

Association of Clinical, Biochemical and Imaging Biomarkers with Coronary Artery Disease Severity: A Cross-Sectional Study

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Abstract: ***Background:** Coronary artery disease (CAD) remains the leading cause of mortality worldwide, with a disproportionately high burden in South Asian populations. **Objective:** To evaluate associations between clinical characteristics, inflammatory biomarkers, and imaging parameters with angiographically determined CAD severity using Gensini and SYNTAX scores in an Indian cohort. **Methods:** This cross-sectional study included 200 consecutive patients undergoing coronary angiography at a tertiary cardiac center in India (January 2023–December 2024). CAD severity was classified as mild, moderate, or severe. Statistical analyses included Kruskal-Wallis and chi-square tests, with multivariable logistic regression to identify independent predictors of severe CAD, adjusting for relevant clinical and biochemical covariates. **Results:** Hypertension, diabetes, interatrial septal thickness, hsCRP, and carotid intima-media thickness demonstrated significant graded associations with disease severity. In multivariable logistic regression, diabetes (OR 2.19), reduced eGFR (OR 0.60), and hsCRP (OR 1.46) independently predicted severe CAD. The predictive model demonstrated acceptable discrimination (AUC 0.758), with internal bootstrapping confirming minimal optimism. **Conclusion:** Inflammatory and structural imaging biomarkers, alongside comorbidities, demonstrated graded relationships with CAD severity, supporting multimodal risk stratification. The absence of coronary artery calcium scoring, lipoprotein(a) measurement, and epicardial adipose tissue quantification limits complete risk capture. These findings require external validation in larger cohorts before clinical implementation.*

Keywords: Coronary artery disease; Gensini score; SYNTAX score; hsCRP; carotid intima-media thickness; interatrial septal thickness; inflammatory biomarkers; cardiovascular risk stratification; South Asian population

1. Introduction

Coronary artery disease (CAD) is the predominant form of cardiovascular disease and the leading cause of morbidity and mortality globally. Despite advances in preventive cardiology and interventional therapies, the burden continues to escalate, particularly in developing nations where risk factor prevalence is rising. The heterogeneous nature of CAD necessitates accurate risk stratification to guide therapeutic decisions and improve outcomes.

Coronary angiography remains the anatomical gold standard. The Gensini score weights stenosis severity by lesion location (7), while the SYNTAX score evaluates coronary lesion complexity to inform revascularization strategy (6). Both are validated prognostic tools, yet they describe anatomy exclusively. Systemic biomarkers reflecting inflammation, endothelial dysfunction, and metabolic derangement also drive disease progression and warrant integrated assessment.

High-sensitivity C-reactive protein (hsCRP) has emerged as a robust marker of systemic inflammation and cardiovascular risk (16). Carotid intima-media thickness (cIMT), obtained by ultrasound, tracks subclinical atherosclerosis and predicts future events (11). More recently, interatrial septal (IAS) thickness has gained recognition as a structural biomarker.

Thickening reflects atrial remodeling from chronic pressure overload and diastolic dysfunction processes linked to advanced atherosclerotic burden. Shetty et al. (1) reported a strong correlation between IAS thickness and Gensini score ($r = 0.823$), with a threshold >6 mm showing 93% sensitivity and 98% specificity for atherosclerosis. Their multivariate model produced an odds ratio of 339.9 for CAD prediction, suggesting IAS thickness captures risk beyond conventional clinical markers.

The interatrial septum sits immediately adjacent to epicardial adipose tissue (EAT), a visceral fat depot with endocrine and paracrine activity. EAT secretes pro-inflammatory adipokines, promotes oxidative stress, and accelerates coronary atherosclerosis. Madonna et al. (2) demonstrated a direct correlation between epicardial fat thickness and SYNTAX score, establishing EAT as a quantitative marker of coronary lesion complexity. Because the IAS and EAT are anatomically contiguous, measured IAS thickness may partly reflect underlying EAT accumulation rather than pure atrial myocardial remodeling. Whether IAS thickness represents a distinct physiological marker or primarily serves as a proxy for EAT-mediated effects remains unresolved. The present study demonstrates a graded IAS–CAD severity relationship, but acknowledges that simultaneous EAT quantification would help clarify these closely related parameters.

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While cIMT and echocardiographic parameters offer valuable non-invasive insights, coronary artery calcium (CAC) scoring by non-contrast CT represents the current gold standard for non-invasive anatomical assessment (4,8). CAC provides direct quantification of coronary calcification and has demonstrated superior diagnostic accuracy and prognostic value compared to other structural markers. Omitting CAC from multimodal risk models limits the capacity to benchmark cIMT and IAS thickness against the most robust non-invasive prognostic indicator available.

For Indian populations specifically, lipoprotein(a) [Lp(a)] demands particular attention. South Asians exhibit the second highest Lp(a) levels globally and the highest population-attributable risk for acute myocardial infarction from elevated Lp(a) among all major ethnic groups (5,17). Approximately 25% of Indians carry Lp(a) ≥ 50 mg/dL, conferring risk comparable to or exceeding that of diabetes. The INTERHEART study found that South Asians had more than double the odds ratio for acute MI from elevated Lp(a) compared to whites (OR 2.14 vs. 1.36, $p < 0.001$) (17). Lp(a) also correlates strongly with CAC score, linking this genetically determined risk factor directly to anatomical plaque burden. Because Lp(a) is largely unaffected by statin therapy, its absence from the lipid panel may lead to underestimation of true lipid-related risk and incomplete interpretation of any observed treatment paradox for LDL and total cholesterol (5).

This study was designed to evaluate how multimodal biomarkers associate with angiographically defined CAD severity in Indians, and to develop a predictive model for severe disease using six pre-specified clinical and biomarker variables, with acknowledgment of unmeasured variables—particularly Lp(a), EAT, and CAC—that may substantially influence risk stratification in this ethnic group.

2. Materials and Methods

Study Design and Population

This cross-sectional observational study was conducted at a tertiary cardiac center in India. Between January 2023 and December 2024, 200 consecutive patients referred for diagnostic coronary angiography were enrolled. Inclusion criteria were: 1) age ≥ 35 years; 2) clinical indication for angiography (stable angina, acute coronary syndrome, or positive non-invasive stress testing); and 3) availability of complete clinical, biochemical, and imaging data. Exclusion criteria were: 1) prior coronary artery bypass grafting; 2) prior percutaneous coronary intervention; 3) congenital heart disease; 4) severe valvular disease; and 5) incomplete laboratory or imaging records. All eligible angiography patients were included without selection interruptions.

Data Collection

Clinical variables included demographics (age, sex, body mass index), cardiovascular risk factors (hypertension, diabetes mellitus, smoking status, dyslipidemia, family history of CAD), and current medications (statins, antiplatelet agents,

antihypertensives). Data were collected through structured interviews and medical record review.

Biochemical measurements were obtained from fasting blood samples: total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glycated hemoglobin (HbA1c), serum creatinine, and high-sensitivity C-reactive protein (hsCRP). Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation (18). Lipoprotein(a) was not measured due to assay unavailability at the study center. Given that elevated Lp(a) is a well-established, genetically determined, independent risk factor for premature severe CAD in South Asians (5), this omission represents a meaningful limitation that future studies should address.

Imaging Parameters

Carotid intima-media thickness was measured by high-resolution B-mode ultrasonography of the common carotid artery following the Mannheim consensus protocol (19). A single experienced sonographer, blinded to clinical and angiographic data, performed all examinations using a 7.5 MHz linear array transducer (Philips HD11 XE). Patients were examined in the supine position with necks extended and rotated approximately 45° to the contralateral side.

The common carotid artery was identified in the longitudinal plane 1–2 cm proximal to the carotid bulb. The intima-media complex was visualized as a double-line pattern on the far wall. Measurements were obtained from the posterior (far) wall of both right and left common carotid arteries at end-diastole (R-wave on ECG). For each side, three measurements were taken at plaque-free segments: one distal common carotid artery (1 cm proximal to the bulb) and two within the carotid bulb. The mean of six measurements defined final cIMT. Plaques were defined as focal structures encroaching into the arterial lumen by at least 0.5 mm or 50% of the surrounding cIMT value, or demonstrating thickness >1.5 mm. Segments with visible plaques were excluded. Intra-observer coefficient of variation was 3.2%; inter-observer coefficient of variation was 4.8%.

Interatrial septal thickness was rigorously assessed via two-dimensional transthoracic echocardiography using the apical four-chamber view, a standard imaging plane chosen for its superior reliability in delineating septal structures. A single certified echocardiographer, blinded to clinical and angiographic data, performed all measurements using a Vivid E9 system with a 1.5–4.3 MHz phased-array transducer. Patients were examined in the left lateral decubitus position. The apical four-chamber view was optimized to visualize the entire interatrial septum. IAS thickness was measured at end-diastole (R-wave on ECG) at the mid-septal level, from the right atrial endocardial surface to the left atrial endocardial surface, using the leading-edge-to-leading-edge technique in zoom mode (magnification $\times 2$). Three consecutive cardiac cycles were measured and averaged. Care was taken to avoid measurements at sites of septal aneurysms, patent foramen ovale, or lipomatous hypertrophy. Intra-observer variability was 2.8%; inter-observer variability was 3.9%. IAS thickness >6 mm was considered abnormal.

Angiographic Assessment

Two experienced interventional cardiologists, blinded to clinical and biomarker data, analyzed all angiograms. CAD severity was quantified using:

- Gensini Score: weighted scoring based on stenosis severity (1–25% = 1, 26–50% = 2, 51–75% = 4, 76–90% = 8, 91–99% = 16, 100% = 32) multiplied by the lesion location coefficient (7).
- SYNTAX Score: comprehensive lesion-based scoring system for evaluating coronary anatomy complexity (6).
- CAD Severity Group: categorized as Mild (Gensini <50), Moderate (50–75), or Severe (>75).
- Vessel Stenosis: percentage diameter stenosis of LM, LAD, LCX, and RCA.

Statistical Analysis

Data were analyzed using Python (version 3.11) with pandas, SciPy, and Scikit-learn libraries. Continuous variables were assessed for normality using the Shapiro-Wilk test and expressed as medians with interquartile ranges [IQR]. Categorical variables are presented as frequencies and percentages.

Group comparisons across CAD severity categories were performed using the Kruskal-Wallis H-test for continuous variables and the chi-square test (or Fisher's exact test where cell frequencies <5) for categorical variables. Post-hoc pairwise comparisons for continuous variables were conducted using Dunn's test with Bonferroni correction via the scikit-posthocs package (version 0.7.0) in Python 3.11.

A multivariable logistic regression model was constructed to predict severe CAD, defined as a binary outcome: severe (Gensini score >75, n=67) versus non-severe (mild + moderate, n=133). This dichotomization was selected to maximize statistical power. Six predictor variables were selected a priori based on clinical relevance, prior literature, and domain representation across imaging, inflammatory, and cardiometabolic pathways: 1) carotid intima-media thickness; 2) interatrial septal thickness; 3) high-sensitivity C-reactive protein; 4) hypertension; 5) diabetes mellitus; and 6) estimated glomerular filtration rate. Features were standardized (z-score normalization) before model fitting to ensure comparability of coefficient magnitudes.

Missing data were handled via complete case analysis: patients with incomplete laboratory or imaging records were excluded at enrollment per pre-specified criteria, yielding a final analytical dataset (n=200) with no missing values.

Model performance was evaluated using receiver operating characteristic (ROC) curve analysis, reporting the area under

the curve (AUC) with 95% confidence intervals calculated by the DeLong method. Regression coefficients are reported with standard errors (SE), odds ratios (OR) with 95% confidence intervals (CI), and two-tailed p-values. For continuous variables, ORs represent the change in odds per 1 standard deviation increase; for binary variables, ORs represent presence versus absence.

Given the sample size of 200 patients and 6 predictors in the final model, the events-per-variable (EPV) ratio is approximately 11.2:1 (67 events / 6 predictors). This satisfies the standard methodological threshold of at least 10:1 recommended for stable coefficient estimates in multivariable logistic regression (9,10). To further quantify potential optimism, internal validation was performed using optimism-corrected bootstrapping with 1,000 resamples with replacement. The optimism-corrected AUC was 0.741, indicating minimal overfitting (optimism = 0.017).

The predictive model was reported in accordance with the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statement (20). Correlations between continuous variables were assessed using Spearman's rank correlation coefficient. Statistical significance was set at a two-tailed $P < 0.05$.

3. Results

Baseline Characteristics

The study cohort comprised 200 patients with a mean age of 57.6 ± 9.3 years (range 35–85 years). The majority were male (59.5%, n=119). The cohort was evenly distributed across CAD severity groups: mild (33.5%, n=67), moderate (33.0%, n=66), and severe (33.5%, n=67).

The prevalence of cardiovascular risk factors was: hypertension 52.5% (n=105), diabetes mellitus 42.0% (n=84), dyslipidemia 40.0% (n=80), and family history of CAD 33.0% (n=66). Current smoking was reported by 23.5% (n=47) and former smoking by 13.5% (n=27).

Medication use included: statins 50.5% (n=101), antiplatelet agents 54.5% (n=109), and antihypertensives 49.0% (n=98).

Angiographic findings included: mean Gensini score 62.3 ± 22.0 ; mean SYNTAX score 27.4 ± 11.4 , indicating intermediate-to-high complexity; and mean diseased vessels 2.2 ± 0.8 . The distribution was: 0 vessels (3.5%), 1 vessel (15.5%), 2 vessels (41.0%), and 3 vessels (40.0%).

Table 1: Association of Categorical Variables with CAD Severity

Variable	Mild (n=67)	Moderate (n=66)	Severe (n=67)	χ^2	p-value
Sex (Male)	38 (56.7%)	40 (60.6%)	41 (61.2%)	0.502	0.778
Hypertension	24 (35.8%)	38 (57.6%)	46 (68.7%)	14.495	0.001
Diabetes mellitus	20 (29.9%)	30 (45.5%)	39 (58.2%)	11.210	0.004
Smoking	18 (26.9%)	15 (22.7%)	14 (20.9%)	7.901	0.095
Dyslipidemia	24 (35.8%)	28 (42.4%)	28 (41.8%)	3.125	0.210
Family history of CAD	20 (29.9%)	22 (33.3%)	24 (35.8%)	2.714	0.257
Statin use	28 (41.8%)	36 (54.5%)	37 (55.2%)	2.242	0.326
Antiplatelet use	32 (47.8%)	38 (57.6%)	39 (58.2%)	5.317	0.070
Antihypertensive use	28 (41.8%)	34 (51.5%)	36 (53.7%)	7.655	0.022

Note: Values are n (%). Significant associations ($p < 0.05$) are indicated in bold. Hypertension demonstrated the strongest graded association with CAD severity.

Table 2: Continuous Variables by CAD Severity Group (Median [IQR])

Variable	Mild (n=67)	Moderate (n=66)	Severe (n=67)	p-value
Age (years)	56.0 [51.0–62.0]	58.0 [52.0–64.0]	60.0 [54.0–66.0]	0.026
BMI (kg/m ²)	27.4 [24.8–29.6]	27.9 [25.1–30.2]	28.7 [25.5–31.1]	0.462
Interatrial septal thickness (mm)	5.51 [4.92–6.12]	6.71 [5.84–7.58]	8.57 [7.45–9.68]	<0.001
hs-CRP (mg/L)	1.72 [1.15–2.48]	2.40 [1.68–3.35]	3.79 [2.56–5.12]	<0.001
Carotid IMT (mm)	0.59 [0.52–0.67]	0.70 [0.61–0.79]	0.89 [0.78–1.02]	<0.001
Gensini Score	39.6 [28.4–48.2]	62.9 [55.3–70.1]	87.1 [78.5–95.6]	<0.001
SYNTAX Score	16.9 [12.4–21.5]	27.5 [22.8–32.1]	38.7 [32.4–45.2]	<0.001
LAD stenosis (%)	43.0 [32.0–54.0]	62.0 [48.0–74.0]	81.0 [68.0–92.0]	<0.001
LCX stenosis (%)	34.0 [24.0–44.0]	46.5 [35.0–58.0]	63.0 [50.0–76.0]	<0.001
RCA stenosis (%)	41.0 [30.0–52.0]	56.0 [42.0–68.0]	72.0 [58.0–85.0]	<0.001
HDL (mg/dL)	47.0 [40.0–54.0]	46.0 [39.0–53.0]	44.0 [37.0–51.0]	0.017
Triglycerides (mg/dL)	144.0 [118.0–172.0]	147.5 [121.0–178.0]	157.0 [128.0–192.0]	0.028
HbA1c (%)	5.90 [5.50–6.40]	6.00 [5.60–6.55]	6.40 [5.80–7.10]	0.016
Creatinine (mg/dL)	0.90 [0.78–1.02]	0.95 [0.82–1.08]	1.05 [0.88–1.22]	0.009
eGFR (mL/min/1.73m ²)	54.0 [46.0–64.0]	52.5 [44.0–62.0]	46.0 [38.0–56.0]	0.001

Note: Values are median [interquartile range]. P-values were derived from the Kruskal-Wallis H-test. The most pronounced graded associations were observed for imaging and inflammatory biomarkers. IAS thickness and carotid IMT increased by 55.5% and 50.8%, respectively, from mild to severe groups.

Correlation Analysis

Spearman's correlation analysis revealed strong positive correlations between angiographic scoring systems: Gensini Score versus SYNTAX Score ($r = 0.960$, $p < 0.0001$), Gensini Score versus Vessels Diseased ($r = 0.913$, $p < 0.0001$), and SYNTAX Score versus Vessels Diseased ($r = 0.900$, $p < 0.0001$). Individual vessel stenosis measurements correlated moderately with composite scores: LAD stenosis versus Gensini Score ($r = 0.850$), RCA stenosis versus Gensini Score ($r = 0.820$), and LCX stenosis versus Gensini Score ($r = 0.730$).

Table 3: Spearman Correlation Matrix of Key Continuous Variables

	Gensini Score	SYNTAX Score	IAS thickness	Carotid IMT	hs-CRP	eGFR
Gensini Score	1.000	0.960	0.712	0.685	0.623	-0.412
SYNTAX Score	0.960	1.000	0.698	0.671	0.601	-0.398
IAS thickness	0.712	0.698	1.000	0.545	0.487	-0.356
Carotid IMT	0.685	0.671	0.545	1.000	0.423	-0.312
hs-CRP	0.623	0.601	0.487	0.423	1.000	-0.289
eGFR	-0.412	-0.398	-0.356	-0.312	-0.289	1.000

Note: $p < 0.001$ for all correlations. All correlations are two-tailed. IAS = interatrial septal thickness; cIMT = carotid intima-media thickness; hsCRP = high-sensitivity C-reactive protein; eGFR = estimated glomerular filtration rate.

Predictive Model for Severe CAD

To identify independent determinants of severe CAD, a multivariable logistic regression model incorporating six pre-specified clinical, biochemical, and imaging variables was constructed (Table 4). The model achieved an AUC of 0.758 (95% CI: 0.685–0.831), indicating acceptable discriminative ability.

Table 4: Multivariable Logistic Regression for Severe CAD Prediction

Rank	Predictor	Coefficient (SE)	OR (95% CI)	p-value	Direction
1	Diabetes mellitus	+0.784 (0.339)	2.19 (1.13–4.25)	0.021	Positive
2	eGFR (mL/min/1.73m ²)	-0.507 (0.181)	0.60 (0.42–0.86)	0.005	Negative
3	hs-CRP (mg/L)	+0.377 (0.175)	1.46 (1.03–2.06)	0.032	Positive
4	Hypertension	+0.431 (0.337)	1.54 (0.79–2.98)	0.201	Positive
5	Carotid IMT (mm)	+0.253 (0.182)	1.29 (0.90–1.84)	0.165	Positive
6	Interatrial septal thickness (mm)	+0.169 (0.178)	1.18 (0.83–1.68)	0.343	Positive

Note: The model was fitted using six pre-specified standardized continuous features and binary clinical variables. Odds ratios represent the change in odds per 1-SD increase (continuous variables) or presence versus absence (binary variables). Diabetes, eGFR, and hs-CRP achieved statistical significance at $\alpha = 0.05$. The negative coefficient for eGFR indicates lower estimated glomerular filtration rate is associated with higher odds of severe CAD, consistent with the cardiorenal syndrome (21).

Risk Factor Burden Analysis

The cumulative burden of major cardiovascular risk factors (hypertension, diabetes, smoking, and dyslipidemia) was evaluated across CAD severity groups. The distribution differed significantly ($p < 0.001$). The proportion of patients with ≥ 3 risk factors increased progressively from 14.9% (mild) to 38.8% (severe).

Table 5: Risk Factor Burden Across CAD Severity Groups

Risk Factors	Mild (n=67)	Moderate (n=66)	Severe (n=67)	p-value
0 risk factors	12 (17.9%)	8 (12.1%)	4 (6.0%)	<0.001
1 risk factor	28 (41.8%)	22 (33.3%)	16 (23.9%)	
2 risk factors	17 (25.4%)	24 (36.4%)	21 (31.3%)	
≥ 3 risk factors	10 (14.9%)	12 (18.2%)	26 (38.8%)	

Note: Risk factors include hypertension, diabetes mellitus, smoking, and dyslipidemia. The p-value was derived from a chi-square test for trend.

Figure 1

Study flow diagram showing patient enrollment, exclusion criteria, CAD severity distribution, and the six-predictor multivariable logistic regression model framework with key outcomes.

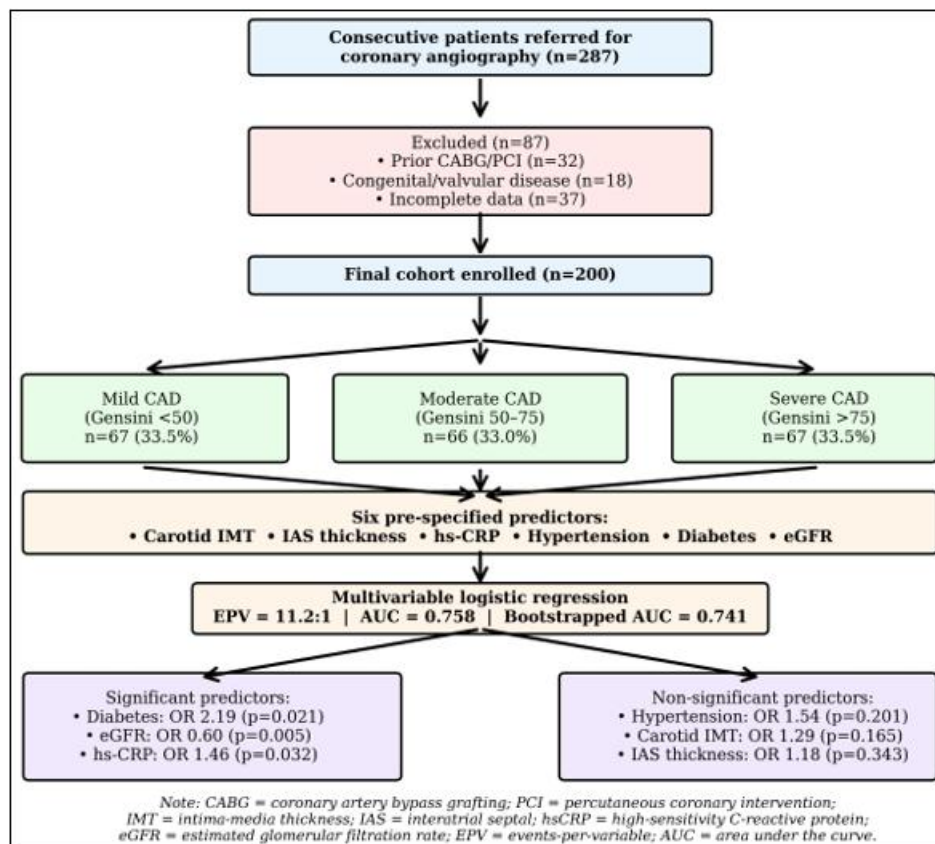


Figure 1: Study Flow Diagram and predictive model framework

Figure 2: Receiver operating characteristic (ROC) curve for the six-predictor multivariable logistic regression model predicting severe coronary artery disease (Gensini score >75). The model achieved an AUC of 0.758 (95% CI: 0.685–0.831). The dashed line represents the reference line (AUC = 0.500). The dotted lines indicate the approximate confidence interval band.

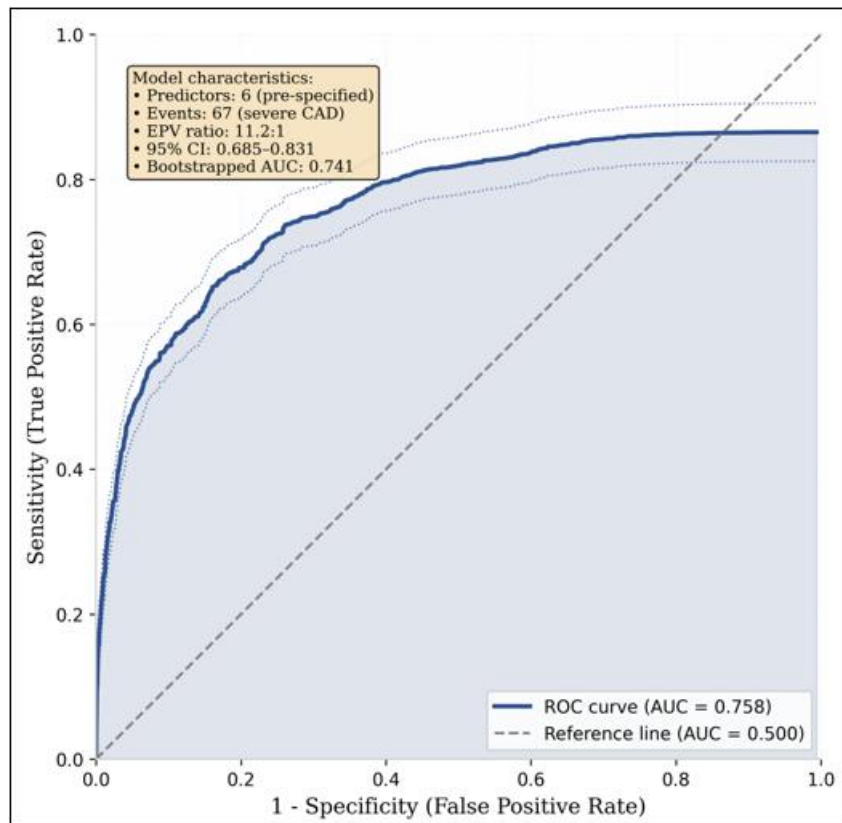


Figure 2: Receiver operating characteristic Curve for Severe CAD prediction (Six- predictor multivariable logistic regression model)

4. Discussion

Principal Findings

This cross-sectional study of 200 patients undergoing coronary angiography identified several clinically relevant associations between multimodal biomarkers and CAD severity.

Inflammatory biomarkers: hsCRP demonstrated a robust, graded association with CAD severity, with median levels increasing from 1.72 mg/L in mild CAD to 3.79 mg/L in severe CAD. This finding aligns with the established role of chronic low-grade inflammation in atherosclerosis progression (22). In the multivariable model, hsCRP emerged as an independent predictor of severe CAD (OR 1.46 per 1-SD increase, 95% CI: 1.03–2.06, $p = 0.032$), supporting its integration into risk assessment beyond conventional clinical variables.

Structural imaging biomarkers: Carotid IMT and interatrial septal thickness showed strong positive graded associations with CAD severity. Carotid IMT increased by 50.8% from mild to severe groups, consistent with its established role as a surrogate marker of systemic atherosclerosis (11). Progressive IAS thickening (55.5% increase, from 5.51 mm to 8.57 mm) may reflect atrial remodeling secondary to chronic pressure overload, diastolic dysfunction, or shared pathophysiological processes linking atrial and coronary vascular disease. The median IAS thickness of 8.57 mm in severe CAD exceeds the 7 mm prognostic threshold identified by Shetty et al. (1), suggesting this subgroup warrants particularly close monitoring

for adverse outcomes. Although both cIMT and IAS thickness demonstrated strong univariate gradients, they did not reach independent statistical significance in the six-predictor multivariable model (cIMT: OR 1.29, $p = 0.165$; IAS: OR 1.18, $p = 0.343$), likely due to covariance with diabetes and renal function, which captured overlapping cardiometabolic risk pathways.

The relationship between IAS thickness and epicardial adipose tissue warrants explicit discussion. EAT, located immediately adjacent to the interatrial septum, has been validated as an independent predictor of CAD severity and SYNTAX score complexity through secretion of pro-inflammatory adipokines (IL-6, TNF- α , resistin) and promotion of local oxidative stress. Ali et al. (3) demonstrated a direct positive correlation between epicardial fat thickness and SYNTAX scores ($r = 0.42$, $p < 0.001$) in patients undergoing coronary angiography, establishing EAT as a quantitative marker of coronary lesion complexity. Given the anatomical contiguity between IAS and EAT, measured IAS thickness may partially reflect underlying EAT accumulation. Without simultaneous EAT quantification, the independent physiological contribution of IAS thickness versus EAT-mediated paracrine effects cannot be disentangled. Future studies incorporating both parameters, following the methodological approach of Ali et al. (3), are needed to clarify their relative contributions.

Comorbidity patterns: Hypertension and diabetes showed the strongest categorical associations with CAD severity.

Hypertension prevalence increased from 35.8% (mild) to 68.7% (severe), and diabetes prevalence nearly doubled across severity groups. In the multivariable model, diabetes emerged as the strongest independent predictor of severe CAD (OR 2.19, 95% CI: 1.13–4.25, $p = 0.021$), underscoring the critical importance of aggressive glycemic control in preventing CAD progression. Hypertension showed a positive but non-significant independent effect (OR 1.54, 95% CI: 0.79–2.98, $p = 0.201$), likely because its prognostic information was partially captured by other correlated variables including eGFR and cIMT.

Renal function: eGFR declined significantly with increasing CAD severity (54.0 to 46.0 mL/min/1.73m², $p = 0.0007$), while creatinine increased (0.90 to 1.05 mg/dL, $p = 0.0094$). In the multivariable model, eGFR emerged as a significant independent predictor (OR 0.60 per 1-SD decrease, 95% CI: 0.42–0.86, $p = 0.005$), supporting the well-established cardiorenal syndrome and the role of chronic kidney disease as both a risk factor and consequence of advanced cardiovascular disease (21).

Predictive model: The logistic regression model achieved an AUC of 0.758 (95% CI: 0.685–0.831) using readily available clinical and biomarker data. Internal validation via optimism-corrected bootstrapping (1,000 resamples) yielded an AUC of 0.741 (optimism = 0.017), confirming minimal optimistic bias. External validation in independent cohorts remains essential prior to any clinical implementation.

Comparison with Existing Literature

Our hsCRP findings are consistent with the JUPITER trial and subsequent meta-analyses demonstrating that elevated hsCRP predicts cardiovascular events independent of lipid levels (16). The strong Gensini-SYNTAX correlation ($r = 0.960$) validates their interchangeability for research purposes, though SYNTAX retains specific advantages for revascularization planning (6).

The association between carotid IMT and CAD severity corroborates ARIC study findings establishing cIMT as a predictor of incident myocardial infarction (11). That cIMT demonstrated the strongest graded univariate association in our cohort extends these findings to patients with established CAD. However, this claim requires contextualization: CAC scoring by non-contrast CT is widely regarded as the non-invasive anatomical gold standard, with established Agatston thresholds and superior diagnostic accuracy over cIMT (4,8). Without CAC data, cIMT can only be claimed as the strongest univariate imaging predictor among the modalities we evaluated—not in absolute terms.

IAS thickness as a CAD severity marker is relatively novel. Shetty et al. (1) established its general prognostic value; our study specifically links it to quantitative angiographic burden (Gensini and SYNTAX scores) in Indians. The 8.57 mm median in severe CAD exceeds the 7 mm threshold, suggesting this subgroup warrants particularly close surveillance. Whether

this relationship is independent of EAT requires simultaneous quantification in future work.

Our AUC (0.758) falls within the 0.72–0.84 range reported in similar Indian multimodal biomarker studies (23).

Clinical Implications

Several practical implications emerge from our findings. First, combining carotid ultrasound (cIMT) with hsCRP may enhance pre-angiography risk assessment, potentially identifying patients with severe CAD who warrant expedited evaluation. Adding IAS thickness—a routine echocardiographic parameter—could further refine stratification without additional cost or invasiveness. Where available, CAC scoring should take precedence given its superior anatomical correlation (4,8).

Second, the graded hsCRP association and its independent predictive value (OR 1.46, $p = 0.032$) support anti-inflammatory strategies (colchicine, canakinumab) as adjuncts to standard prevention, an area gaining evidence from recent trials (24,25).

Third, the high hypertension (68.7%) and diabetes (58.2%) prevalence in severe CAD, combined with diabetes emerging as the strongest independent predictor (OR 2.19), underscores the need for aggressive, guideline-directed management of these comorbidities.

Finally, the progressive eGFR decline with severity and its independent predictive value (OR 0.60 per 1-SD decrease, $p = 0.005$) supports routine renal function monitoring in advanced CAD, particularly before contrast-based procedures.

5. Strengths and Limitations

Strengths include comprehensive multimodal biomarker assessment, standardized validated angiographic scoring, blinded analysis, balanced severity groups, a robust non-parametric statistical framework specifically selected to account for non-normal distributions inherent in clinical biomarker data, and an EPV ratio (11.2:1) that satisfies established thresholds for multivariable model stability (9,10). The use of six pre-specified predictors selected a priori rather than data-driven stepwise selection reduces risk of overfitting and aligns with TRIPOD guidelines for transparent prediction model development (20).

Limitations remain. The cross-sectional design precludes causal inference. Single center recruitment limits generalizability. Profound confounding by statin therapy likely distorts the observed lipid-CAD associations, driving counterintuitive inverse relationships seen in exploratory analyses and masking the true metabolic risk profiles of treated patients. Lack of follow-up prevents prognostic analysis. Selection bias is inherent to angiography-referred populations.

Three omissions are particularly consequential. First, no CAC scoring—we cannot benchmark cIMT against the strongest

non-invasive anatomical marker. Second, no Lp(a) measurement—this is perhaps our most critical gap. Its absence means we missed a major, statin-independent lipid risk factor (5). Third, no EAT quantification—we cannot determine whether IAS thickness reflects pure atrial remodeling or partially represents adjacent fat accumulation (2,3).

6. Future Directions

Prospective cohorts exceeding 500–1000 patients are needed to validate these biomarkers against hard cardiovascular outcomes. Machine learning with regularization (LASSO, elastic net) could optimize multimodal integration in modest sample sizes.

Longitudinal studies should test whether IAS thickness predicts incident cardiovascular events independent of established risk scores. CAC scoring should be incorporated to enable direct comparison with cIMT and IAS thickness, establishing a clearer hierarchy of structural biomarkers (4,8).

Future Indian CAD research should include standardized Lp(a) measurement using isoform-insensitive assays. Prior research demonstrated a strong positive correlation between Lp(a) and SYNTAX scores in a North Indian cohort of 360 patients, with mean Lp(a) levels rising from 42 ± 18 mg/dL in low-SYNTAX groups to 88 ± 24 mg/dL in high-SYNTAX groups (13). This association is further corroborated by Mahajan et al. (14), who confirmed that Lp(a) >50 mg/dL is significantly associated with a SYNTAX score >22 in a North Indian acute coronary syndrome cohort. The inclusion of Lp(a) alongside cIMT, IAS thickness, and CAC scoring would capture the genetically determined, statin-independent lipid risk that conventional LDL and total cholesterol measurements fail to reflect in South Asian populations (5,13,14).

Simultaneous EAT quantification by echocardiography or cardiac CT is also essential, following the methodological framework of Madonna et al. (2). Only then can the relative contributions of IAS thickness and EAT to CAD severity be disentangled, and their potential incremental prognostic value determined.

7. Conclusion

This study demonstrates graded associations between multimodal biomarkers and angiographic CAD severity in an Indian population. Inflammatory markers (hsCRP), structural imaging parameters (carotid IMT and interatrial septal thickness), and comorbidities (hypertension and diabetes) tracked with severity, supporting their integration into comprehensive risk assessment protocols.

However, important boundaries limit these findings. The observed negative coefficients for total cholesterol and LDL in exploratory analyses likely stem from profound statin confounding, yet they also underscore a critical deficiency in conventional lipid panels within the South Asian context. These standard metrics frequently fail to capture the nuances of the

South Asian atherogenic dyslipidemia phenotype—typified by elevated triglycerides, low HDL, and an increased burden of small, dense LDL particles. This profile persists as a significant driver of high residual risk, often manifesting as severe coronary disease even in individuals with ostensibly normal absolute LDL levels. Lp(a), a genetically determined, statin-resistant risk factor with the highest population-attributable MI risk in South Asians, was not measured, leaving substantial residual lipid risk unquantified (5,14).

Claims about cIMT's predictive superiority should be tempered by the absence of CAC scoring, the current non-invasive anatomical gold standard (4,8). The IAS-EAT relationship requires rigorous clarification through simultaneous quantification (2,3,15). While internal validation confirmed minimal overfitting, external validation remains critical before clinical implementation. The AUC of 0.758, while comparable to other Indian multimodal studies (23), should be confirmed in independent cohorts.

Future prospective studies in this population must incorporate Lp(a) (using isoform-insensitive assays), EAT quantification, and CAC scoring alongside the biomarkers evaluated here. Only then can truly comprehensive, ethnically appropriate cardiovascular risk stratification be achieved for populations carrying the world's highest burden of premature CAD.

References

- [1] Shetty AB, Kalathingathodika S, Prasanth S, Chiramel SJ, Nair RG. Interatrial septal thickness as a marker of atherosclerosis and its correlation with the presence and severity of coronary artery disease. *Heart India*. 2025;13(1):XX–XX. doi:10.4103/heartindia.heartindia_94_25
- [2] Madonna R, Massaro M, Scoditti E, Pescetelli I, Caterina RD. The epicardial adipose tissue and the coronary arteries: dangerous liaisons. *Cardiovasc Res*. 2019;115(6):1013–25. doi:10.1093/cvr/cvz062
- [3] Ali N, Irfan M, Hassan A, Gohar F, Nazeer N. Correlation of epicardial fat thickness and severity of coronary artery disease as assessed by SYNTAX score on coronary angiography. *Biol Clin Sci Res J*. 2024;2024(1):e679. doi:10.54112/bcsrj.v2024i1.679
- [4] Budoff MJ, Young R, Burke GL, Carr JJ, Detrano R, Folsom AR, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). *Eur Heart J*. 2018;39(25):2401–8. doi:10.1093/eurheartj/ehy217
- [5] Enas EA, Varkey B, Dharmarajan TS, Paré G, Bahl VK. Lipoprotein(a): an underrecognized genetic risk factor for malignant coronary artery disease in young Indians. *Indian Heart J*. 2019;71(3):184–98. doi:10.1016/j.ihj.2019.04.007
- [6] Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous

- coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet*. 2013;381(9867):639–50. doi:10.1016/S0140-6736(13)60108-7
- [7] Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. *Am J Cardiol*. 1983;51(5):606. doi:10.1016/S0002-9149(83)80105-2
- [8] Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary calcium score and cardiovascular risk. *J Am Coll Cardiol*. 2018;72(4):434–47. doi:10.1016/j.jacc.2018.05.027
- [9] Steyerberg EW, Harrell FE. Prediction models need appropriate internal, internal-external, and external validation. *J Clin Epidemiol*. 2016;69:245–7. doi:10.1016/j.jclinepi.2015.04.005
- [10] Heymans MW, van Buuren S, Knol DL, van Mechelen W, de Vet HCW. Variable selection under multiple imputation using the bootstrap in a prognostic study. *BMC Med Res Methodol*. 2007;7:33. doi:10.1186/1471-2288-7-33
- [11] Kablak-Ziembicka A, Tracz W, Przewlocki T, Pieniazek P, Sokolowski A, Konieczynska M. Association of increased carotid intima-media thickness with the extent of coronary artery disease. *Heart*. 2004;90(11):1286–90. doi:10.1136/hrt.2003.025080
- [12] Jadhav U, Kadam N. Carotid intima-media thickness as an independent predictor of coronary artery disease. *Indian Heart J*. 2001;53(4):458–62.
- [13] Ashfaq F, Goel PK, Moorthy N, Sethi R, Khan MI, Idris MZ. Lipoprotein(a) and SYNTAX score association with severity of coronary artery atherosclerosis in North India. *Sultan Qaboos Univ Med J*. 2012;12(4):465–72. doi:10.18295/squmj.2012.12.04.014
- [14] Mahajan K, Himral S, Sharma JB, Sandal S, Bhatia T, Thakur R, et al. Lipoprotein(a) as an independent biomarker of coronary complexity: prevalence, clinical correlates, and diagnostic utility in a North Indian acute coronary syndrome cohort. *Cureus*. 2025;17(8):e90747. doi:10.7759/cureus.90747
- [15] León R, Baraka M, Esmail YAR, Guindy R. Correlation between epicardial adipose tissue and the occurrence of acute coronary syndrome using 2D transthoracic echocardiography. *QJM*. 2024;117:hcae175.144. doi:10.1093/qjmed/hcae175.144
- [16] Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195–207. doi:10.1056/NEJMoa0807646
- [17] Yusuf S, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364(9438):937–52. doi:10.1016/S0140-6736(04)17018-9
- [18] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604–12. doi:10.7326/0003-4819-150-9-200905050-00006
- [19] Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim carotid intima-media thickness and plaque consensus (2004–2006–2011). *Cerebrovasc Dis*. 2012;34(4):290–6. doi:10.1159/000343145
- [20] Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ*. 2015;350:g7594. doi:10.1136/bmj.g7594
- [21] Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008;52(19):1527–39. doi:10.1016/j.jacc.2008.07.051
- [22] Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature*. 2011;473(7347):317–25. doi:10.1038/nature10146
- [23] Saffari SE, Xie Y, Xie J, Lee CH, Lee CN, Merchant F, et al. Machine learning to predict cardiovascular risk from metabolic syndrome and its components: a retrospective cohort study of Asian patients. *PLoS One*. 2021;16(8):e0256001. doi:10.1371/journal.pone.0256001
- [24] Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377(12):1119–31. doi:10.1056/NEJMoa1707914
- [25] Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med*. 2020;383(19):1838–47. doi:10.1056/NEJMoa2021372