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Association of Lipoprotein(a) and ApoB/ApoA1 Ratio with SYNTAX Score in Premature Myocardial Infarction: an Age-Stratified Study from Northeast India

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ABSTRACT

Background: *Conventional lipid parameters may not adequately reflect coronary lesion complexity in myocardial infarction (MI), particularly in premature cases. Advanced lipid markers such as lipoprotein(a) [Lp(a)], apolipoprotein B (ApoB) and the ApoB/ApoA1 ratio may better represent atherogenic burden.*

Aim: *To evaluate the association between lipid parameters and SYNTAX score in patients with premature MI. An exploratory age-stratified analysis comparing patients aged <45 years and 45–55 years was additionally performed.*

Methods: *In this hospital-based cross-sectional study, consecutive MI patients aged ≤55 years with angiographically confirmed coronary artery disease (CAD) were enrolled. Blood samples were collected at admission prior to initiation of therapy for assessment of lipid profile, including Lp(a), ApoA1, ApoB and ApoB/ApoA1 ratio. SYNTAX score was categorized as low (≤22) or high (>22). Associations were analysed using Student's t-test, Spearman correlation, multivariate logistic regression and receiver operating characteristic (ROC) curve analysis.*

Results: *Among 100 patients (mean age 46.5 ± 6.2 years; 85% males), 37% had high SYNTAX scores as well as significantly higher Lp(a), ApoB and ApoB/ApoA1 ratio ($p<0.01$), while conventional lipid parameters were not significantly different. These associations appeared more pronounced among patients aged <45 years and formal interaction analysis provided additional evidence of an age-dependent relationship between Lp(a) and high SYNTAX score [interaction odds ratio (OR) 0.952, 95% confidence interval (CI) 0.917–0.989, $p=0.011$]. SYNTAX score correlated positively with Lp(a) ($\rho=0.275$, $p=0.006$), ApoB ($\rho=0.347$, $p<0.001$) and ApoB/ApoA1 ratio ($\rho=0.352$, $p<0.001$). In multivariable analysis, hypertension independently predicted high SYNTAX score (adjusted OR 3.46, $p=0.012$), whereas associations of advanced lipid markers were attenuated after multivariable adjustment. ROC analysis showed modest discriminative ability for Lp(a) (AUC 0.64, 95% CI: 0.52–0.77), with limited performance for ApoB and ApoB/ApoA1 ratio.*

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Conclusion: *Advanced lipid markers, particularly Lp(a) and ApoB/ApoA1 ratio, were associated with greater angiographic complexity in premature MI. Exploratory analyses suggested stronger associations among patients aged <45 years, particularly for Lp(a), and formal interaction analysis further supported an age-dependent relationship between Lp(a) and high SYNTAX score. However, their modest discriminative ability and lack of independent association after multivariable adjustment suggest that these markers should be considered adjunctive indicators of atherogenic burden rather than standalone predictors.*

Keywords: lipoprotein(a), ApoB/ApoA1 ratio, premature myocardial infarction, SYNTAX score, coronary artery disease, advanced lipid markers.

INTRODUCTION

Coronary artery disease (CAD) continues to be one of the leading causes of morbidity and mortality worldwide (1, 2). Although traditionally regarded as a condition affecting older individuals, the incidence of CAD in younger and middle-aged populations has been steadily increasing, particularly in developing countries such as India. Premature CAD is generally defined as occurring in men under 55 years and women under 65 years, with an especially concerning burden being observed in individuals younger than 45 years (3). Very premature CAD (<45 years) represents a distinct high-risk subgroup.

South Asians exhibit a heightened susceptibility to premature CAD, which has been attributed to a combination of genetic predisposition, characteristic patterns of dyslipidaemia and elevated levels of lipoprotein(a) [Lp(a)] (3-5). Conventional lipid parameters, including total cholesterol and low-density lipoprotein (LDL) cholesterol, have long been used for cardiovascular risk assessment; however, these measures may not adequately capture the overall atherogenic burden or the complexity of coronary lesions. In contrast, apolipoprotein B (ApoB) reflects the total number of circulating atherogenic lipoprotein particles, while apolipoprotein A1 (ApoA1) represents anti-atherogenic high-density lipoprotein particles. The ApoB/ApoA1 ratio therefore provides an integrated measure of atherogenic balance and has been shown to be a strong predictor of cardiovascular risk (6). Similarly, Lp(a), a genetically determined lipoprotein, has emerged as an independent risk factor for CAD and is particularly implicated in early-onset disease (7). The SYNTAX score is a validated angiographic tool used to quantify the severity and anatomical complexity of coronary artery disease, with higher scores reflecting more extensive and complex coronary involvement and being associated with adverse clinical outcomes (8).

While prior studies have examined the association between lipid parameters and CAD severity, findings have been inconsistent, especially regarding the role of advanced lipid markers in younger patients presenting with myocardial infarction (MI) (9-11). Furthermore, the relationship between these advanced lipid markers and coronary lesion complexity remains incompletely understood. This gap is particularly relevant in Northeast India, a region with distinct ethnic and genetic characteristics that may influence cardiovascular risk profiles. Data regarding advanced lipid markers and angiographic complexity among premature MI patients from Northeast India remain limited.

In this context, we formulated the hypothesis that advanced lipid markers, specifically Lp(a), ApoB and ApoB/ApoA1 ratio were associated with increased coronary lesion complexity, as assessed by the SYNTAX score. Accordingly, the primary objective of this study was to evaluate the association between advanced lipid markers (Lp(a), ApoB, ApoB/ApoA1 ratio) and coronary lesion complexity in patients with premature MI. Secondary objectives included examining whether these associations differ between patients aged <45 years and those aged 45–55 years, thereby exploring potential age-dependent variations in lipid-mediated atherogenesis.

MATERIALS AND METHODS

This was a single-centre cross-sectional observational study conducted in the Department of Cardiology at a tertiary care teaching hospital.

The study was carried out over a period of 18 months, from January 1, 2023 to June 2024. Patients presenting with acute MI, including both ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI), were selected in accordance with the universal definition of MI (12).

A total of 112 consecutive patients aged ≤55 years with MI who underwent coronary angiography during the study period were initially screened. Of these, 12 patients were excluded due to the presence of non-obstructive coronary arteries or angiographically normal coronary anatomy. The final study cohort comprised 100 consecutive patients aged ≤55 years who met all inclusion criteria. Therefore, our study represents a selected cohort of MI patients with obstructive CAD. This study population was specifically selected to evaluate lipid-associated determinants of coronary lesion complexity in premature MI.

For exploratory post hoc analysis, patients were stratified into two age groups (<45 years and 45–55 years) to evaluate potential age-related differences in lipid-associated risk. All patients were enrolled consecutively without any pre-specified sampling strategy. The study protocol was approved by the Institutional Ethics Committee of Gauhati Medical College and Hospital, and written informed consent was obtained from all participants prior to enrolment.

The sample size was calculated based on the expected correlation between lipoprotein(a) and SYNTAX score. Assuming a moderate correlation coefficient ($r = 0.30$), with a two-sided alpha error of 0.05 and statistical power of 80%, the minimum required sample size was estimated to be 85 patients using standard correlation sample size formulae. The final sample size of 100 patients was therefore considered adequate to detect statistically significant associations. However, subgroup analyses were exploratory in nature and may be underpowered.

Eligibility criteria

Inclusion criteria comprised age ≤55 years; angiographically proven CAD, defined as ≥50% stenosis in at least one major epicardial coronary artery; and provision of written informed consent.

Exclusion criteria were as follows: use of lipid-lowering therapy within the preceding four weeks; secondary causes of dyslipidaemia, including hypothyroidism, chronic liver disease, or nephrotic syndrome; chronic kidney disease, malignancy, or other debilitating systemic illness; acute or chronic inflammatory disorders, autoimmune diseases, or sepsis; pregnancy or lactation; age >55 years; and refusal to provide informed consent.

All patients underwent a comprehensive clinical evaluation, including assessment of demographic characteristics, cardiovascular risk factors, detailed medical history and physical examination. Routine laboratory investigations, electrocardiography and two-dimensional echocardiography were performed in all patients.

In addition to conventional lipid profile assessment, advanced lipid parameters were measured, including Lp(a), ApoA1, ApoB and ApoB/ApoA1 ratio. Blood samples were obtained within 24 hours of admission prior to initiation of statin therapy. All lipid parameters were analysed using the VITROS 5600 Integrated System autoanalyzer (Ortho Clinical Diagnostics, USA). ApoA1, ApoB and Lp(a) levels were measured using immunoturbidimetric assays. Calibration and internal quality control procedures were performed using manufacturer-provided standards in accordance with established laboratory protocols.

Coronary angiography was performed using standard percutaneous techniques via radial or femoral arterial access. Coronary lesions were assessed in multiple orthogonal views to ensure accurate evaluation. The severity and complexity of CAD were quantified using the SYNTAX score, calculated by experienced cardiologists who were blinded to the lipid profile data. Based on the SYNTAX score, patients were categorized into two groups: low SYNTAX score (≤22) and high SYNTAX score (>22). The SYNTAX score was calculated using the standard SYNTAX algorithm.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY). Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are expressed as frequencies and percentages. Normality of continuous variables was assessed using the Shapiro–Wilk test. Depending on data distribution, group comparisons between low and high SYNTAX score groups were performed using independent Student's t-test or appropriate non-parametric tests. This initial analysis was intended to determine whether patients with more complex

CAD demonstrated higher levels of advanced lipid markers. To evaluate whether lipid marker levels were associated with progressively increasing coronary lesion complexity across the full range of SYNTAX scores, Spearman rank correlation analysis was performed. This non-parametric method was selected because it does not assume normal distribution or a strictly linear relationship and therefore allows assessment of continuous associations between lipid markers and SYNTAX score.

Although correlation analysis characterizes overall trends across the continuous spectrum of SYNTAX scores, clinical decision-making often requires identification of patients with complex CAD. Accordingly, SYNTAX score was additionally categorized into low (≤22) and high (>22) groups according to the standard SYNTAX trial threshold (8). Multivariable logistic regression analysis was subsequently performed to identify independent predictors of high SYNTAX score after adjustment for major cardiovascular risk factors, including hypertension, diabetes mellitus and smoking. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). To minimize overfitting, the number of variables included in the regression model was restricted according to the event-per-variable principle. ApoB was excluded from the multivariable model because of potential collinearity with the ApoB/ApoA1 ratio.

Receiver operating characteristic (ROC) curve analysis was then performed as an exploratory assessment of the discriminative ability of lipid markers for identifying patients with high SYNTAX scores. Area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and optimal cut-off values determined using the Youden index were calculated. Formal interaction analyses were additionally performed by incorporating interaction terms (age group × Lp(a) and age group × ApoB/ApoA1 ratio) into multivariable logistic regression models to explore potential age-dependent effects.

A two-sided p-value <0.05 was considered statistically significant. Given the exploratory nature of the study and modest sample size, adjustment for multiple comparisons was not performed and findings should be interpreted as hypothesis-generating. Residual confounding cannot be excluded. Multivariable linear regression using continuous SYNTAX score was additionally performed as a sensitivity analysis.

RESULTS

A total of 100 patients were included in the present study. The mean age of the study population was 46.5 ± 6.2 years and 85% of all participants were males. The baseline clinical characteristics of the study population are presented in Table 1.

Based on angiographic assessment using the SYNTAX scoring system, 63 patients (63%) were categorized as having low SYNTAX scores (≤22), while the remaining 37 (37%) had high SYNTAX scores (>22). This distribution indicates that although the majority of patients had less complex CAD, a substantial proportion exhibited significant angiographic complexity. Patients with high

TABLE 1. Baseline characteristics

Variable	Overall (n=100)
Age (years)	46.5 ± 6.2
Male sex, n (%)	85 (85%)
Diabetes mellitus, n (%)	13 (13%)
Hypertension, n (%)	34 (34%)
Smoking, n (%)	42 (42%)
BMI ≥ 25 kg/m², n (%)	29 (29%)
STEMI, n (%)	71 (71%)
NSTEMI, n (%)	29 (29%)

BMI=body mass index; STEMI=ST-elevation myocardial infarction; NSTEMI=non-ST-elevation myocardial infarction

TABLE 2. Lipid markers by SYNTAX score

Parameter	Low SYNTAX (n=63)	High SYNTAX (n=37)	p-value
Lp(a) (mg/dL)	33.36 ± 26.83	50.16 ± 24.23	0.002
ApoB (mg/dL)	95.47 ± 24.87	108.64 ± 18.98	0.007
ApoB/ApoA1 ratio	1.07 ± 0.31	1.24 ± 0.30	0.009
Total cholesterol (mg/dL)	169.29 ± 47.84	180.49 ± 49.83	0.268
HDL cholesterol (mg/dL)	34.92 ± 7.00	36.00 ± 8.07	0.484
LDL cholesterol (mg/dL)	128.22 ± 38.47	118.05 ± 39.04	0.207
Non-HDL cholesterol (mg/dL)	134.37 ± 46.52	144.49 ± 47.75	0.301
Triglycerides (mg/dL)	192.89 ± 115.37	183.03 ± 74.78	0.643

Lp=lipoprotein; ApoB=apolipoprotein B; ApoA1=apolipoprotein A1; HDL=high-density lipoprotein; LDL=low-density lipoprotein

TABLE 3. Age-stratified association of advanced lipid markers with SYNTAX score

Parameter	<45 years Low SYNTAX (n=32)	<45 years High SYNTAX (n=18)	p-value	45–55 years Low SYNTAX (n=31)	45–55 years High SYNTAX (n=19)	p-value
Lp(a) (mg/dL)	24.72 ± 21.50	54.26 ± 28.75	<0.001	42.28 ± 29.12	46.28 ± 19.00	0.598
ApoB (mg/dL)	98.63 ± 24.08	111.50 ± 17.80	0.037	92.20 ± 25.64	105.92 ± 20.12	0.053
ApoB/ApoA1 ratio	1.12 ± 0.30	1.36 ± 0.32	0.010	1.03 ± 0.31	1.13 ± 0.24	0.231

Lp=lipoprotein ; ApoA1=apolipoprotein A1; ApoB=apolipoprotein B

SYNTAX scores had significantly higher Lp(a) levels compared to those with low SYNTAX scores (50.16 ± 24.23 mg/dL *vs* 33.36 ± 26.83 mg/dL, p = 0.002) (Table 2), indicating a positive association between Lp(a) and coronary lesion complexity. ApoB and ApoB/ApoA1 ratio also demonstrated significant associations with SYNTAX score. Patients with high SYNTAX scores had higher ApoB levels (p = 0.007) and higher ApoB/ApoA1 ratios (p = 0.009) compared to those with low SYNTAX scores (Table 2). However, conventional lipid parameters, including LDL cholesterol, HDL cholesterol, triglycerides and ApoA1, did not show significant differences between SYNTAX groups, suggesting that advanced lipid markers may better reflect atherogenic burden in this population.

For exploratory post hoc analysis, patients were stratified into two age groups (<45 years and 45–55 years) to assess potential age-related differences in lipid-associated coronary lesion complexity. In this exploratory analysis, the associations between advanced lipid markers and SYNTAX score were predominantly observed in patients aged <45 years. In this subgroup, Lp(a) and ApoB/ApoA1 ratio were significantly higher in patients with high SYNTAX scores compared to those with low SYNTAX scores. In contrast, no statistically significant associations were observed between lipid markers and SYNTAX score in patients aged 45–55 years (Table 3). Formal interaction analysis was performed by introducing product terms into the multivariable logistic regression model. The age group × Lp(a) interaction term was statistically significant (interaction OR 0.952, 95% CI 0.917–0.989, p=0.011), providing additional evidence of an age-dependent association between Lp(a) and high SYNTAX score, with the relationship appearing stronger among patients aged <45 years (very premature MI) than among those aged 45–55 years. In contrast, no significant interaction was observed between age group and the ApoB/ApoA1 ratio in either the logistic (OR 0.288, 95% CI 0.013–6.545, p=0.435) or linear regression model (p=0.948).

Spearman correlation analysis was performed to further evaluate the relationship between lipid markers and coronary lesion complexity. There was a modest positive correlation between Lp(a) and SYNTAX score (ρ = 0.275, p = 0.006). Stronger correlations were noted for ApoB (ρ = 0.347, p < 0.001) and ApoB/ApoA1 ratio (ρ = 0.352, p < 0.001), suggesting that ApoB-related markers may reflect overall atherogenic particle burden, while Lp(a) may represent an additional pathway contributing to disease complexity. However, despite demonstrating significant continuous correlations with SYNTAX score, the ApoB/ApoA1 ratio did not retain independent association with high SYNTAX score after multivariable adjustment in logistic regression analysis. There were no significant correlations between SYNTAX score and conventional lipid parameters, including LDL cholesterol, HDL cholesterol, triglycerides, or ApoA1.

To identify independent predictors of high SYNTAX score, multivariable logistic regression analysis was performed using a restricted model (Table 4). Variables included in the model were hypertension, diabetes, smoking and lipid parameters based on clinical relevance. Hypertension emerged as an independent predictor of high SYNTAX score (adjusted OR 3.46, p = 0.012). The unadjusted association between Lp(a) and high SYNTAX score was at the threshold of conventional statistical significance (OR 1.02, 95% CI 1.00–1.03, p=0.050), but this association was attenuated and no longer significant after multivariable adjustment (p=0.171). Similarly, the ApoB/ApoA1 ratio was not independently associated with high SYNTAX score in the adjusted model (adjusted OR 2.24, 95% CI 0.47–10.69,

TABLE 4. Univariate and multivariable logistic regression analysis for predictors of high SYNTAX score

Variable	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age	1.02	0.96–1.08	0.533	—	—	—
Diabetes mellitus	2.39	0.73–7.84	0.152	2.63	0.75–9.22	0.131
Hypertension	2.93	1.19–7.20	0.019	3.46	1.31–9.11	0.012
Smoking	0.52	0.21–1.29	0.159	0.52	0.19–1.43	0.206
Lp(a)*	1.02	1.00–1.03	0.050	1.01	0.99–1.03	0.171
ApoB/ApoA1 ratio	2.42	0.61–9.57	0.209	2.24	0.47–10.69	0.310

OR *per* 1 mg/dL increase: *p=0.050 is at the threshold of conventional significance and should not be interpreted as a positive finding. Lp=lipoprotein; OR=odds ratio; CI=confidence interval

TABLE 5. Diagnostic performance of lipid parameters for predicting high SYNTAX score

Parameter	AUC (95% CI)	SE	p-value	Cut-off	Sensitivity (%)	Specificity (%)	PPV	NPV	Diagnostic accuracy
Lp(a)	0.64 (0.52–0.77)	0.06	0.024	32	83%	54%	0.42	0.88	0.62
ApoB	0.60 (0.48–0.73)	0.06	0.104	95.87	83%	45%	0.38	0.86	0.56
ApoB/ApoA1	0.60 (0.48–0.73)	0.06	0.112	0.99	90%	41%	0.38	0.91	0.55

CI=confidence interval; SE=standard error; PPV=positive predictive value; NPV=negative predictive value

p=0.310). Although the body mass index (BMI) was recorded and 29% of patients had BMI ≥25 kg/m², it was not included in the regression model to minimize the risk of overfitting, which is acknowledged as a limitation. Furthermore, family history of premature CAD was not systematically collected and therefore could not be incorporated into the multivariable analysis.

As a sensitivity analysis, multivariable linear regression was additionally performed using continuous SYNTAX score as the dependent variable (Supplementary table S1). The findings were broadly consistent with the primary logistic regression analysis. Hypertension remained independently associated with higher SYNTAX score (β=4.87, p=0.012), while the ApoB/ApoA1 ratio demonstrated a significant positive association with coronary lesion complexity (β=9.05, p=0.004). In contrast, Lp(a) showed a positive but non-significant association after adjustment (β=0.058, p=0.116). The attenuation of the associations between Lp(a), ApoB/ApoA1 ratio and high SYNTAX score after multivariable adjustment likely reflects both confounding by hypertension, which shares pathophysiological pathways with atherogenic dyslipidaemia, and limited statistical power, given the relatively small number of events and the intercorrelation among predictors.

Receiver operating characteristic curve analysis was performed as an exploratory assessment of the discriminative ability of lipid markers (Table 5). Lipoprotein(a) demonstrated modest discriminative ability, with an AUC of 0.64 (95% CI: 0.52–0.77, p = 0.024), indicating limited but statistically significant ability to differentiate between low and high SYNTAX score groups (Table 5, Figure 1). ApoB and ApoB/ApoA1 ratio also showed modest discriminative ability (AUC = 0.60), which did

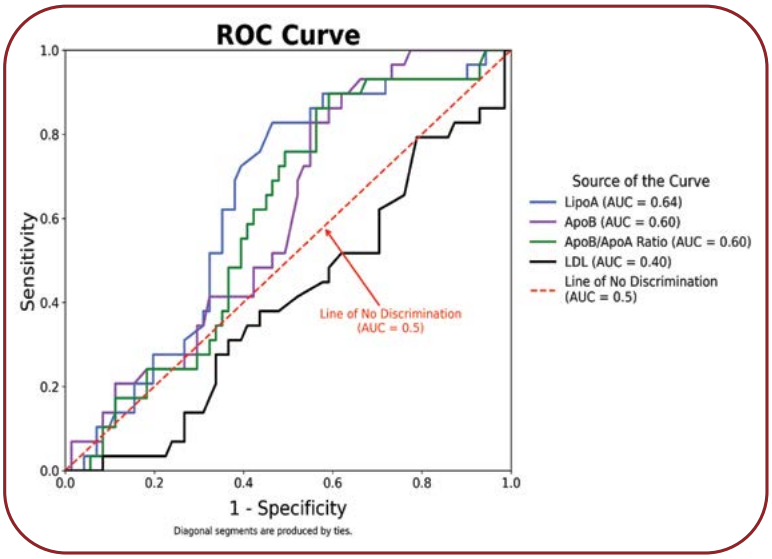

FIGURE 1. Receiver operating characteristic (ROC) curves for Lp(a), ApoB and ApoB/ApoA1 ratio for predicting high SYNTAX score (>22). All three curves are displayed on common axes. Area under the curve (AUC) values with 95% confidence interval (CI): Lp(a) 0.64 (95% CI 0.52–0.77, p=0.024); ApoB 0.60 (95% CI 0.48–0.73, p=0.104); and ApoB/ApoA1 ratio 0.60 (95% CI 0.48–0.73, p=0.112)

not reach statistical significance. The Youden-derived cut-off values for all three markers demonstrated high sensitivity (83–90%) but only modest specificity (41–54%), resulting in a considerable proportion of false-positive classifications. While these findings suggest that advanced lipid markers may have value in identifying patients with more complex CAD, their overall discriminative performance as standalone screening tools for high SYNTAX score was limited. Accordingly, these results should be interpreted cautiously and viewed as exploratory rather than definitive evidence of clinical utility.

DISCUSSION

The present study provides important insights into the relationship between advanced lipid markers and CAD complexity in patients with premature MI, particularly within a Northeast Indian population. The main finding was that Lp(a), ApoB and ApoB/ApoA1 ratio demonstrated significant associations with angiographic severity as assessed by SYNTAX score, whereas conventional lipid parameters did not. A notable finding was the apparent age-related variation in these associations, with exploratory analyses suggesting stronger relationships among patients aged <45 years. Formal interaction analysis further supported an age-dependent association between Lp(a) and high SYNTAX score (interaction OR 0.952, 95% CI 0.917–0.989, p=0.011), indicating that the relationship between Lp(a) and coronary lesion complexity was more pronounced in patients aged <45 years than in those aged 45–55 years. This observation is biologically plausible, as genetically determined risk factors such as Lp(a) may contribute proportionally more to coronary atherosclerotic burden at younger ages, when the cumulative effects of acquired cardiovascular risk factors, including hypertension and diabetes, are typically less substantial. In contrast, no significant interaction was observed for the ApoB/ApoA1 ratio (interaction p=0.435), and any apparent age-related differences for this marker should therefore be considered exploratory and hypothesis-generating. Correlation analysis demonstrated modest but significant positive associations between advanced lipid markers and SYNTAX score. However, in multivariable analysis, only hypertension remained an independent predictor of high SYNTAX score. Before interpretation, it is important to distinguish between statistically significant univariable associations, which reflect crude unadjusted relationships, and statistically significant independent associations identified in multivariable analysis, which account for coexisting clinical risk factors and therefore carry stronger inferential significance. Accordingly, the present findings suggest that advanced lipid markers may reflect overall atherogenic burden and coronary lesion complexity, but may not independently predict angiographic severity after adjustment for conventional cardiovascular risk factors.

Our results are consistent with prior evidence highlighting the limitations of conventional lipid parameters in reflecting coronary disease complexity. Ashfaq *et al* demonstrated a significant association between Lp(a) levels and both SYNTAX score and extent of vessel involvement (13). A recent Indian study evaluating extended lipid profiles in ACS patients reported significantly elevated lipid markers in ACS compared to controls but found no correlation between Lp(a) and SYNTAX score (10). The large multinational INTERHEART study, which included approximately 30,000 participants from 52 countries, identified the ApoB/ApoA1 ratio as a powerful predictor of myocardial infarction, surpassing traditional risk factors such as hypertension, smoking and diabetes (4, 14). The strength of this association was consistent across different ages, genders and ethnic groups, highlighting the broad applicability of the ApoB/ApoA1 ratio in cardiovascular risk assessment. A higher ApoB/ApoA1 ratio has been observed as a better risk predictor of CAD in various other studies (14-16).

In our study, ROC curve analysis demonstrated only modest discriminative ability for Lp(a) (AUC 0.64, p=0.024), while ApoB and the ApoB/ApoA1 ratio showed limited discriminatory performance (AUC 0.60 each). The Youden-derived cut-off values prioritised sensitivity (81–84%) over specificity (46–57%), resulting in substantial false-positive rates and limiting the utility of these markers as standalone screening tools for high SYNTAX score. An important methodological consideration is that lipid measurements, including Lp(a), were obtained within 24 hours of MI onset. As Lp(a) is a weakly positive acute-phase reactant, transient elevations of approximately 10–30% above baseline may occur during the acute phase of MI, with levels typically returning to steady

state within 4–6 weeks (17). Consequently, the higher Lp(a) concentrations observed among patients with high SYNTAX scores may partly reflect acute-phase responses superimposed on an underlying chronically elevated atherogenic burden. Our findings are consistent with those reported by Gupta *et al*, who demonstrate that although lipid parameters may show associations with angiographic severity, their discriminative ability remains limited (10). Similar to their observations, the modest AUC values in our study suggest that advanced lipid markers should not be considered standalone predictive tools but rather as adjunctive markers reflecting underlying atherogenic burden.

Given the modest discriminative performance observed in the present study, advanced lipid markers such as Lp(a) and ApoB-related parameters may be most appropriately considered as adjunctive second-line investigations in selected patients with premature MI. Their clinical utility may be greatest in individuals who demonstrate unexpectedly complex angiographic disease despite a low or intermediate conventional cardiovascular risk profile, or in those with a strong family history of premature CAD in the absence of significant conventional lipid abnormalities. In such settings, assessment of Lp(a) and ApoB-related markers may assist in refining residual atherogenic risk estimation and potentially guide the intensity of lipid-lowering strategies, including consideration of emerging targeted therapies. Nevertheless, the findings of the present study also reinforce that optimization of classical cardiovascular risk factor control remains the primary therapeutic priority, even in younger patients with premature MI.

Study limitations

The present study should be interpreted in the context of several limitations. Firstly, the cross-sectional design precludes inference regarding causality or temporal relationships. Secondly, the single-centre setting and relatively modest sample size may limit generalisability and statistical power; consequently, the post hoc subgroup analyses should be regarded as exploratory and hypothesis-generating. Thirdly, BMI was recorded but excluded from the multivariable model due to the event-per-variable constraint; therefore, BMI-mediated confounding cannot be excluded, and the likely direction of this omission is a modest upward bias in the estimated lipid marker associations. Fourthly, family history of premature CAD was not systematically collected and therefore could not be included as a covariate; given the known heritability of Lp(a), positive family history would be positively associated with both elevated Lp(a) and complex CAD, introducing potential upward confounding. Fifthly, Lp(a) and lipid samples were collected within 24 hours of MI onset; Lp(a) is a weakly positive acute-phase reactant and transient elevations of approximately 10–30% above chronic baseline cannot be excluded, potentially amplifying group differences. Sixthly, the cohort comprised 85% male patients, consistent with the known sex distribution of premature MI but limiting generalisability to women, in whom hormonal and metabolic influences on Lp(a) and coronary plaque phenotype may differ. With only 15 female patients, formal sex-stratified analysis was not feasible and gender-specific confounding cannot be excluded.

CONCLUSION

Advanced lipid markers, particularly Lp(a) and the ApoB/ApoA1 ratio, were associated with greater coronary lesion complexity in patients with premature MI, with formal interaction analysis suggesting that the relationship between Lp(a) and angiographic severity is more pronounced in patients aged <45 years, whereas no significant age-dependent effect was observed for the ApoB/ApoA1 ratio. However, the modest discriminative performance of these markers and attenuation of associations after multivariable adjustment indicate that they should be regarded as adjunctive indicators of atherogenic burden rather than independent predictors of angiographic severity. Larger prospective multicentre studies are needed to validate these findings and further clarify the role of advanced lipid markers in risk stratification among patients with premature myocardial infarction. ❑

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Variable	β	SE	95% CI	t	p-value
Constant (Intercept)	3.42	4.18	−4.83 to 11.67	0.82	0.415
Hypertension	4.87	1.90	1.12 to 8.62	2.56	0.012
Diabetes mellitus	3.14	2.74	−0.82 to 7.10	1.14	0.121
Smoking	−0.10	1.91	−3.89 to 3.69	−0.05	0.960
Lp(a) (per mg/dL)	0.058	0.037	−0.015 to 0.131	1.58	0.116
ApoB/ApoA1 ratio	9.05	3.07	2.94 to 15.15	2.95	0.004
Model fit: $R^2 = 0.198$ | Adjusted $R^2 = 0.147$ | $F(5,94) = 4.63$ | Overall p = 0.001					

SUPPLEMENTARY TABLE S1. Multivariable linear regression analysis with continuous SYNTAX score as dependent variable

Angiographic parameter	Overall (n=100)	Low SYNTAX score (≤22, n=63)	High SYNTAX score (>22, n=37)	p
Single-vessel disease	38 (38%)	36 (57%)	2 (5%)	<0.001
Double-vessel disease	34 (34%)	27 (43%)	7 (19%)	0.014
Triple-vessel disease	28 (28%)	0 (0%)	28 (76%)	<0.001
Left main involvement	6 (6%)	0 (0%)	6 (16%)	<0.001
Prior revascularisation				
Prior PCI	4 (4%)	3 (5%)	1 (3%)	0.617
Prior CABG	1 (1%)	0 (0%)	1 (3%)	0.370

SUPPLEMENTARY TABLE S2. Angiographic characteristics by SYNTAX score group