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The relationship between atherogenic index of plasma and plaque vulnerabilities: an optical coherence tomography study

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Abstract

Background Atherogenic index of plasma (AIP) has been recommended as a marker of plasma atherogenicity. The impact of AIP on plaque characteristics is not fully understood.

Purpose The study investigates the relationship between AIP and coronary plaque features in patients with acute coronary syndrome (ACS).

Methods From January 2016 to June 2017 pre-intervention optical coherence tomography (OCT) was performed in 522 ACS patients. AIP was defined as the base 10 logarithm of the ratio of the concentrations of triglyceride to high-density lipoprotein cholesterol. Patients were divided into four groups according to AIP quartiles.

Results A total of 332 patients were included for the analysis. The prevalence of thin-cap fibroatheroma (TCFA) (group I [lowest] 9.09% vs group II 16.5% vs group III 44.7% vs group IV [highest] 52.9%), macrophage accumulation (group I 18.2% vs group II 22.4% vs group III 31.8% vs group IV 47.1%), plaque rupture (group I 10.4% vs group II 14.1% vs group III 17.6% vs group IV 34.1%) and plaque erosion (group I 2.6% vs group II 2.4% vs group III 14.1% vs group IV 12.9%) were significantly different among AIP quartiles. Multivariate logistic regression revealed the risk of TCFA (odds ratio 11.130, 95% confidence interval 4.186–29.593, $p < 0.001$) and plaque rupture (OR 5.332, 95% CI 2.040–13.937, $p < 0.001$) increased in group IV compared to group I. Receiver operating characteristics curve showed the predictive value of AIP for TCFA and plaque rupture were 0.720 and 0.669 respectively.

Conclusion(s) AIP is an independent predictor for vulnerable plaques beyond traditional factors. It can be integrated in clinical practice for risk stratification of ACS patients.

Trial registration All patients gave their consent to participate in the study and the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University approved it (2020047X).

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Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide, with atherosclerosis being the primary underlying cause of CAD [1]. Hyperlipidemia is a significant risk factor for developing atherosclerosis and coronary artery disease [2]. The Atherogenic Index of Plasma (AIP) is calculated as the logarithm of the ratio between triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C). It can reflect the lipid profile by correlating with the size of lipoprotein particles [3]. AIP has been identified as an independent cardiovascular risk factor [4]. Studies have demonstrated the prognostic role of AIP in arterial stiffness, myocardial infarction and ischemic stroke [5–8]. In diabetic patients, AIP is related with major adverse cardiovascular event risk [9].

Optical coherence tomography (OCT) is an intracoronary imaging technique that uses light waves to capture high-resolution (10–15 μm), cross-sectional images, showing excellent correlation with histological findings [10]. OCT is particularly valuable for the detection and characterization of atherosclerotic plaques [11]. Its ability to provide detailed information of the arterial wall and plaque composition enables clinicians to assess plaque vulnerability, guide interventional procedures, and improve the management of CAD patients [12].

However, there is limited evidence on the association between AIP and atherosclerotic plaque characteristics. Therefore, the present study aims to investigate the relationship between AIP values and plaque vulnerabilities.

Methods

Study design and population

Acute coronary syndrome (ACS) patients who underwent pre-intervention OCT examination were retrospectively recruited from Beijing Anzhen Hospital, between January 2016 and December 2017. Exclusion criteria were leukopenia or thrombocytopenia, severe hepatic or renal dysfunction, ongoing inflammatory or malignant disease, extreme age (<18 or >80 years old), in stent restenosis (ISR), data of HDL-C, TG levels were not available on admission, and poor quality of OCT images. Patients were categorized into four groups based on AIP quartiles. Demographic information, medical history, laboratory test results, and coronary angiography data were collected from medical records for analysis. Hypertension was defined as documented history of hypertension or a systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of ≥ 90 mmHg or anti-hypertension therapy at admission. Diabetes mellitus was diagnosed in a patient who met at least one of the following criteria: documented history of diabetes mellitus, use of hypoglycemia agents, fasting glucose of ≥ 126 mg/dL, 2-h plasma glucose level of ≥ 200 mg/dL in the oral glucose tolerance test, classic symptom with casual plasma glucose level of ≥ 200 mg/dL, or hemoglobin A1c of ≥ 6.5%. Smoking status was identified as current smokers (active smoking within 1 month). To ensure quality and validity, all data were manually extracted. The study received approval from our institution's ethics committee, and written informed consent was obtained from all participating patients.

Intracoronary imaging acquisition and analysis

In all patients, the frequency-domain OCT system (C7-XRTM OCT Intravascular Imaging System, St. Jude Medical, St. Paul, MN, USA) was used for left and right coronary artery system.

OCT image analysis was conducted using an offline review workstation (IlumienOptis, St Jude Medical). Following the current consensus standard for OCT [13], fibrous plaque exhibited high backscattering and a relatively homogeneous signal. Fibrocalcific plaque appeared as a poorly defined signal or a heterogeneous region with a sharply defined border. Fibroatheroma, a type of atherosclerotic plaque with a necrotic core, showed low backscatter and a high attenuation region with a poorly defined edge, covered by a fibrous cap. Thin-cap fibroatheroma (TCFA) was defined as plaque with lipid content spanning more than two quadrants and a fibrous cap thickness (FCT) of ≤ 65 μm. Macrophage accumulation presented as rich signals in distinct or confluent punctate regions, exceeding the intensity of background speckle noise. Microvessels were identified as signal-poor, circular structures with a diameter < 250 μm, observed in more than three consecutive cross-sectional OCT images. Cholesterol crystals appeared as thin, linear, high-intensity regions usually attached to fibrous caps or necrotic cores. Thrombus was identified as a mass located on the luminal surface or floating within the lumen. Plaque rupture was characterized by intimal tearing, disruption, or dissection of the fibrous cap.

The culprit lesion was identified by abnormal manifestations of coronary angiography, electrocardiogram, echocardiography, or left ventricular angiogram if available. In patients with multiple stenoses, the lesion with the most severe stenosis or with evidence of plaque rupture or erosion on OCT (if available) was considered to be the culprit. The identification of culprit and non-culprit lesions were at the discretion of interventional cardiologists. In patients undergoing revascularization, OCT imaging was performed before the intervention of the culprit lesion.

OCT images analysis was performed independently by two readers who were not involved in the data-entry process of baseline information. When there was a discrepancy between the two readers, a third physician would reexam the original OCT images. Twenty patients were

randomly selected to evaluate inter- and intra- observer agreement, as assessed by two independent investigators and by the same investigator at two separate time points with at least a two-week interval, respectively. The inter-observer kappa values for TCFA and plaque rupture were 0.71 and 0.69; The intra-observer kappa values for TCFA and plaque rupture were 0.70 and 0.80.

For each lipidic plaque, FCT was measured 3 times at its thinnest part, and the average value was calculated. Ruptured segments were excluded for FCT measurement due to contradictory identification of the fibrous cap silhouette. Interclass correlation coefficient (ICC) was used to evaluate imaging analysis reproducibility. The inter- and intra-observer ICC values of minimal FCT were 0.978 and 0.992.

Statistical analysis

Continuous data are expressed as mean ± standard deviation (SD) and were compared using the Student's t or Mann–Whitney U test, as appropriate. Test of normality was used for non-parametric/parametric discrimination. Categorical variables are described as absolute numbers or percentages and analyzed using the Chi-square or Fisher exact test as appropriate.

To assess whether baseline characteristics and AIP levels had an impact on TCFA and plaque rupture, multivariable logistic regression model was used to adjust confounders and calculate odds ratios (OR) and 95% confidence intervals (CI). In addition, if more than two risk factors existed, interaction among them was tested. All tests were two-sided, and a p value <0.05 was established as the level of statistical significance for all tests. The predictive value of AIP for TCFA and ruptured plaque was evaluated by receiver operating characteristic (ROC) analysis, based on which the area under the ROC curve (AUC) and optimal cut-off value with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were determined. All data were processed using SPSS version 24.0 software (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

During our study period, there were 2210 patients who presented with acute coronary syndrome underwent PCI procedures at our study center. A total of 305 of these intervention procedures were OCT-guided, and no pre-intervention procedures were permitted for OCT-guided interventions. A total of 332 patients (332 vessels) were included in the analysis (Fig. 1). The clinical characteristics, laboratory testing and coronary angiography data are shown in Table 1.

The mean age of participants was 55.2 ± 12.0 years. Age, serum levels of creatinine, triglyceride, HDL cholesterol,

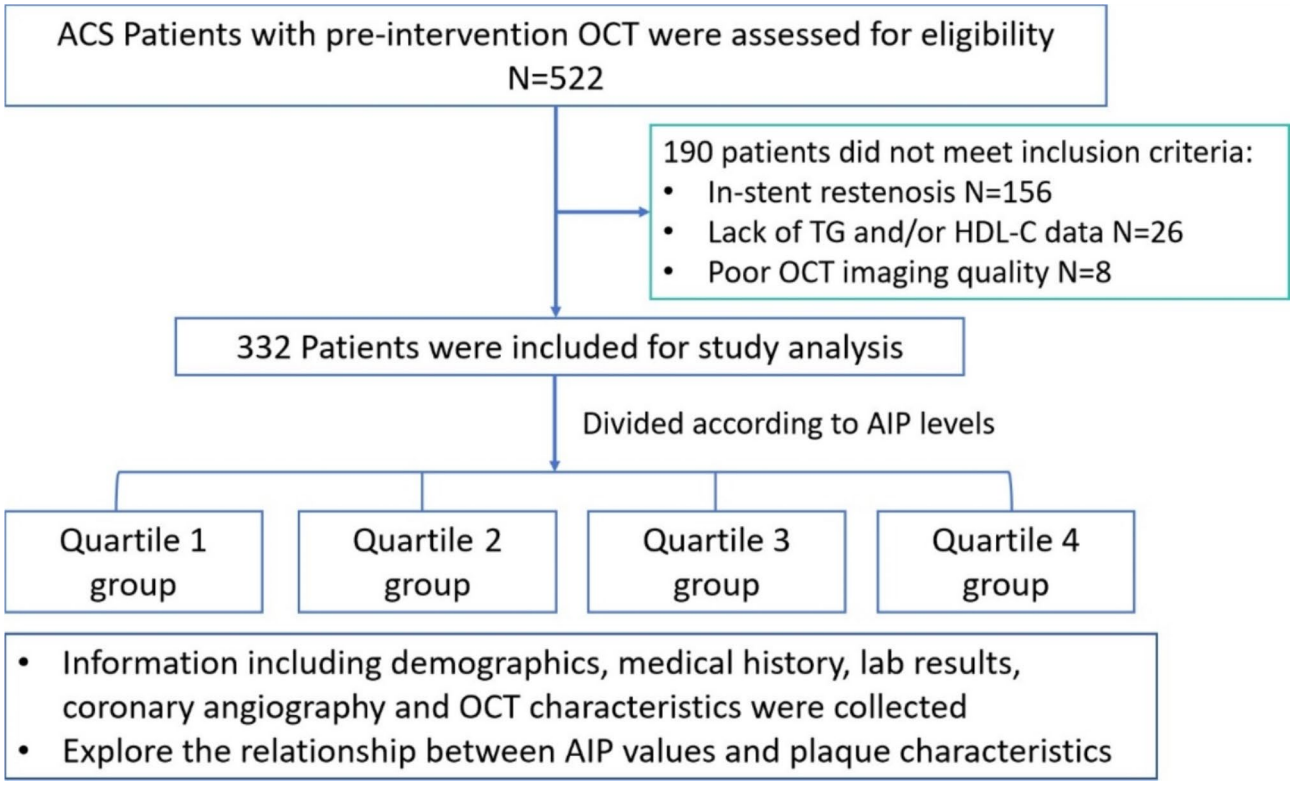

Fig. 1 Study flow chart

Table 1 Baseline characteristics

	Total population N = 332	AIP group				
		Quartile 1 (N = 77)	Quartile 2 (N = 85)	Quartile 3 (N = 85)	Quartile 4 (N = 85)	P value
Female	78 (23.5%)	23 (29.9%)	18 (21.2%)	26 (30.6%)	11 (12.9%)	0.022*
Age (y.o.)	55.2 ± 12.0	58.8 ± 12.8	55.2 ± 11.4	55.6 ± 11.0	51.8 ± 12.1	0.003*
Clinical presentation						0.144
STEMI	39 (11.7%)	6 (7.8%)	13 (15.3%)	14 (16.5%)	8 (9.4%)	
NSTE-ACS	293 (88.3%)	71 (92.2%)	72 (93.5%)	71 (83.5%)	77 (90.6%)	
Hypertension	181 (54.5%)	37 (48.1%)	45 (52.9%)	47 (55.3%)	52 (61.2%)	0.403
Diabetes	99 (29.8%)	11 (14.3%)	26 (30.6%)	33 (38.8%)	29 (34.1%)	0.005*
Smoking	165 (49.7%)	26 (33.8%)	44 (51.8%)	42 (49.4%)	53 (62.4%)	0.004*
Previous PCI	88 (26.5%)	18 (23.4%)	17 (20.0%)	26 (30.6%)	27 (31.8%)	0.244
Creatinine (μmol/L)	4.0 ± 1.0	67.0 ± 13.5	73.2 ± 15.7	72.6 ± 16.4	75.3 ± 14.8	0.007*
HbA1c (%)	1.8 ± 1.6	6.1 ± 1.3	6.3 ± 1.1	6.5 ± 1.0	6.4 ± 1.5	0.402
Total cholesterol (mmol/L)	1.0 ± 0.3	3.9 ± 0.9	3.9 ± 0.9	3.8 ± 1.0	4.3 ± 1.2	0.004*
Triglyceride (mmol/L)	2.3 ± 0.8	0.9 ± 0.2	1.3 ± 0.3	1.8 ± 0.5	3.3 ± 2.6	< 0.001*
HDL-C (mmol/L)	72.1 ± 15.4	1.3 ± 0.3	1.1 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	< 0.001*
LDL-C (mmol/L)	6.3 ± 1.2	2.2 ± 0.8	2.4 ± 0.7	2.2 ± 0.9	2.4 ± 0.7	0.337
Coronary angiography						0.759
LM	4 (1.2%)	0 (0%)	1 (1.2%)	1 (1.2%)	2 (2.4%)	
LAD	183 (55.1%)	39 (50.6%)	52 (61.2%)	50 (58.8%)	42 (49.4%)	
LCX	58 (17.5%)	15 (19.5%)	13 (15.3%)	15 (17.6%)	15 (17.6%)	
RCA	87 (26.2%)	23 (29.9%)	19 (22.4%)	19 (22.4%)	26 (30.6%)	

Definition of AIP quartiles: Quartile 1 AIP < -0.015, Quartile 2 -0.015 ≤ AIP < 0.1795, Quartile 3 0.1795 ≤ AIP < 0.3767, Quartile 4 AIP ≥ 0.3767

Table 2 OCT findings

	Total population (N = 332)	AIP group				
		Quartile 1 (N = 77)	Quartile 2 (N = 85)	Quartile 3 (N = 85)	Quartile 4 (N = 85)	P value
Fibrous plaque	109 (33%)	30 (39.0%)	29 (34.1%)	27 (31.8%)	23 (27.1%)	0.412
Lipid plaque	269 (81.8%)	54 (70.1%)	73 (85.9%)	69 (81.2%)	73 (85.9%)	0.04*
Calcific plaque	154 (46.5%)	40 (51.9%)	42 (49.4%)	35 (41.2%)	37 (43.5%)	0.513
TCFA	104 (31.5%)	7 (9.09%)	14 (16.5%)	38 (44.7%)	45 (52.9%)	< 0.001*
Macrophage accumulation	100 (30.3%)	14 (18.2%)	19 (22.4%)	27 (31.8%)	40 (47.1%)	< 0.001*
Microvessel	69 (21%)	15 (19.5%)	14 (16.5%)	22 (25.9%)	18 (21.2%)	0.482
Spotty calcification	61 (18.5%)	11 (14.3%)	10 (11.8%)	20 (23.5%)	19 (22.4%)	0.127
Thrombus	69 (20.8%)	11 (14.3%)	22 (25.9%)	11 (12.9%)	25 (29.4%)	0.219
Plaque rupture	64 (19.3%)	8 (10.4%)	12 (14.1%)	15 (17.6%)	29 (34.1%)	< 0.001*
Plaque erosion	27 (8.2%)	2 (2.6%)	2 (2.4%)	12 (14.1%)	11 (12.9%)	0.003*
Healed plaque	57 (17.2%)	15 (19.5%)	16 (18.8%)	12 (14.1%)	14 (16.5%)	0.777
minFCT (μm)	99.7 ± 41.6	116.3 ± 50.4	103.1 ± 28.4	92.4 ± 39.2	90.8 ± 44.6	0.002*
MLA (mm^2)	2.2 ± 1.2	2.2 ± 1.3	2.1 ± 0.9	2.3 ± 1.4	2.0 ± 1.1	0.791

MLA, minimal lumen area

total cholesterol, prevalence of diabetes, smoking were significantly different among the AIP quartile groups. Other baseline characteristics showed no statistical difference among groups.

OCT derived plaque characteristics

The OCT findings from each group are summarized in Table 2. Typical OCT images from patients of different AIP groups are illustrated in Fig. 2. The frequencies of plaque vulnerability features (including TCFA, macrophage infiltration, plaque rupture and plaque erosion) increased as the AIP value increased. Minimal FCT value was also significantly different among the 4 groups. There was no significant difference in the prevalence of calcific plaque, micro-vessel, spotty calcification, thrombus and healed plaque.

Multivariate analysis findings

To assess the impact of AIP value on TCFA and plaque rupture, multivariate regression analyses were

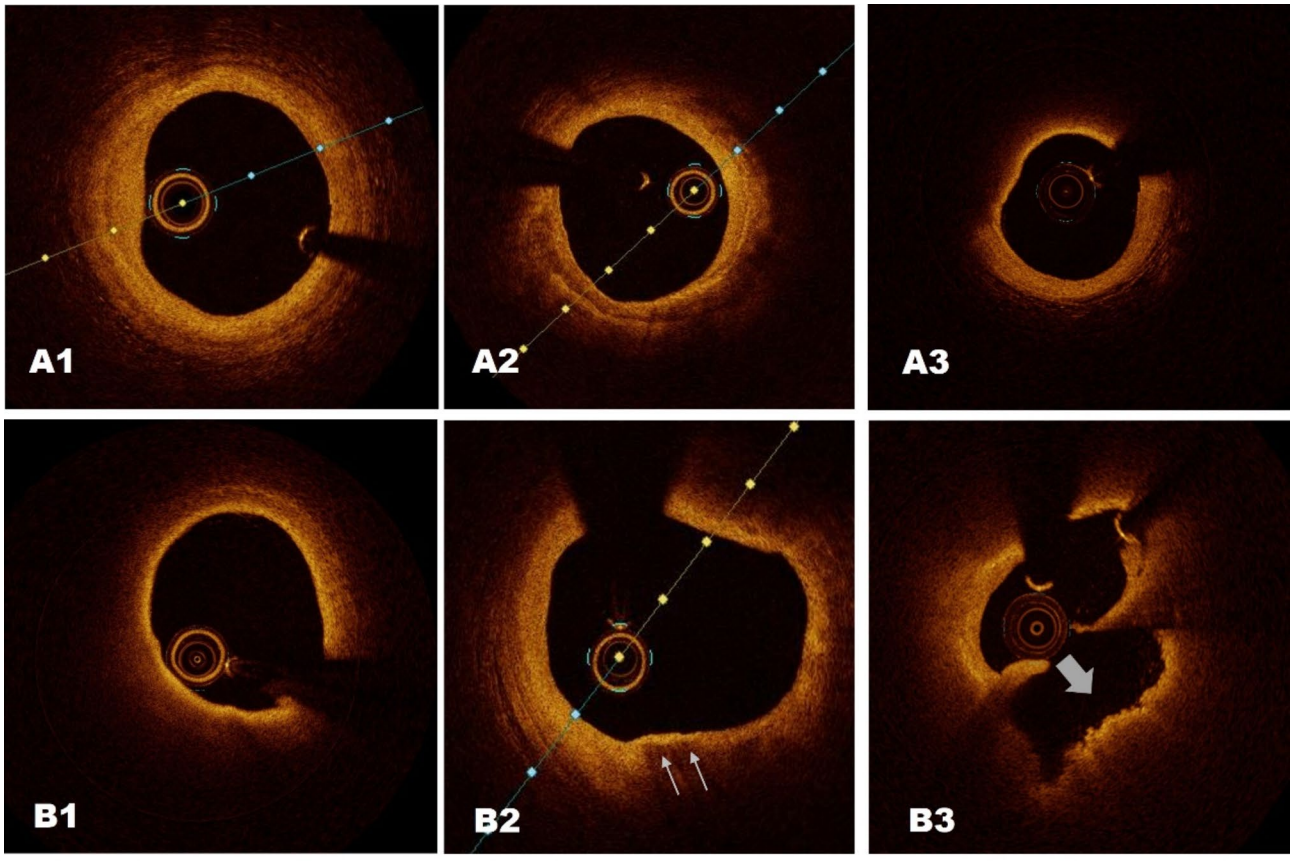

Fig. 2 Representative OCT figures. **A**: typical images from patients in quartile 1 group; A1 fibrotic plaque, A2 calcific plaque, A3 lipid plaque **B**: typical images from patients in quartile 4 group; B1 TCFA, B2 macrophage infiltration, with arrows pointing at the macrophages, B3 plaque rupture, with arrow pointing at the captivity formed by the plaque rupture

Table 3 Multivariate analysis of AIP values and plaque vulnerabilities

TCFA Multivariate model		
AIP group	**OR (95% CI)**	**P value**
Quartile 1, < -0.015	Reference	Reference
Quartile 2, [-0.015, 0.1795)	1.436 (0.515–4.003)	0.49
Quartile 3, [0.1795, 0.3767)	8.132 (3.109–21.273)	< 0.001
Quartile 4, ≥ 0.3767	11.130 (4.186–29.593)	< 0.001
Plaque rupture Multivariate model		
AIP group	**OR (95% CI)**	**P value**
Quartile 1, < -0.015	Reference	Reference
Quartile 2, [-0.015, 0.1795)	1.448 (0.533–3.928)	0.468
Quartile 3, [0.1795, 0.3767)	1.931 (0.716–5.207)	0.193
Quartile 4, ≥ 0.3767	5.332 (2.040–13.937)	< 0.001

Adjusted for age, sex, diagnosis, diabetes, hypertension, smoking, LDL-C and creatinine

performed. We included risk factors that's been reported to impact plaque vulnerability in the regression analysis. Age, sex, diagnosis, diabetes, hypertension, smoking, history of revascularization LDL-cholesterol, creatinine and AIP values were included in the analyses. As shown in Table 3, higher AIP values are independently associated with increased presence of TCFA and plaque rupture.

Predictive value of AIP for plaque vulnerability

Based on ROC curve analyses (Fig. 3), the optimal cut-offs for AIP were 0.186 for lesions with TCFA presence and 0.305 for plaque rupture prevalence. AUC values for TCFA and plaque rupture were 0.720 and 0.669, respectively. The sensitivity, specificity, positive predictive value, and negative predictive values for TCFA prediction were: 0.798, 0.629, 49.1%, 87.1%.

The sensitivity, specificity, positive predictive value, and negative predictive values for plaque rupture prediction were: 0.578, 0.692, 31.1%, 87.3%. We also performed ROC curve analyses for TG and HDL-C respectively. The predictive values of TG for TCFA and plaque rupture were 0.339 and 0.636; The predictive values of HDL-C for TCFA and plaque rupture were 0.661 and 0.648.

To further validate the predictive value of optimal AIP cut-off values for TCFA and plaque rupture, we divided the patients into higher AIP and lower AIP groups according to the optimal cut-off points respectively. After adjusting for confounding factors including age, sex, diagnosis, diabetes, hypertension, smoking, history of revascularization, the OR of higher AIP was 6.666 for

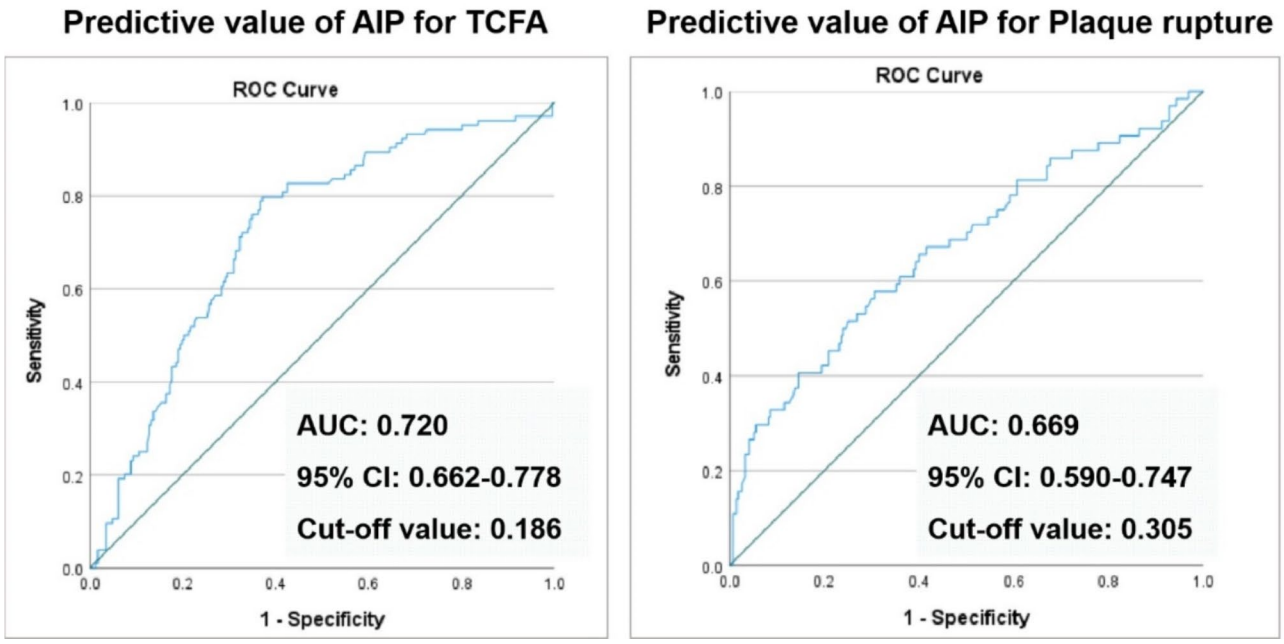

Fig. 3 Predictive value of AIP for plaque vulnerability characteristics

TCFA (95% CI 3.754–11.837) and 3.244 for plaque rupture (95% CI 1.786–5.893) compared with lower AIP.

Discussion

The present study explored the relationship between AIP and plaque vulnerabilities defined by OCT in patients with acute coronary syndromes. Our study indicates that (1) Patients with higher AIP levels have increased prevalence of TCFA, macrophage accumulation, plaque rupture and plaque erosion; (2) AIP is an independent associated factor for TCFA and plaque rupture; (3) the ROC curves showed that AIP has high predictive value for TCFA and plaque rupture.

Dyslipidemia plays a critical role in the progression of atherosclerotic plaque [14]. The instability and potential rupture of these plaques are central to the development of acute cardiovascular events. Atherogenic index of plasma reflects the imbalances between triglycerides and HDL cholesterol, both of which are critical in atherogenesis. AIP correlates with the size and density of lipoprotein particles, with a higher index suggesting a predominance of smaller, denser, more atherogenic particles [15].

Abundant research has demonstrated that AIP is a better predictor of cardiovascular risk compared to traditional lipid measurements alone. Elevated AIP was found to be positively and independently associated with mortality risk in an elderly population [16]. In a recent meta-analysis, elevated AIP was associated with increased risk of cardiovascular death, revascularization, no-reflow phenomenon, and stent thrombosis in patients diagnosed with coronary artery disease [17]. AIP is also a valuable marker for assessing cardiovascular risk in individuals with diabetes. Diabetes is often associated with dyslipidemia, which contributes to an increased AIP in diabetic individuals. AIP was proven to be an independent predictor for CAD risk in diabetic patients [18]. In diabetic patients, AIP independently influenced prognosis, being associated with an increased risk of MACEs, all-cause mortality, cardiovascular death, and non-fatal myocardial infarction [9]. Another study found that in diabetic patients undergoing PCI, higher levels of the AIP was related to more MACCEs and was not affected by LDL-C levels [19]. In prediabetic individuals with unstable angina, elevated AIP was linked to adverse cardiovascular outcomes [20].

Existing studies have shown that higher AIP values are predictive of an increased risk of atherosclerosis. Rapid coronary plaque progression measured by coronary CTA was proven to be independently correlated with elevated AIP values [21]. Another study revealed that higher AIP levels was associated with higher coronary artery calcium scores, indicating more extensive atherosclerotic plaque burden [22]. In terms of carotid artery atherosclerosis, increased carotid intima-media thickness has been linked to higher AIP values [23]. A cross-sectional study also showed that AIP was independently associated with symptomatic carotid artery stenosis [24].

Vulnerable plaques are a specific type of atherosclerotic plaque prone to rupture, leading to thrombus formation and subsequent acute cardiovascular events such as heart attacks and strokes. Pathology studies revealed

the features of vulnerable plaques, which were characterized by thin fibrous cap, large lipid core and increased inflammation [25]. Intravascular ultrasound studies have provided robust evidence indicating that TCFA was associated with adverse cardiovascular outcomes [26]. OCT has unprecedented high resolution and can provide visualization of coronary microstructures. Previous OCT studies have described the in vivo characteristics of vulnerable plaques and spatial distribution of thin cap fibroatheromas as major precursors to plaque rupture [27]. The presence of TCFA detected by OCT was also shown to be a predictor of subsequent rapid plaque progression [28, 29].

To the best of our knowledge, our study is the first one to illustrate the association between AIP levels and plaque characteristics determined by OCT. The prevalence of TCFA, macrophage accumulation, plaque rupture and plaque erosion differed significantly in different AIP groups. Our study demonstrated that AIP was an independent associated factor for TCFA and plaque ruptures. Pathology and imaging studies have confirmed that plaque rupture and plaque erosion are the primary causes of acute coronary syndrome [30]. The role of inflammation in plaque instability has been thoroughly investigated. Macrophage infiltration is more common at sites of plaque rupture compared with non-ruptured sites [31]. Previous studies showed a link between AIP and cardiovascular risk, and our research suggests that AIP may influence clinical outcomes by altering plaque properties.

Triglycerides play an indirect yet significant role in the development of atherosclerotic plaques [32, 33]: High levels of triglycerides often correlate with smaller, denser LDL particles, which are more prone to enter arterial walls, become oxidized, and trigger inflammation. Triglyceride-rich particles can also activate inflammatory pathways. When triglyceride remnants are retained in the arterial walls, they attract immune cells like monocytes and macrophages. These cells ingest oxidized lipoproteins and become foam cells.

HDLs have been proven to involve in athero-protective actions [34, 35]: HDLs can exhibit anti-inflammatory and anti-oxidant effects during the early stages of atherosclerosis; During the midstage of atherosclerosis, HDL can promote cholesterol efflux from plaque macrophages and emigration of macrophages to local draining lymph nodes.

AIP is calculated as the ratio of triglyceride to HDL, therefore higher AIP levels indicate the imbalance between these two properties. We assume that AIP reflects the integrated influence of pro-atherosclerotic and athero-protective actions, which could explain our study findings. However, our present study cannot provide solid evidence for the conclusion. Therefore, future research is needed to validate our hypothesis.

Limitations

The present study has several limitations. Firstly, this is a retrospective, observational, single center study, therefore selection bias is not adjusted. However, the baseline characteristics showed no significant differences among groups except for lipid profiles, diabetes, and creatinine. Secondly, patients' treatment before hospitalization was not available, so we cannot rule out the effects of different therapies on the study results. Due to lack of lipid lowering treatment information, we could hardly perform a sensitivity analysis for patients with and without statins usage. There was also lack of baseline information about patients' BMI, hs-CRP, LP(a) in our study. Thirdly, follow up data of these patients are not available. Future studies are required to investigate the impact of AIP on clinical outcomes.

Conclusions

Increased AIP is an independent associated factor for TCFA and plaque rupture. AIP values can predict plaque vulnerability features. Our research suggests that AIP has additive value for predicting atherosclerosis progression and plaque instability risk.

Abbreviations

AIP	Atherogenic index of plasma
ACS	Acute coronary syndrome
OCT	Optical coherence tomography
TCFA	Thin-cap fibroatheroma
CAD	Coronary artery disease
TG	Triglycerides
HDL-C	High-density lipoprotein cholesterol
CTO	Chronic total occlusion
ISR	In stent restenosis
SD	Standard deviation
OR	Odds ratios
CI	Confidence intervals
ROC	Receiver operating characteristic
FCT	Fibrous cap thickness
MACE	Major adverse cardiovascular events
PCI	Percutaneous coronary intervention
HbA1c	Glycated haemoglobin
LM	Left main
LAD	Left anterior descending artery
LCX	Left circumflex artery
RCA	Right coronary artery
MLA	Minimal lumen area

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Author contributions

SJW as the first author was responsible for the study design, data acquisition, image analysis, manuscript completion; ZJW and YJZ were responsible for the study design and draft revision; YNG, WL and RTW were responsible for image acquisition and analysis; QM, JYS, WH,SJ et al. made contributions to data acquisition.

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Availability of data and materials
The datasets generated and analyzed for the study are available from the corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Clinical Research Ethics Committee of Beijing Anzhen Hospital, Capital Medical University, and all patients were informed and agreed to participate in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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