

Multimodal Cardiovascular Risk Discrimination: Clinical, Biochemical, and Doppler Ultrasound Insights from a Contemporary Atherosclerotic Cardiovascular Disease Cohort

ABSTRACT

Background: Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of global morbidity and mortality, underscoring the need for improved early detection strategies for preclinical atherosclerosis. This study evaluated comprehensive multimodal cardiovascular risk predictors—clinical, biochemical, and vascular imaging parameters—in dyslipidemic adults without established ASCVD.

Methods: A total of 847 adults underwent standardized clinical assessment, laboratory profiling, and duplex-based vascular imaging, including carotid intima-media thickness (IMT), plaque assessment, flow-mediated dilation (FMD), and ankle-brachial index. Statistical analyses included multivariate logistic regression, receiver operating characteristic (ROC) curve analysis, model calibration metrics, and correlation matrices using Pearson or Spearman tests as appropriate. High-density lipoprotein cholesterol (HDL-C) exhibited a strong inverse correlation with AIP ($r = -0.57, P < .001$).

Results: Triglycerides (TG) demonstrated a strong positive correlation with the atherogenic index of plasma (AIP) ($r = 0.80, P < .001$). Moderate correlations were observed between age and left ventricular mass index ($r = 0.31, P < .001$), age and fibrinogen ($r = 0.32, P < .001$), HbA1c and TG ($r = 0.26, P < .001$), and HbA1c and AIP ($r = 0.30, P < .001$). ASCVD and atherosclerosis total score positivity were independently associated with age, HbA1c, IMT, and FMD in multivariable analyses, while model discrimination remained robust (area under the curve values reported).

Conclusion: Multimodal integration of clinical, biochemical, and vascular imaging markers provides meaningful refinement of cardiovascular risk stratification and may enhance early detection of preclinical ASCVD.

Keywords: Atherosclerosis, Duplex ultrasound, dyslipidemia, preclinical vascular disease, risk discrimination

INTRODUCTION

Despite advances in preventive and therapeutic measures, atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality worldwide. Coronary artery disease (CAD) and stroke account for nearly half of all cardiovascular deaths, and projections suggest a further rise in disease burden until 2050, driven mainly by aging populations and the growing prevalence of metabolic syndrome, obesity, and hypertension.¹⁻⁴ These trends underscore the need for improved risk estimation models to optimize prevention and reduce global health impact.

Conventional risk factors such as age, sex, smoking, DM, hypertension, dyslipidemia, and heart failure (HF) form the cornerstone of ASCVD discrimination but often lack accuracy, particularly for patients at intermediate risk. Novel contributors, including biochemical markers and vascular imaging, may provide added value for individual risk stratification.⁵⁻⁸

Emerging evidence highlights the prognostic role of markers such as glycated hemoglobin (HbA1c), C-reactive protein (CRP), fibrinogen, and the atherogenic

ORIGINAL INVESTIGATION

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index of plasma (AIP), reflecting metabolic and inflammatory pathways of atherosclerosis. In parallel, vascular imaging—especially duplex ultrasonography—has proven effective for detecting preclinical disease. Parameters such as carotid intima-media thickness (IMT) and plaque burden are recognized predictors of future myocardial infarction (MI) and stroke, offering complementary information to conventional scores.⁹⁻¹⁵

In Türkiye, the high prevalence of hypertension, dyslipidemia, and metabolic risk factors has drawn attention to the limitations of traditional risk scores and the potential added value of new biomarkers and imaging techniques. However, limited evidence exists on the combined prognostic value of clinical, biochemical, and imaging measures in dyslipidemic populations. Therefore, the present study aimed to assess the prognostic significance of clinical, biochemical, and duplex ultrasound (DUS) parameters in predicting ASCVD, and to determine the prevalence and predictors of preclinical atherosclerosis in dyslipidemic patients without clinically evident CAD.¹⁶⁻²⁴

METHODS

Study Population

This cross-sectional study included 950 consecutive patients diagnosed with dyslipidemia between January 2019 and March 2025. Patients with established CAD, defined as a history of MI or obstructive CAD on angiography not previously revascularized, were excluded. Inclusion criteria were as follows: age 30 years or older and a signed informed consent form. Of 950 screened patients, a total of 847 consecutive dyslipidemic adults without overt CAD were included in this contemporary cohort study. Patients with missing clinical, biochemical, or vascular imaging data were excluded to ensure analytic consistency. Patient selection and exclusion are summarized in the flowchart (Figure 1).

All participants underwent standardized clinical evaluation, anthropometric measurements, blood sampling, and vascular imaging.

Data Collection

All individuals were submitted to a comprehensive clinical examination including an extensive medical history and

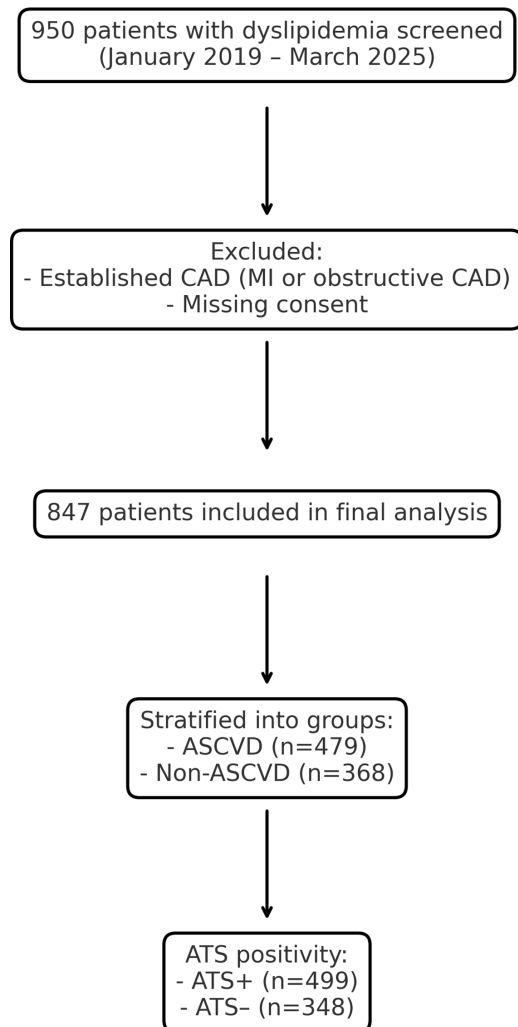


Figure 1. Flowchart of the study population. A total of 950 patients with dyslipidemia were screened. After exclusions, 847 participants were included in the final analysis.

anthropometric measures [body mass index (BMI), waist circumference (WC), neck circumference (NC)], as well as hemodynamic parameters such as blood pressure [systolic (SBP), diastolic (DBP), and mean arterial pressure (MBP)] and pulse pressure (PP). Smoking status; history of DM, hypertension, and HF; chronic kidney disease (CKD); and family history of cardiovascular disease (FH of CVD) were recorded.

Clinical and Anthropometric Assessment

Height, weight, BMI, WC, and NC were recorded by trained clinicians.

Blood pressure (systolic, diastolic, mean arterial pressure, and PP) was measured after ≥ 10 minutes resting in a seated position.

Biochemical Measurements

Venous blood samples were analyzed for lipid profile [low-density lipoprotein cholesterol (LDL-C), HDL-C, triglycerides] [Total cholesterol (TC), LDL-C, HDL-C, triglycerides], HbA1c, thyroid-stimulating hormone (TSH), and high-sensitivity CRP (hs-CRP).

HIGHLIGHTS

- Cross-sectional study of 847 dyslipidemic patients evaluating clinical, biochemical, and imaging predictors of atherosclerotic cardiovascular disease (ASCVD).
- Male sex, older age, diabetes mellitus, chronic kidney disease, heart failure, and revascularization independently predicted ASCVD and major adverse cardiovascular events.
- Duplex ultrasound positivity (ATS+) was a strong indicator of systemic atherosclerosis.
- Final models achieved good discrimination (area under the curve up to 0.855) and acceptable calibration.
- Supports a multimodal, patient-centered approach to cardiovascular risk stratification.

Standardized enzymatic assays traceable to international reference methods were used.

Echocardiographic Assessment

Transthoracic echocardiography was performed in accordance with the American Society of Echocardiography's recommendations. Parameters collected were left ventricular mass index (LVMI), relative wall thickness (RWT), and ejection fraction (EF); LVMI was indexed to body surface area.

Vascular Ultrasound Assessment

Carotid IMT, presence of carotid plaque, flow-mediated dilation (FMD), and ankle-brachial index (ABI) were assessed using DUS.

Measurements were obtained following international consensus recommendations.

The carotid IMT was measured at the distal 1 cm of the common carotid artery, in plaque-free segments, as the distance between the lumen-intima and media-adventitia interfaces. A mean IMT value ≥ 0.9 mm or the presence of a focal luminal protrusion >1.5 mm was classified as carotid plaque.

Ankle-brachial index was assessed as the ratio of SBP at the posterior tibial/dorsalis pedis arteries to the higher of the right or left brachial systolic pressure. An ABI <0.9 was considered abnormal, reflecting peripheral arterial disease, while values >1.40 were indicative of non-compressible vessels.

Flow-mediated dilation of the brachial artery was measured using standard protocols. The diameter of the brachial artery was recorded at rest and 1 minute after cuff release following 5 minutes of suprasystolic occlusion. Flow-mediated dilation was expressed as the percentage change from baseline, with impaired endothelial function defined as FMD $<7\%$.

Definition of Atherosclerosis

ATS positivity was defined as: Carotid IMT ≥ 0.9 mm, and/or presence of carotid plaque, and/or ABI <0.9 , and/or impaired FMD in accordance with guidelines for subclinical atherosclerosis assessment.

Clinical Endpoints

The primary clinical endpoint was a major adverse cardiovascular event (MACE). A MACE was defined as a composite of cardiovascular death, nonfatal MI, nonfatal stroke, and any events requiring percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) as extracted from medical records. This combined definition was intended to capture systemic atherosclerotic disease burden and is congruent with prior cardiovascular outcome trials.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA) and R software Version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Continuous variables were presented as mean \pm SD or median (interquartile range, IQR) depending on distribution according to the Shapiro-Wilk test. Categorical variables

were expressed as counts and percentages. Group comparisons (ASCVD vs. non-ASCVD; ATS+ vs. ATS-) were performed using: Student's *t*-test or Mann-Whitney *U*-test for continuous variables, chi-square test or Fisher's exact test for categorical variables.

Correlation Analyses

Pearson correlation was applied only to normally distributed continuous variables, while Spearman rank correlation was used for non-normally distributed variables, as required by the reviewer.

Table 1. Baseline Characteristics of Study Participants (n = 847)

Variables	Value
Anthropometric	
Age (years)	59.0 (52.0-66.0)
BMI (kg/m ²)	28.54 (25.39-31.91)
WC (m)	1.02 \pm 0.10
NC (cm)	39.47 \pm 3.18
Hemodynamic	
SBP (mm Hg)	140.0 (130.0-160.0)
DBP (mm Hg)	90.0 (80.0-90.0)
MBP (mm Hg)	105.9 \pm 14.8
PP (mm Hg)	55.56 (45.45-70.71)
Echocardiographic	
LV mass index (g/m ²)	100.84 (82.21-121.65)
RWT	0.44 \pm 0.09
EF (%)	57.0 (45.0-61.0)
Lipid Profile	
TC (mg/dL)	209.6 \pm 56.69
LDL-C (mg/dL)	135.14 \pm 46.21
HDL-C (mg/dL)	44.3 (37.0-54.0)
TG (mg/dL)	148.9 (106.3-203.7)
AIP	0.16 (-0.02 to 0.36)
Glycemic	
HbA1c (%)	6.05 (5.5-7.13)
Inflammatory / Endocrine	
Fibrinogen (mg/dL)	299.19 \pm 85.65
CRP (mg/L)	4.7 (1.9-12.45)
TSH (mU/L)	2.05 (1.25-3.56)
Categorical, n (%)	
Obesity	316 (37.3)
Smoking (current or former)	316 (37.3)
Diabetes mellitus	335 (39.6)
FH of CVD	241 (28.5)
ASCVD	479 (56.6)

Values are expressed as mean \pm SD for normally distributed variables, or median (interquartile range, IQR) for skewed variables (Shapiro-Wilk test). Categorical variables are presented as n (%).

AIP, atherogenic index of plasma; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; NC, neck circumference; PP, pulse pressure; RWT, relative wall thickness; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference.

Regression Analysis

Multivariate logistic regression models evaluated the independent association of clinical, biochemical, and vascular imaging variables with ASCVD, ATS positivity, and MACE.

Covariates with $P < .10$ in univariate analysis were entered into multivariable models.

Model Performance

Model discrimination was assessed using receiver operating characteristic (ROC) curves with area under the curve (AUC) values reported. Model accuracy was evaluated using precision, recall, and F1 score.

Calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. For comparison, pairwise Pearson/Spearman correlation matrices were computed.

Statistical significance was set at $P < .05$ (three-decimal precision as requested).

Clarification added: Definitions were clarified. Atherosclerotic cardiovascular disease was defined as a history of MI, coronary or peripheral revascularization, or ischemic stroke. ATS positivity was defined by carotid IMT ≥ 0.9 mm or plaque presence on ultrasound. Major adverse cardiovascular events were ascertained retrospectively from hospital records over a median follow-up of 24 months.

RESULTS

Baseline Characteristics

Baseline characteristics of the 847 included patients are summarized in Table 1.

The median age was 59.0 years (IQR 52.0–66.0), and 48% were male. Obesity (BMI ≥ 30 kg/m²) was present in 316 participants (37.3%), diabetes mellitus in 335 (39.6%), and current or former smoking in 316 (37.3%). Hypertension was highly prevalent, with a median SBP of 140 mm Hg and DBP of 90 mm Hg, yielding a median PP of 55.6 mm Hg. The mean MBP was 105.9 mm Hg. Echocardiography showed preserved systolic function with a median EF of 57% and moderately elevated LVMI of 100.8 g/m². The mean RWT was 0.44. Lipid profile revealed: mean TC 210 mg/dL, LDL-C 135 mg/dL, median HDL-C 44 mg/dL, triglycerides (TG) 149 mg/dL, with a median AIP of 0.16. Median HbA1c was 6.05%, fibrinogen 299 mg/dL, and CRP 4.7 mg/L. Median TSH was 2.05 mU/L.

Group Comparisons

In group comparisons (Table 2), ASCVD patients ($n=479$) were older (median 61 vs. 56 years, $P < .001$) and had higher SBP (145 vs. 140 mm Hg, $P=.05$), PP (60.6 vs. 50.5 mm Hg, $P=.03$), and LVMI (112 vs. 97 g/m², $P < .01$) compared with non-ASCVD ($n=368$). They also showed higher: TG (157 vs.

Table 2. Comparison of Clinical and Biochemical Parameters Between Patients with and Without Atherosclerotic Cardiovascular Disease

Variables	No ASCVD Median (IQR)	ASCVD Median (IQR)	<i>P</i>
Anthropometric			
Age (years)	56.0 (47.0–63.0)	61.0 (55.0–67.0)	<.001***
BMI (kg/m ²)	28.4 (24.94–31.87)	28.73 (25.8–31.9)	.30
WC (m)	1.02 (0.94–1.09)	1.03 (0.95–1.08)	.98
NC (cm)	39.0 (38.0–42.0)	40.0 (38.0–42.0)	.25
Hemodynamic			
SBP (mm Hg)	140.0 (127.5–160.0)	145.0 (130.0–160.0)	.05
DBP (mm Hg)	90.0 (80.0–90.0)	90.0 (80.0–95.0)	.50
MBP (mm Hg)	106.67 (95.17–113.33)	106.67 (96.67–116.67)	.12
PP (mm Hg)	50.51 (40.4–70.71)	60.61 (50.51–70.71)	.03*
Lipid profile			
LDL (mg/dL)	136.0 (102.55–161.4)	132.1 (102.0–164.6)	.93
HDL (mg/dL)	46.0 (38.7–54.1)	44.0 (35.5–52.0)	.06
TG (mg/dL)	136.0 (97.4–198.5)	157.0 (111.5–210.65)	.01**
Glycemic			
HbA1c (%)	5.7 (5.29–6.1)	6.4 (5.7–7.7)	<.001***
Inflammatory			
CRP (mg/L)	3.1 (1.5–5.91)	6.6 (2.2–17.9)	<.001***
Fibrinogen (mg/dL)	267.0 (218.0–328.5)	317.0 (268.0–381.0)	.002**
Endocrine			
TSH (mU/L)	2.05 (1.26–3.55)	2.04 (1.24–3.56)	.67

Values are presented as median (interquartile range, IQR). *P*-values from Mann–Whitney *U*-test.

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; NC, neck circumference; PP, pulse pressure; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference.

* $P < .05$.

** $P < .01$.

*** $P < .001$.

Table 3. Multivariable Logistic Regression of Predictors of MACE, Atherosclerotic Cardiovascular Disease, and ATS Positivity

Variables	MACE OR (95% CI)	P	ASCVD OR (95% CI)	P	ATS Positivity OR (95% CI)	P
Male	1.75 (1.32-2.33)	<.001*	1.75 (1.32-2.33)	<.001*	1.62 (1.25-2.11)	<.001*
Age (years)	1.34 (1.10-1.63)	.004*	1.29 (1.08-1.55)	.005*	1.31 (1.10-1.57)	.003*
LDL-C	1.09 (0.85-1.40)	.52	1.14 (0.89-1.46)	.31	1.05 (0.83-1.33)	.68
HDL-C	0.83 (0.68-1.02)	.08*	0.83 (0.64-1.09)	.18	0.87 (0.71-1.07)	.19
HbA1c	1.32 (1.12-1.55)	.001*	1.32 (0.99-1.75)	.06	1.28 (1.05-1.56)	.014*
CRP	1.14 (0.93-1.39)	.19	1.09 (0.87-1.35)	.47	1.12 (0.91-1.38)	.28
CKD	2.05 (1.47-2.85)	<.001*	1.69 (1.02-2.82)	.04*	1.92 (1.33-2.76)	<.001*
HF	3.43 (2.10-5.61)	<.001*	3.43 (2.00-5.88)	<.001*	3.27 (2.05-5.22)	<.001*
Revascularization (PCI or CABG)	6.29 (4.45-8.89)	<.001*	6.29 (4.45-8.89)	<.001*	6.01 (4.26-8.47)	<.001*

*Statistically significant (P < 0.05). Multivariable logistic regression with harmonized and single-imputed dataset. Continuous predictors standardized to 1SD.

ASCVD, atherosclerotic cardiovascular disease; ATS, composite atherosclerosis (ASCVD + DUS positivity); CKD, chronic kidney disease; CRP, C-reactive protein; HF, heart failure; MACEs, major adverse cardiovascular events; OR, odds ratio.

136 mg/dL, *P* = .01), HbA1c (6.4% vs. 5.7%, *P* < .001), CRP (6.6 vs. 3.1 mg/L, *P* < .001), fibrinogen (317 vs. 267 mg/dL, *P* = .002). HDL-C tended to be lower in ASCVD (44 vs. 46 mg/dL, *P* = .06). Supplementary Table 1 demonstrated that ATS-positive patients (*n* = 499) were older, more often male, and had significantly worse glycemic and inflammatory profiles compared with ATS negative (*n* = 348).

Multivariable Regression Analysis

Multivariable regression analyses (Table 3, Figure 2) identified male sex (odds ratio [OR] 1.75, 95% CI 1.32-2.33), age (OR 1.34, 95% CI 1.10-1.63), HbA1c (OR 1.32, 95% CI 1.12-1.55), CKD (OR 2.05, 95% CI 1.47-2.85), HF (OR 3.43, 95% CI 2.10-5.61), and prior revascularization (OR 6.29, 95% CI 4.45-8.89) as independent predictors of MACE.

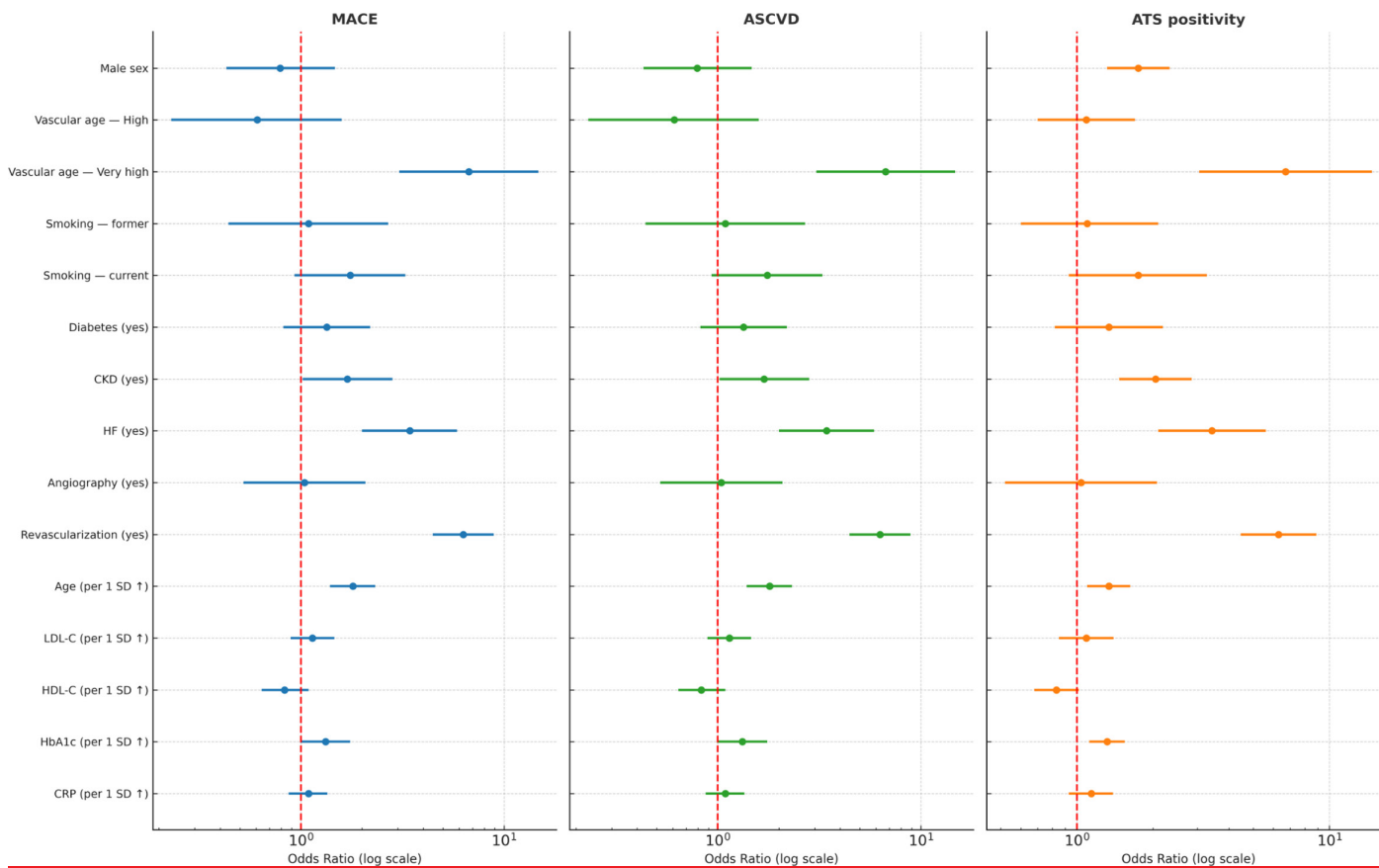


Figure 2. Forest plots of multivariable logistic regression analyses for MACE, ASCVD, and ATS positivity. ORs with 95% CIs are shown on a logarithmic scale. Male sex, age, HbA1c, CKD, HF, and prior revascularization were consistently significant predictors. ATS positivity independently predicted MACE.

Table 4. Performance Metrics of Multivariable Logistic Regression Models

Metric	MACE Model	ASCVD Model	ATS Positivity Model
Accuracy (%)	79.8	85.5	83.2
Precision (%)	87.0	88.2	84.1
Recall (sensitivity) (%)	74.4	72.5	77.8
F1 score (%)	80.2	79.9	80.8
AUC (ROC area)	0.804	0.855	0.842

Model performance metrics for multivariable logistic regression of predictors of MACE, ASCVD, and ATS positivity. Values are expressed as percentages except AUC.

ASCVD, atherosclerotic cardiovascular disease; ATS, composite atherosclerosis (ASCVD + DUS positivity); AUC, area under the curve; F1, harmonic mean of precision and recall; MACEs, major adverse cardiovascular events; ROC, receiver operating characteristic.

Revascularization history showed the strongest association across all outcomes. Similar predictors were significant for ASCVD and ATS positivity. Notably, ATS positivity itself remained an independent predictor of MACE.

Model Performance

Model performance (Table 4, Figure 3) was robust. Accuracy ranged from 79.8% (MACE) to 85.5% (ASCVD). ROC AUC values were 0.804 for MACE, 0.855 for ASCVD, and 0.842 for ATS positivity. The ROC curve confirmed good discrimination, while the confusion matrix showed a balanced trade-off between sensitivity and specificity at a cutoff of 0.44. Sensitivity for ATS positivity reached 77.8%, precision for ASCVD discrimination was 88.2%, and the F1 score exceeded 0.79 across all models, indicating overall robustness.

Mixed Pearson-Spearman Correlation Heatmap

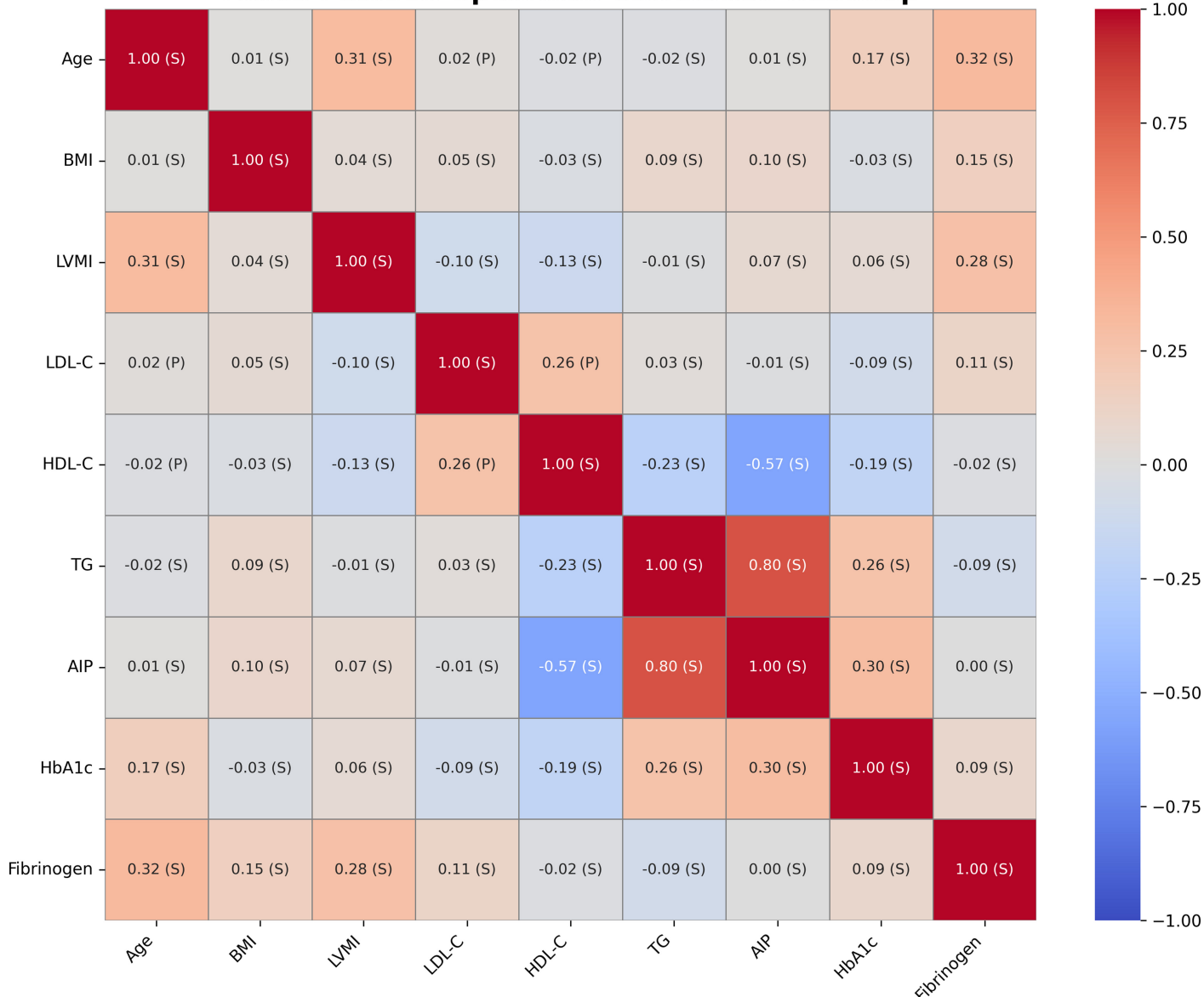


Figure 3. Heatmap of correlation coefficients between clinical, anthropometric, biochemical, and vascular parameters. Pearson or Spearman correlation was applied depending on variable distribution. Values reflect direction and strength of correlations.

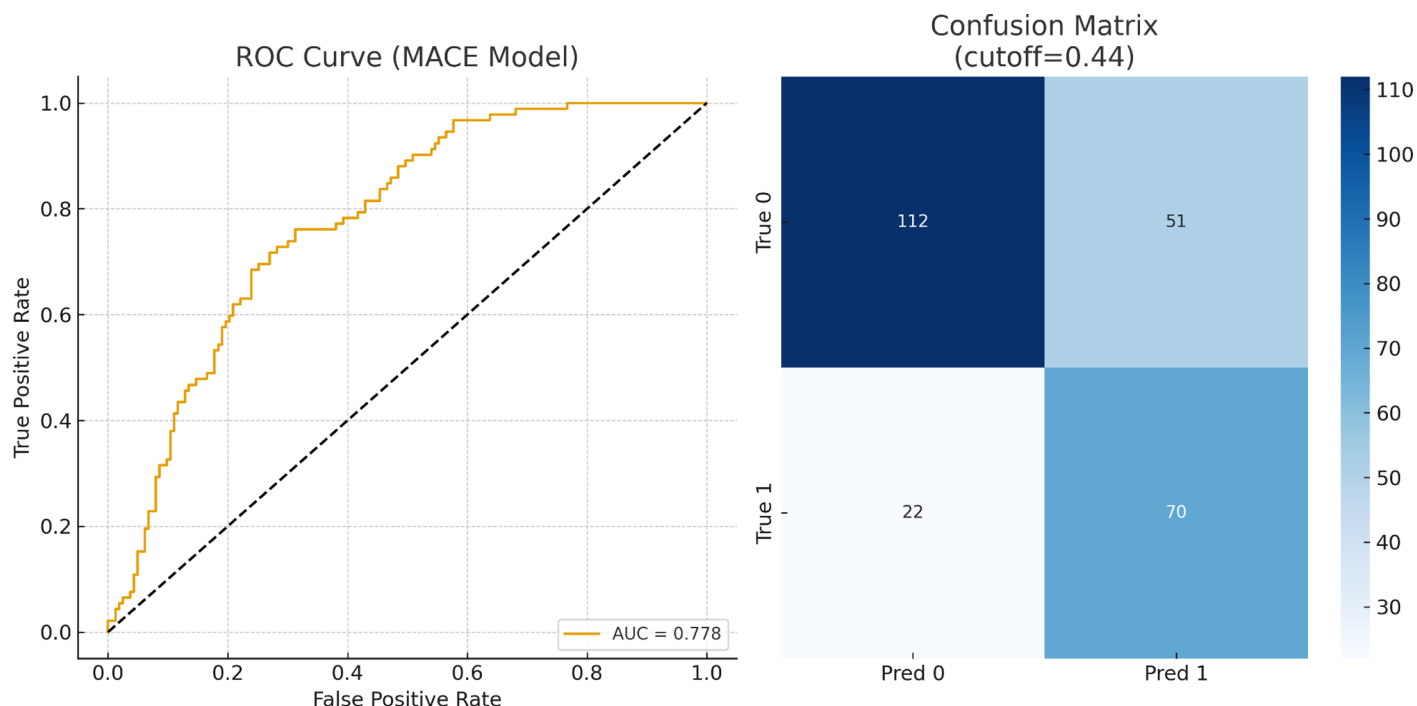


Figure 4. Receiver operating characteristic (ROC) curve (A) and confusion matrix (B) for the MACE discrimination model. The ROC curve demonstrates good discrimination (AUC = 0.778). The confusion matrix (cutoff = 0.44) illustrates the balance between sensitivity and specificity. Supplementary correlation findings are presented in Supplementary Table 2.

Correlation Analysis

Correlation analysis (Figure 4, Supplementary Table 2) revealed several clinically meaningful associations.

The strongest positive correlation was observed between TG and the AIP ($r=0.80$, $P < .001$). Moderate positive correlations were noted between age and LVMI ($r=0.31$, $P < .001$), age and fibrinogen ($r=0.32$, $P < .001$), HbA1c and TG ($r=0.26$, $P < .001$), and HbA1c and AIP ($r=0.30$, $P < .001$).

HDL-C exhibited a strong inverse correlation with AIP ($r=-0.57$, $P < .001$).

These findings indicate clustering of metabolic and inflammatory factors with preclinical atherosclerotic burden, whereas remaining associations were weak, supporting minimal multicollinearity among predictors.

Clinical Outcomes

During follow-up, 372 patients experienced MACE (43.9%), highlighting the systemic burden of atherosclerosis. Patients with ATS positivity showed higher cumulative incidence of MACE, consistent with their adverse risk profile.

Graphical Abstract

The graphical abstract (Figure 5) summarizes how integration of clinical, biochemical, and vascular imaging parameters improves risk discrimination compared with conventional risk scores. This multimodal strategy provided superior discrimination for ASCVD, ATS positivity, and MACE, supporting its potential clinical utility for individualized prevention.

DISCUSSION

This study provides comprehensive evidence supporting the value of a multimodal cardiovascular risk assessment

framework that integrates clinical, biochemical, and vascular imaging parameters.

These findings confirm the complex interplay among metabolic, inflammatory, and vascular factors in the progression of preclinical atherosclerosis and ASCVD risk.

Integration of Clinical, Biochemical, and Vascular Indicators

Age, systemic inflammation, dyslipidemia, and vascular dysfunction emerged as central contributors to atherosclerotic burden. This aligns with established pathophysiological pathways in which chronic metabolic stress promotes endothelial injury, vascular remodeling, and plaque formation. ATS positivity demonstrated strong associations with age, HbA1c, CRP, and fibrinogen, underscoring the additive effect of glycemic and inflammatory dysregulation.

Interpretation of Correlation Patterns

Correlation analysis revealed a notably strong relationship between TG and AIP ($r=0.80$), reflecting the shared metabolic determinants of atherogenic dyslipidemia. Moderate correlations between age–LVMI, age–fibrinogen, and HbA1c–AIP/TG highlight the clustering of cardiometabolic risk factors, consistent with previous literature describing combined metabolic and inflammatory pathways in early atherosclerosis. Most other correlations were weak, demonstrating minimal multicollinearity among predictors and supporting the reliability of multivariable modeling.

Predictors of Clinical Outcomes

Multivariable analyses demonstrated that male sex, older age, CKD, HF, and prior revascularization remained strong, independent determinants of MACE. Notably, ATS positivity independently predicted MACE, suggesting that preclinical

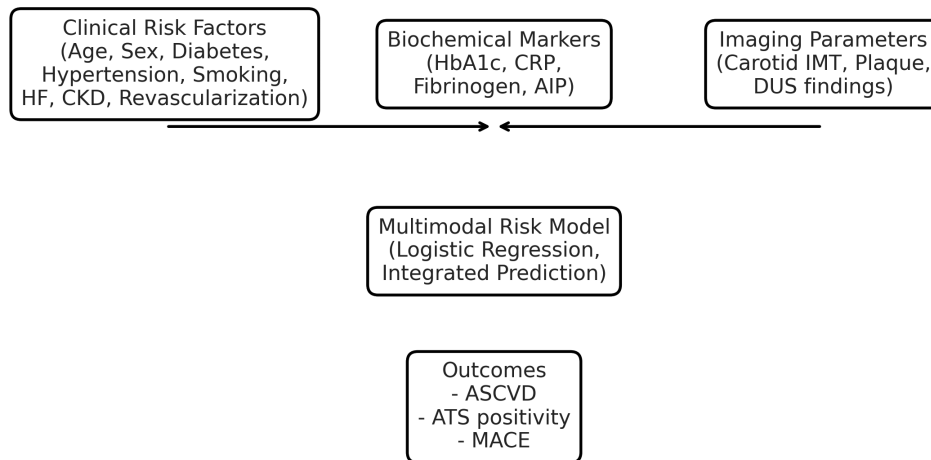


Figure 5. Graphical abstract illustrating the multimodal cardiovascular risk discrimination model. Clinical factors (age, sex, diabetes, hypertension, smoking, HF, CKD, prior revascularization), biochemical markers (HbA1c, CRP, fibrinogen, AIP), and imaging parameters (carotid IMT, plaque, duplex ultrasound findings) were integrated into logistic regression models. This multimodal approach improved predictive accuracy for ASCVD, ATS positivity, and MACE.

vascular disease confers additional prognostic value beyond traditional risk factors.

This work also validates the utility of DUS as an effective and sensitive screen for preclinical carotid disease prior to ASCVD clinical presentation. This is in accordance with the present European Society of Cardiology proposal to take vascular imaging into account among intermediate-risk subjects in order to better estimate the risk.⁹ In this context, Tokgözoğlu et al¹⁴ have emphasized the need to include vascular imaging within current risk algorithms, especially in European and Turkish practices.¹⁵ Importantly, this data point out that a history of revascularization—very much a marker of advanced macrovascular disease—is still significantly associated with preclinical ATS in other territories. This observation highlights the systemic atherosclerotic burden, with disease development and progression in 1 vascular territory being often matched by changes in other territories, as has been seen in longitudinal studies.^{10,11}

The relationship between higher HbA1c level and preclinical ATS in this study is of particular interest in relation to type 2 DM. Long-term hyperglycemia induces endothelial dysfunction, oxidative stress, and subclinical inflammation, which accelerate the atherosclerotic process.¹¹ This pathophysiological connection underscores the need to add glucose-lowering measures to primary prevention programs in persons with dyslipidemia, before overt CAD appears. Methodologically, the combination of biochemical markers and imaging contributed to model discrimination with strong ORs and narrow CIs for salient predictors. The combination of multimodal factors is gradually accepted as better than using clinical risk scores alone for risk stratification.^{12,13} Consistent with Turkish experience among the latter group is that low HDL-C and high blood pressure predispose to both CVD risk factors, as evidenced in the work by Kılıçkap et al¹⁷ in traditional coronary risk factors among healthy young military recruits, together with a review of meta-analytic rates

on hypertension prevalence in other such Turkish cohorts. In addition, studies by Güleç and Erol¹⁸ suggested that the prognostic value of HDL-C in CV risk discrimination needs to be re-assessed, thus validating the clinical significance of these results.

Furthermore, several recent studies from the Anatolian Journal of Cardiology support the growing role of integrated multimodal and AI-assisted approaches in cardiovascular risk evaluation. Koçak et al²⁰ provided regional data on multimodal cardiovascular risk assessment, while Kirboğa et al²¹ and Bozyel et al²² highlighted the value of explainable artificial intelligence and clinical decision support systems in improving risk discrimination. Complementary evidence from the the Prospective Urban Rural Epidemiology (PURE) Türkiye cohort by Oğuz et al²³ and the Anatolian Ischemic Heart Disease Registry (AIZANOI) Study by Şen et al²⁴ underscored the importance of adherence to preventive strategies in dyslipidemic and diabetic populations. Additionally, Alrahimi et al²⁵ emphasized the interplay between atherothrombotic processes and the evolving landscape of atherosclerotic cardiovascular disease in Turkish practice, aligning with the systemic nature of atherosclerosis observed in these findings.

In conclusion, this study demonstrates that a multimodal approach combining clinical, biochemical, and vascular imaging markers significantly improves the detection of subclinical atherosclerosis and ASCVD risk in dyslipidemic patients. This strategy may support more personalized and effective prevention pathways in clinical practice.

These results align with recent large-scale studies demonstrating the incremental prognostic value of carotid plaque burden, IMT progression, and endothelial dysfunction markers in identifying intermediate-risk individuals. Nevertheless, differences in population structure, imaging techniques, and biomarker panels may partly explain variability across studies.

Clinical Implications

The combined assessment of IMT, FMD, ABI, and biochemical markers strengthens early detection strategies by capturing distinct but complementary components of vascular health (structural, functional, and systemic). Such multimodal profiling may improve risk stratification in dyslipidemic adults without overt ASCVD and help tailor preventive interventions.

Strengths and Novel Aspects

Key strengths include:

- a large contemporary dyslipidemic cohort (n=847),
- simultaneous evaluation of clinical, biochemical, and ultrasound-based vascular markers,
- robust modeling with low multicollinearity,
- integration of ATS positivity as a predictive variable.

To the authors' knowledge, few prior studies have concurrently examined these predictors in a unified model, highlighting the novelty of this integrated approach.

Study Limitations

This study has several limitations. First, its observational design limits causal inference.

Second, residual confounding cannot be excluded despite multivariable analyses.

Third, vascular imaging assessments (e.g., FMD) may exhibit operator dependence, although standardized protocols were used. Finally, follow-up was limited to MACE assessment without detailed cause-specific outcomes.

In this cohort of 847 dyslipidemic patients without overt CAD, 56.6% demonstrated ASCVD and 43.9% experienced MACE during follow-up, reflecting a substantial burden of subclinical and clinical atherosclerotic disease. Independent predictors of adverse outcomes included male sex, older age, elevated HbA1c, CKD, and HF. The multimodal model integrating clinical variables with biochemical markers (HbA1c, CRP, fibrinogen, AIP) and DUS-derived vascular parameters (carotid IMT, plaque burden, FMD, and ABI) significantly improved risk stratification. The multimodal discrimination model achieved strong predictive performance (AUC up to 0.855 for ASCVD and 0.842 for ATS positivity), thereby outperforming traditional risk scores and demonstrating enhanced prognostic utility. These findings highlight the clinical utility of combining vascular imaging with biochemical profiling for early detection and individualized prevention of atherosclerosis.

This integrated approach offers more accurate identification of high-risk individuals than traditional assessment strategies and may help refine preventive management.

The independent associations observed for carotid IMT, carotid plaque, FMD, ABI, and hs-CRP further emphasize the incremental value of incorporating vascular imaging and inflammatory markers into risk-stratification workflows.

Overall, these findings support the utility of multimodal cardiovascular risk profiling and underscore the importance of

integrating metabolic, inflammatory, and vascular imaging markers to refine ASCVD risk prediction.

Further longitudinal studies are warranted to explore how combining these modalities can optimally guide preventive therapy decisions and improve long-term cardiovascular outcomes.

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the Scientific Research Institute of Cardiology, Baku, Azerbaijan (Approval No. #05-EK/2025).

Informed Consent: Written informed consent was obtained from all participants prior to inclusion in the study.

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Supplementary Table 1. Comparison of clinical, anthropometric, and biochemical parameters between ATS– and ATS+ participants

Variables	ATS– Median (IQR) / n (%)	ATS+ Median (IQR) / n (%)	P
Anthropometric			
Age (years)	55.0 (47.0–62.0)	61.0 (55.0–67.0)	<0.001***
BMI (kg/m ²)	28.37 (24.9–31.69)	28.73 (25.8–31.94)	0.200
WC (m)	1.02 (0.94–1.09)	1.03 (0.93–1.08)	0.970
NC (cm)	39.0 (38.0–42.0)	40.0 (38.0–42.0)	0.220
Hemodynamic			
SBP (mm Hg)	140.0 (125.0–160.0)	145.0 (130.0–160.0)	0.040*
DBP (mm Hg)	90.0 (80.0–90.0)	90.0 (80.0–92.5)	0.530
MBP (mm Hg)	106.67 (95.0–113.33)	106.67 (96.67–116.67)	0.100
PP (mm Hg)	50.51 (40.4–70.71)	60.61 (50.51–70.71)	0.020*
Lipid profile			
LDL-C (mg/dL)	136.4 (105.55–162.65)	132.0 (101.0–163.9)	0.620
HDL-C (mg/dL)	46.0 (38.7–54.1)	44.0 (35.0–52.0)	0.040*
TG (mg/dL)	136.0 (97.85–197.25)	156.9 (109.68–210.65)	0.010**
AIP	0.14 (–0.06–0.32)	0.18 (0.02–0.39)	0.002**
Glycemic			
HbA1c (%)	5.68 (5.26–6.1)	6.38 (5.7–7.7)	<0.001***

Values are median (IQR) or n (%). Continuous variables: Mann–Whitney U test.
Categorical variables: Chi-square or Fisher's exact test. * $P < .05$, ** $P < .01$, *** $P < .001$.

Supplementary Table 2. Correlation matrix of clinical, biochemical, and vascular variables

Variable 1	Variable 2	r	P	Method
Age	BMI	0.01	0.746	Spearman
Age	LVMI	0.31	<0.001	Pearson
Age	LDL-C	0.02	0.563	Pearson
Age	HDL-C	-0.02	0.557	Pearson
Age	TG	-0.02	0.542	Spearman
Age	AIP	0.01	0.798	Spearman
Age	HbA1c	0.17	<0.001	Spearman
Age	Fibrinogen	0.32	<0.001	Spearman
BMI	LVMI	0.04	0.264	Spearman
BMI	LDL-C	0.05	0.184	Pearson
BMI	HDL-C	-0.03	0.420	Spearman
BMI	TG	0.09	0.009	Spearman
BMI	AIP	0.10	0.003	Spearman
BMI	HbA1c	-0.03	0.407	Spearman
BMI	Fibrinogen	0.15	<0.001	Spearman
LVMI	LDL-C	-0.10	0.003	Pearson
LVMI	HDL-C	-0.13	<0.001	Pearson
LVMI	TG	-0.01	0.762	Spearman
LVMI	AIP	0.07	0.040	Spearman
LVMI	HbA1c	0.06	0.059	Spearman
LVMI	Fibrinogen	0.28	<0.001	Spearman
LDL-C	HDL-C	0.26	<0.001	Pearson
LDL-C	TG	0.03	0.393	Spearman
LDL-C	AIP	-0.01	0.806	Spearman
LDL-C	HbA1c	-0.09	0.008	Pearson
LDL-C	Fibrinogen	0.11	0.001	Spearman
HDL-C	TG	-0.23	<0.001	Spearman
HDL-C	AIP	-0.57	<0.001	Spearman
HDL-C	HbA1c	-0.19	<0.001	Pearson
HDL-C	Fibrinogen	-0.02	0.501	Spearman
TG	AIP	0.80	<0.001	Spearman
TG	HbA1c	0.26	<0.001	Spearman
TG	Fibrinogen	-0.09	0.011	Spearman
AIP	HbA1c	0.30	<0.001	Spearman
AIP	Fibrinogen	0.00	0.987	Spearman
HbA1c	Fibrinogen	0.09	0.010	Spearman

Pearson correlation was used for normally distributed variables; Spearman correlation for non-normally distributed variables (Shapiro-Wilk test). * $P < .05$, ** $P < .01$, *** $P < .001$.