
Sex,n(%)					0.064
Female	556 (49.6%)	303 (53.0%)	110 (45.1%)	143 (46.9%)	
Male	565 (50.4%)	269 (47.0%)	134 (54.9%)	162 (53.1%)	
BMI, kg/m^2	24.4 ± 3.5	24.5 ± 3.4	24.2 ± 3.3	24.3 ± 3.7	0.6
Obesity,n(%)	157 (14.0%)	88 (15.4%)	25 (10.2%)	44 (14.4%)	0.15
Smoking status, n(%)[a]	199 (17.8%)	97 (17.0%)	43 (17.6%)	59 (19.3%)	0.7
Diabetes,n(%)	147 (13.1%)	51 (8.9%)	30 (12.3%)	66 (21.6%)	< 0.001
Hypertension,n(%)	637 (56.8%)	278 (48.6%)	150 (61.5%)	209 (68.5%)	< 0.001
SBP,mm Hg	145 ± 23	142 ± 23	147 ± 23	150 ± 22	< 0.001
DBP,mm Hg	87 ± 15	86 ± 15	87 ± 15	88 ± 14	0.3
Hemoglobin,g/L	134.3 ± 19.1	135.7 ± 19.3	136.4 ± 17.6	130.0 ± 19.3	< 0.001
Scr,μmol/L	68.1 ± 18.6	66.8 ± 19.1	68.2 ± 16.7	70.6 ± 18.9	0.004
BUN,mmol/L	5.9 ± 2.0	5.8 ± 2.2	5.6 ± 1.7	6.1 ± 1.7	< 0.001
TG,mmol/L	1.7 ± 1.3	1.8 ± 1.4	1.7 ± 0.9	1.7 ± 1.5	0.5
TC,mmol/L	4.6 ± 1.1	4.6 ± 1.0	4.6 ± 1.0	4.4 ± 1.1	< 0.001
HDL-C,mmol/L	1.4 ± 0.9	1.6 ± 1.2	1.3 ± 0.4	1.2 ± 0.7	< 0.001
LDL-C,mmol/L	2.6 ± 0.8	2.7 ± 0.8	2.7 ± 0.8	2.5 ± 0.9	0.002
Medication Use,n(%)					
Antihypertensive	510 (45.5%)	215 (37.6%)	117 (48.0%)	178 (58.4%)	< 0.001
Statins	568 (50.7%)	210 (36.7%)	154 (63.1%)	204 (66.9%)	< 0.001
Aspirin	442 (39.4%)	165 (28.8%)	117 (48.0%)	160 (52.5%)	< 0.001
AIP	0.1 (-0.1, 0.3)	0.0 (-0.1, 0.2)	0.1 (-0.1, 0.3)	0.2 (0.0, 0.3)	< 0.001

Continuous variables are described as mean ± SD or median (interquartile range)

BMI Body mass index, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *Scr* Serum creatinine, *BUN* Blood urea nitrogen, *TG* Triglyceride, *TC* Total cholesterol, *HDL-C HDL cholesterol* LDL-C LDL cholesterol, *AIP* Atherogenic index of plasma

[a] Current smoking

15 revascularization events. The risk of MACEs per 1000 person-years was significantly greater among women than among men in those with a greater burden of calcification (Fig. 2).

Figure 3 shows the Kaplan–Meier curve for end events classified by CAC. The results revealed significantly lower survival ($P < 0.001$) in the group with a high CAC burden, including CAC Agatston score, CAC mass, CAC volume, and the number of CAC. As is shown in Table 3, for each additional unit of CAC Agatston score, CAC LCX, CAC LAD, CAC LMA, CAC RCA, CAC mass, and CAC volume converted with base 10, the risk of MACEs increased by 48%(HR 1.48, 95% CI 1.32, 1.65), 27% (HR 1.27, 95% CI 1.14, 1.41), 27% (HR 1.27, 95% CI 1.14, 1.41), 39% (HR 1.39, 95% CI 1.25, 1.56), 38% (HR 1.38, 95% CI 1.25, 1.54), 41% (HR 1.41, 95% CI 1.27, 1.56), 73% (HR 1.73, 95% CI 1.5, 1.99), and 57% (HR 1.57, 95% CI 1.38, 1.79), respectively.

Based on the multivariate Cox regression model, when the CAC burden is a continuous variable, the discriminative power and risk reclassification of CAC mass are slightly better than the CAC Agatston score and CAC volume (Figure S3). The category-free NRIs (95% CIs) for the CAC mass, CAC Agatston score, and CAC volume were 0.379 (-0.007–0.881), 0.339 (0.003–0.899), and 0.339 (0.034–1.036), respectively. Additionally, when CAC was treated as a categorical variable, the CAC Agatston score showed slightly better discriminatory power and risk reclassification than CAC mass and CAC volume. The category-free NRIs (95% CIs) for CAC Agatston score, CAC mass, and CAC volume in this categorical analysis were also 0.037 (-0.029–0.512), 0.028(-0.027–0.537), and 0.036(-0.029–0.502), respectively (Table 4).

Associations between AIP and CAC, as well as between AIP and MACEs, in patients

The multivariate generalized linear regression coefficients of CAC and AIP are shown in Table 5. The results indicate that CAC and AIP are positively linearly correlated. Table 6 shows the relationship between AIP and MACE risk. The multivariate adjustment HRs (95% CIs) for the AIP quartiles were 1.00 (reference), 1.95 (0.9–4.24), 1.43

Table 2 Baseline characteristics of the study population by AIP quartile

Characteristics	Quartile of AIP				*P*
	Quartile 1 ≤-0.111	Quartile 2 -0.110–0.073	Quartile 3 0.074–0.253	Quartile 4 >0.253	
Total n	283	277	283	278	
Age(years)	65.0 ± 12.8	62.4 ± 12.8	62.4 ± 11.3	61.8 ± 12.9	0.014
Sex(Male,n%)	118 (42.4%)	141 (50.0%)	149 (53.0%)	157 (56.1%)	0.01
BMI, kg/m^2	23.1 ± 3.3	24.6 ± 3.5	24.8 ± 3.3	25.1 ± 3.5	< 0.001
Obesity,n(%)	18 (6.5%)	41 (14.5%)	49 (17.4%)	49 (17.5%)	< 0.001
Smoking(n%)[a]	35 (12.6%)	53 (18.8%)	57 (20.3%)	54 (19.3%)	0.073
Diabetes,n(%)	31 (11.2%)	31 (11.0%)	38 (13.5%)	47 (16.8%)	0.14
Hypertension,n(%)	129 (46.4%)	153 (54.3%)	177 (63.0%)	178 (63.6%)	< 0.001
SBP,mm Hg	140 ± 22	145 ± 24	148 ± 22	148 ± 24	< 0.001
DBP,mm Hg	83 ± 14	88 ± 14	89 ± 14	88 ± 15	< 0.001
Hemoglobin,g/L	128.8 ± 20.4	134.9 ± 17.6	137.6 ± 17.7	135.9 ± 19.6	< 0.001
Scr,μmol/L	65.1 ± 16.6	69.4 ± 19.6	66.8 ± 16.2	71.0 ± 21.0	0.002
BUN,mmol/L	5.9 ± 2.4	6.0 ± 2.0	5.7 ± 1.7	5.9 ± 1.6	0.3
TG,mmol/L	1.0 ± 0.5	1.6 ± 1.1	1.7 ± 1.0	2.7 ± 1.8	< 0.001
TC,mmol/L	4.6 ± 1.1	4.5 ± 1.0	4.5 ± 1.0	4.6 ± 1.1	0.6
HDL-C,mmol/L	1.9 ± 0.9	1.6 ± 1.1	1.2 ± 0.8	1.0 ± 0.7	< 0.001
LDL-C,mmol/L	2.5 ± 0.8	2.6 ± 0.8	2.7 ± 0.8	2.7 ± 0.9	0.08
Medication Use,n(%)					
Antihypertensive	100 (36.0%)	126 (44.7%)	136 (48.4%)	148 (52.9%)	< 0.001
Statins	127 (45.7%)	142 (50.4%)	133 (47.3%)	166 (59.3%)	0.006
Aspirin	91 (32.7%)	101 (35.8%)	118 (42.0%)	132 (47.1%)	0.002
CAC Agaston	84.1 ± 208.3	105.8 ± 315.9	156.6 ± 343.8	323.6 ± 645.5	< 0.001

Continuous variables are described as mean ± SD or median (interquartile range)

BMI Body mass index, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *Scr* Serum creatinine, *BUN* Blood urea nitrogen, *TG* Triglyceride, *TC* Total cholesterol, *HDL-C HDL cholesterol* LDL-C LDL cholesterol, *AIP* Atherogenic index of plasma, *CAC* Coronary artery calcification

[a] Current smoking

(0.62–3.28), and 3.77 (1.85–7.69). In the dose–response analysis of the whole cohort, AIP was significantly positively correlated with CAC Agatston and MACEs. Risk thresholds were reached at AIP values of 0.08 and 0.09, respectively (Fig. 4). Similarly, the relationships between the AIP and CAC (CAC volume, CAC mass) also showed positive linear correlations (Figure S4).

AIP mediated the association of CAC with MACEs

The mediating function of the AIP in the CAC burden and MACEs risk was explored through causal mediation analysis. Figure 5 shows the mediating model and approach. The results revealed that CAC Agatston score and CAC mass significantly indirectly affected MACE risk through the AIP ($P < 0.05$). It is estimated that 8.16% and 16.5% are mediated by AIP, respectively. However, the mediating effect of CAC volume tended to be nonsignificant ($P = 0.137$). Additionally, this study explored the mediating effects of AIP components, including HDL-C and TG. Although the direct effects were significant for both lipids, the mediating role of HDL-C and TG tended to be nonsignificant (Figure S5 and Figure S6).

Discussion

To the best of our knowledge, this study is the first to report the mediating effect of the AIP between CAC burden and MACEs risk. The findings of this study include the following observations: (1) AIP is associated with CAC incidence, and the optimal threshold for predicting CAC (CAC Agatston score positive) is 0.08. (2) AIP was independently associated with an increased risk of MACEs. (3) AIP significantly mediated the association between CAC and MACE risk. This association was also confirmed when the independent variables were calcification mass and volume.

Coronary artery disease (CAD) is a significant public health problem, resulting in approximately 17.5 million deaths per year [22]. Ischaemic heart disease (IHD), caused by atherosclerosis, is a significant contributor to cardiovascular disease. Studies have shown that the CAC can predict CVD [4, 23, 24]. In addition,

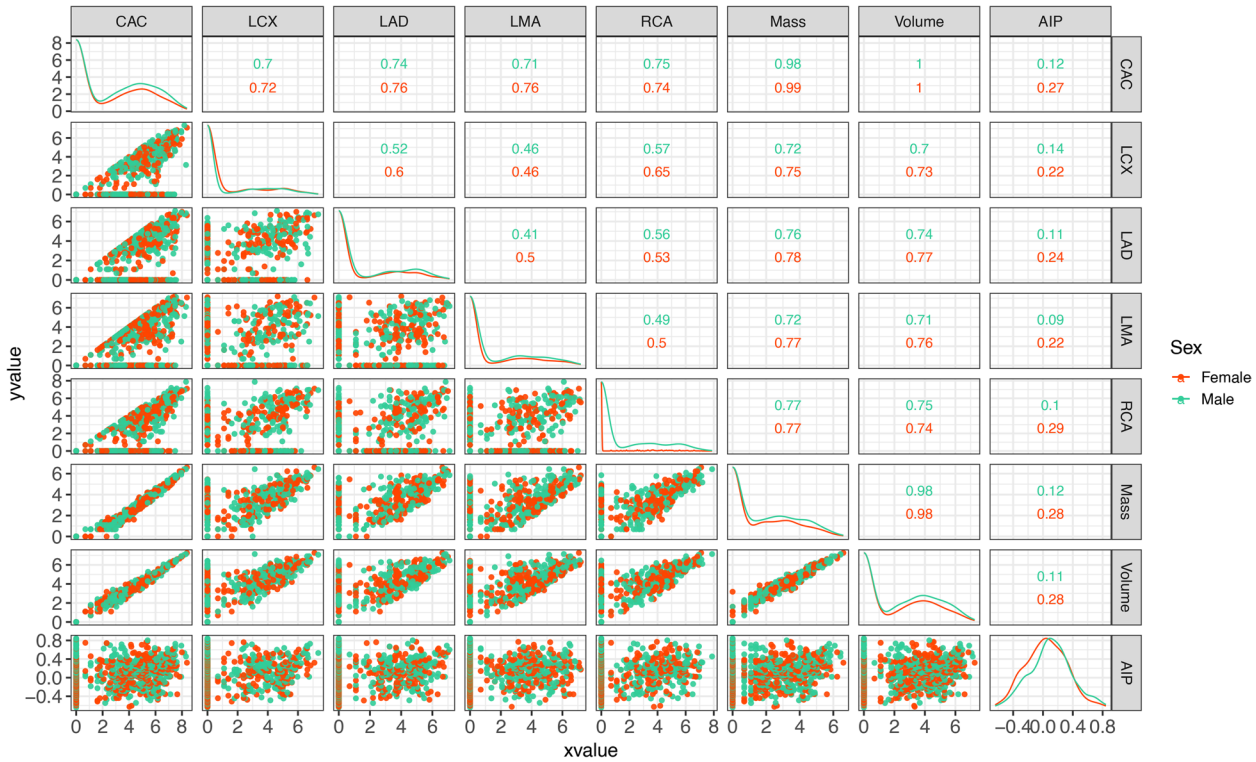

Fig. 1 Correlation between CAC image characteristics and AIP. The correlation between AIP and CAC image features was observed by gender grouping

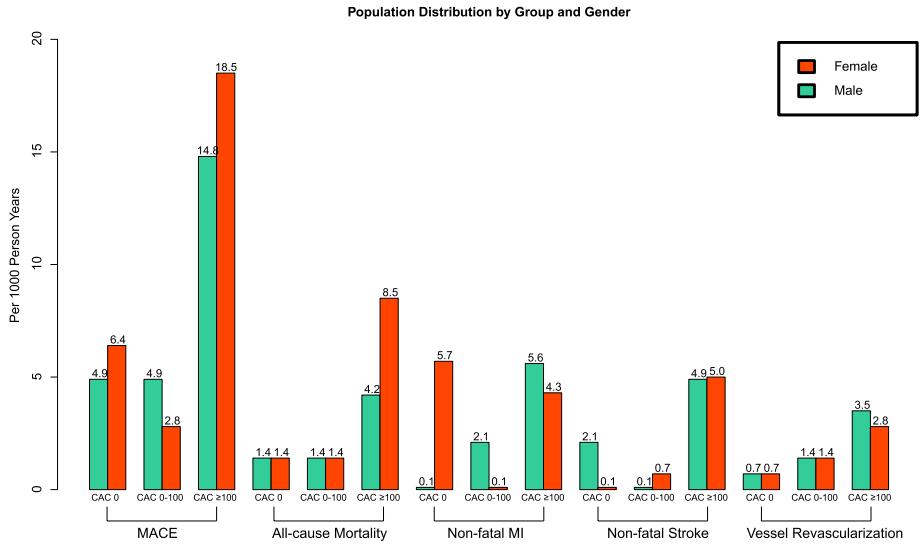

Fig. 2 Incidence of MACEs per 1000 person-years grouped by CAC. The incidence of MACEs, all-cause death, nonfatal myocardial infarction, nonfatal stroke, and target vessel reconstruction were estimated per 1000 person-years. Red bars represent females and green bars represent males

individuals with a CAC score > 10 had a four- to eight-fold increased risk of dying within ten years compared with those with a CAC score of 0 [25]. More importantly, CAC measures can improve risk assessment with traditional methods, which may underestimate those individuals who benefit from early prevention interventions [26, 27]. However, the high cost of coronary CT remains a major economic challenge, especially in

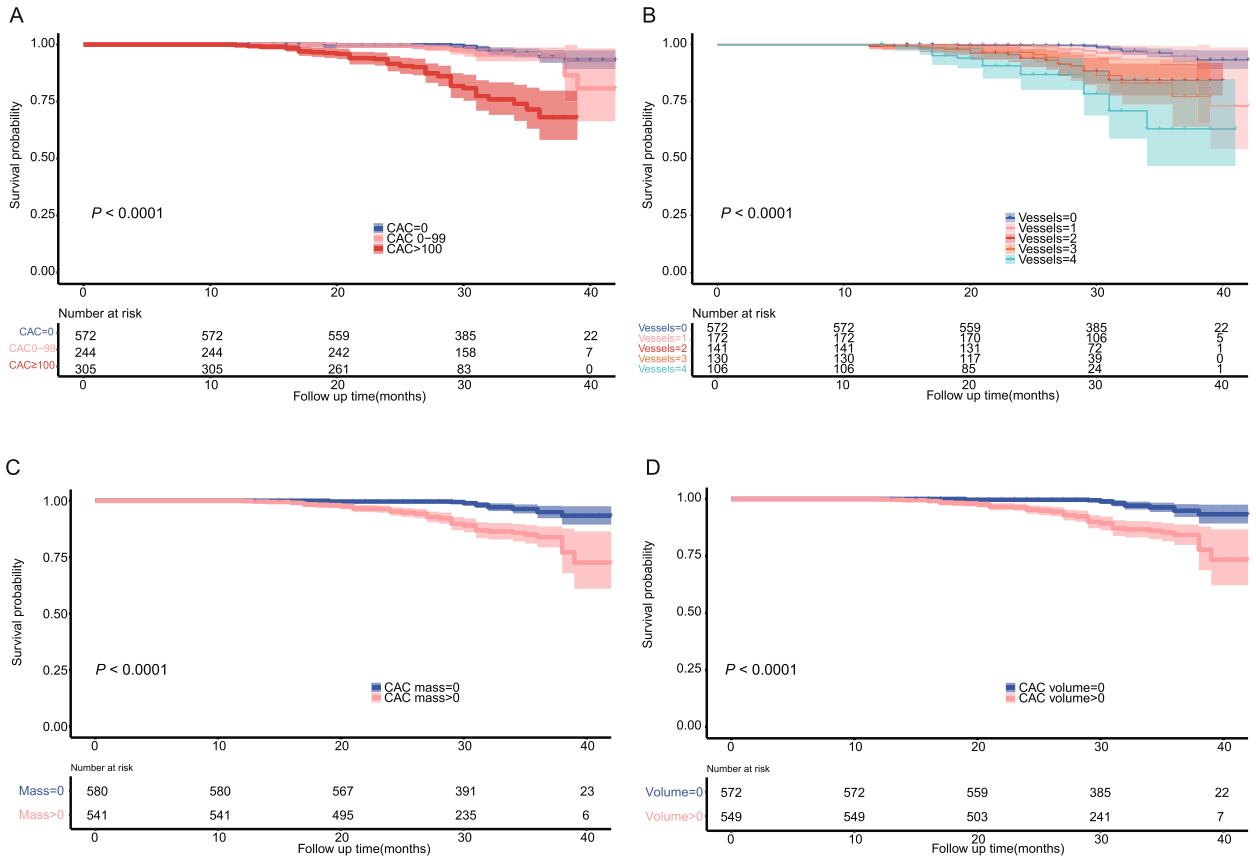

Fig. 3 Kaplan–Meier survival curves show the overall MACEs survival rate in populations with different calcification imaging features. **A** Kaplan–Meier survival curves for MACEs were plotted according to the degree of CAC Agatston burden. **B** Kaplan–Meier survival curve of MACEs was drawn according to the number of vessels with calcification. **C** Kaplan–Meier survival curves for MACEs according to CAC mass or not. **D** Kaplan–Meier survival curves for MACEs according to CAC volume or not

Table 3 Associations of CAC imaging characteristics with MACE

Imaging Characteristics	HRs of Endpoints				
	MACEs	All-cause Mortality	Nonfatal MI	Nonfatal Stroke	Revascularization
CAC Agatson	1.48(1.32–1.65)	1.65(1.34–2.03)	1.33(1.11–1.59)	1.7(1.33–2.17)	1.36(1.04–1.77)
CAC RCA	1.41(1.27–1.56)	1.59(1.34–1.89)	1.3(1.09–1.56)	1.61(1.32–1.98)	1.24(0.99–1.56)
CAC LCX	1.27(1.14–1.41)	1.29(1.08–1.54)	1.4(1.17–1.69)	1.22(0.99–1.51)	1.05(0.83–1.34)
CAC LMA	1.38(1.25–1.54)	1.53(1.28–1.84)	1.27(1.05–1.52)	1.57(1.26–1.96)	1.25(0.98–1.58)
CAC LAD	1.39(1.25–1.56)	1.49(1.23–1.82)	1.33(1.1–1.6)	1.55(1.24–1.94)	1.41(1.09–1.82)
CAC Mass	1.73(1.5–1.99)	2.02(1.56–2.62)	1.52(1.2–1.93)	1.99(1.48–2.68)	1.53(1.08–2.16)
CAC Volume	1.57(1.38–1.79)	1.78(1.4–2.27)	1.41(1.14–1.73)	1.86(1.4–2.47)	1.86(1.4–2.47)

Data are presented as HR (95% CI)

Adjusted for age (continuous), sex (male or female), BMI (< 28 or ≥ 28), smoking status (no or yes), hypertension (no or yes), diabetes (no or yes), aspirin (no or yes), statins (no or yes), antihypertensive drugs (no or yes), LDL-C (continuous), TC (continuous), Scr (continuous), BUN (continuous), and hemoglobin (continuous)

MACE Major adverse cardiovascular events, *CAC* Coronary artery calcification, *LMA* Left main artery, *LAD* Left anterior descending, *LCX* Left circumflex, *RCA* Right coronary artery, *MI* Myocardial Infarction

developing countries, and there is an urgent need for convenient biomarkers for the prediction of cardiovascular events.In recent years, an increasing number of scholars have focused on the biological and lipid markers related to CVD. Early and accurate identification of people at increased disease risk allows for risk

Table 4 Continuous NRI for Multivariable Cox Proportional Hazard Models Comparison

Model	Type NRI	Category-free NRI (95% CI)			
		CAC as continuous variables		CAC as categorical variable	
		Contious NRI	95%CI (Bootstrap)	Contious NRI	95%CI (Bootstrap)
Model 2 vs. Model 1	Total	0.339	0.003–0.899	0.037	-0.029–0.512
	Event	0.464	0.119–0.951	0.093	0.002–0.549
	Nonevent	-0.125	-0.178–0.018	-0.056	-0.113–0.01
Model 3 vs. Model 1	Total	0.379	-0.007–0.881	0.028	-0.027–0.537
	Event	0.476	0.091–0.934	0.089	0.004–0.589
	Nonevent	-0.097	-0.141–0.000	-0.061	-0.115–0.011
Model 4 vs. Model 1	Total	0.339	0.034–1.036	0.036	-0.029–0.502
	Event	0.456	0.134–1.041	0.093	0.002–0.548
	Nonevent	-0.116	-0.165–0.007	-0.056	-0.113–0.01

Model 1 Adjusted for age (continuous), sex (male or female), BMI (< 28 or ≥ 28), smoking status (no or yes), hypertension (no or yes), diabetes (no or yes), aspirin (no or yes), statins (no or yes), antihypertensive drugs (no or yes), LDL-C (continuous), TC (continuous), Scr (continuous), BUN (continuous), and hemoglobin (continuous)

Model 2:Model 1 + CAC Agatston

Model 3:Model 1 + CAC mass

Model 4:Model 1 + CAC volume

Table 5 Linear regression analysis between CAC and AIP

Characteristics	β(95% CI)	*P*
CAC Agatston	0.06(0.05–0.07)	< 0.001
CAC volume	0.07(0.05–0.09)	< 0.001
CAC mass	0.09(0.07–0.11)	< 0.001

Data are presented as β(95% CI)

Adjusted for age (continuous), sex (male or female), BMI (continuous), LDL-C (continuous), Scr (continuous), BUN (continuous), and hemoglobin (continuous)

AIP Atherogenic index of plasma, *CAC* Coronary artery calcification

Table 6 Associations of AIP level with MACE

AIP	HR (95% CI)	*P*
AIP levels		
Q1	Ref	-
Q2	1.95(0 9–4.24)	0.09
Q3	1 .43(0.62–3 28)	0.4
Q4	3.77(1 85–7.69)	< 0.001
AIP(per 1-SD)	1.19(1.1–1.3)	< 0.001

Data are presented as HR (95% CI)

Adjusted for age (continuous), sex (male or female), BMI (< 28 or ≥ 28), smoking status (no or yes), hypertension (no or yes), diabetes (no or yes), aspirin (no or yes), statins (no or yes), antihypertensive drugs (no or yes), LDL-C (continuous), Scr (continuous), BUN (continuous), and hemoglobin (continuous)

AIP Atherogenic index of plasma, *MACEs* Major adverse cardiovascular events

assessment and preventive treatment. As early as 1954, there were reports confirming the relationship between blood lipids and the risk of MI [28, 29]. Since then, research on lipids and atherosclerosis has increased, and lipids have been used as important targets for reducing blood lipids and reducing the risk of CVD [30]. Although a lot of previous data has shown this relationship. However, the correlation was inconsistent [31–36]. While the AIP is a complex biomarker reflecting the balance of TG and HDL-C, impaired TG metabolism is considered a residual risk factor that exceeds the LDL-C level and is closely related to the occurrence of CVD and subsequent adverse clinical outcomes [37–39]. In the past, sufficient epidemiological data have been available to confirm the relationship between AIP and cardiovascular events, such as CVD and MACEs [40–44]. These data are consistent with this study.

The pathogenesis of CAC is very complex, and metabolic disorders and inflammatory responses play a crucial role. Lipid-driven, maladaptive intimal inflammation is an essential feature of atherosclerosis. In a retrospective longitudinal study of 1124 participants, the AIP was closely linked to the progression of CAC [45]. It is worth noting that another study confirmed this view, showing that AIP was a good predictor of CAC progression, mainly among individuals with less severe CAC at baseline (CAC ≤ 100) [46]. Current studies lack the in-depth exploration necessary to assess the link between CAC and MACE at an early stage, and it remains uncertain whether lipid metabolism disorders mediate CAC and MACEs. Based on the analysis and discussion of the results, it is reasonable to speculate that in patients with elevated AIP, improving the reduction of blood lipids can reduce the risk of CVD to some extent, especially for CAC-positive individuals.

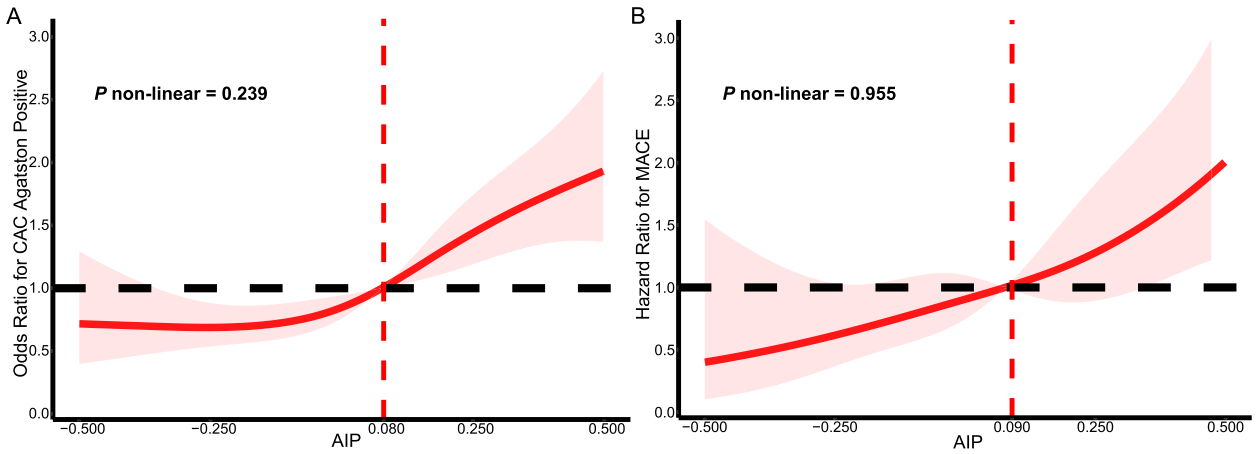

Fig. 4 Association between AIP and CAC, as well as MACEs. **A** Dose–response relationship between AIP and CAC. **B** Dose–response relationship between AIP and MACEs. Ors and HRs were adjusted for age (continuous), sex (male or female), BMI (< 28 or ≥ 28), smoking status (no or yes), hypertension (no or yes), diabetes (no or yes), aspirin (no or yes), statins (no or yes), antihypertensive drugs (no or yes), LDL-C (continuous), Scr (continuous), BUN (continuous), and hemoglobin (continuous). Solid red lines indicate hazard ratios, shaded areas indicate 95% CI

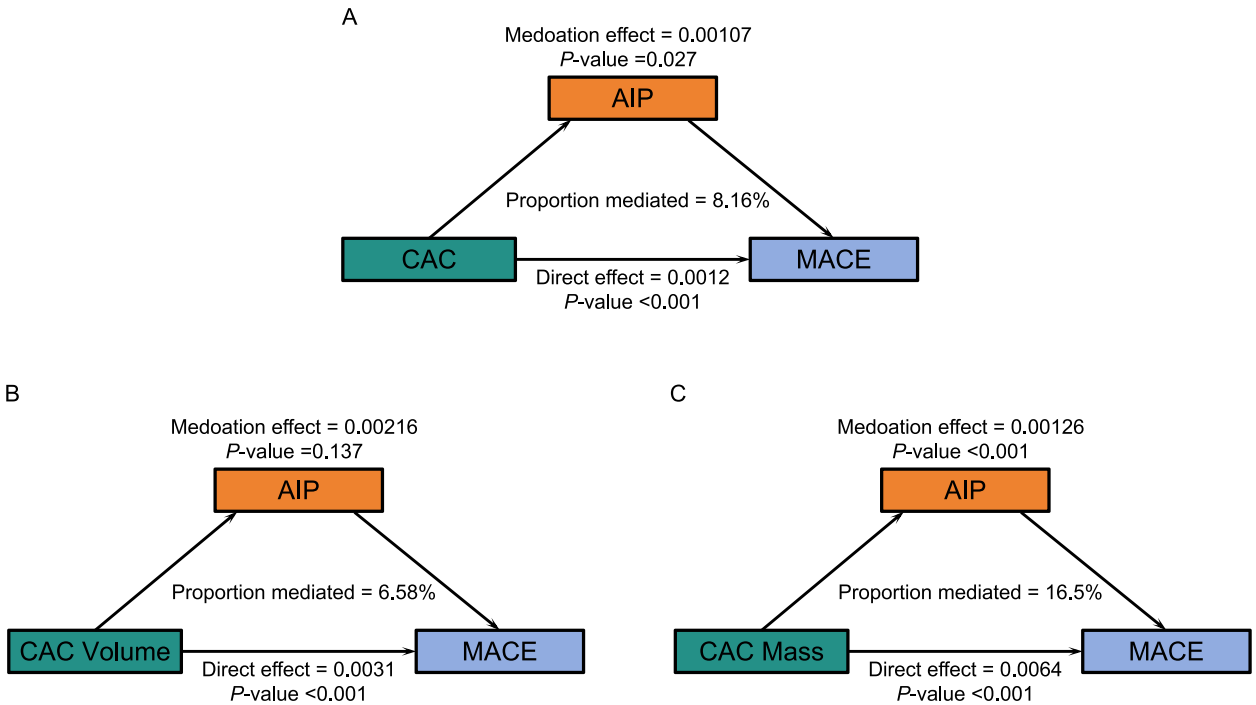

Fig. 5 Mediating effect of AIP in the relationship between CAC and MACEs. Mediating independent variables **A** CAC Agatston; **B** CAC volume; **C** CAC mass. Adjusted for age (continuous), sex (male or female), BMI (< 28 or ≥ 28), smoking status (no or yes), hypertension (no or yes), diabetes (no or yes), aspirin (no or yes), statins (no or yes), antihypertensive drugs (no or yes), LDL-C (continuous), Scr (continuous), BUN (continuous), and hemoglobin (continuous)

Notably, CAC mass, CAC volume, and other measures are also related to the risk of MACEs. The Agatston score to measure the degree of CAC and predict cardiovascular events has limitations because of the difficulty in accurately evaluating small or very-low-density plaques, which may be more dangerous because previous reports have shown that, compared with culprit lesions in individuals with stable angina (SAP), the risk of CAD associated with these small or very low-density plaques is greater. There is a significant association between culprit

lesions in acute coronary syndrome (ACS) patients and low-density or spotty calcification.

In addition, the Agatston score implicitly assumes that the same CAC score is equally predictive of cardiovascular events, regardless of its location in the coronary artery. However, previous results suggest that proximal vascular calcification is more likely to rupture and lead to occlusion than at other sites [25, 47], resulting in more serious consequences. Moreover, distal lesions are more often associated with multivessel disease than with isolated coronary artery disease [48]. The results of a study assessing CAC burden in asymptomatic individuals suggest that the number of CAC, as well as the CAC LMA and CAC LCX, are associated with increased mortality. The CAC Agatston score did not provide additional incremental value in mortality prediction [11]. Therefore, assessing the prognostic value of different sites of calcification and the number of coronary arteries affected by calcification may be more clinically meaningful.

The change in volume score was more minor (9–16%) than the change in Agatston score. Furthermore, it eliminates the assumption that the association between coronary plaque and CVD events is more significant in low-density calcified plaques than in high-density plaques. CAC Agatston and CAC volume do not reflect direct physical measurements of calcification because of the effects of its image post-processing. In contrast, assessing CAC mass allows for a more prepared quantification of CAC and an appreciation of the differences in the way these measurements are made. Mass spectrometry, which measures the absolute mass of the mineral, provides a continuous measurement in milligrams. CAC mass is considered a better measure to replace the Agatston score or CAC volume because it has better accuracy and repeatability when evaluating CAC quantitatively [49, 50]. The mean interscan variability was 9.3%. Our results show that the CAC mass offers a greater additional incremental value than the CAC mass. However, due to the lack of perfect standard references, their wide application in clinical practice and research has not been realized.

Strengths and limitations of the study

This study focused on whether lipid metabolism disorders in CAC disease mediate the relationship between CAC and MACE risk. To our knowledge, this study is the first on this topic to be reported. In addition, this study carefully adjusted for multiple potential confounding factors, including lifestyle and baseline medical history. However, several limitations should also be considered. First, the study participants were from a medical centre with a small number of participants and did not include multiethnic participants. Second, although this study adjusted for statin use, it did not include detailed information about additional lipids. Third, the participants in this study were followed up for a short person-year period, and longer follow-up records are needed. Finally, the included studies were observational, which limits the ability to establish a causal relationship between the AIP and cardiovascular outcomes.

Conclusions

This study revealed that CAC Agatston score, CAC mass, and CAC volume were related to the risk of MACEs. In addition, there was a significant linear positivecorrelation between AIP and MACE incidence. AIP, as a mediating variable, partially mediates the potential effect of CAC on MACE risk.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02255-1.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Authors' contributions

H.Y. and Y.L. collected the data, analyzed the data, and wrote the first draft. G.F. explained the results. C.S. contributed to data validation. Y.C. revised the manuscript. Z.W. conceived the study design.

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Availability of data and materials

The data used in this study may be obtained from the corresponding authors upon reasonable request.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study has been approved by the Ethics Committee of the Affiliated Hospital of Jiangsu University (registration number: KY2021K1226). All participants signed informed consent forms.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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