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Association of Lipoprotein(a) with Coronary Artery Disease Presence and Severity According to CAD-RADS on Coronary CT Angiography

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Abstract

Background: Lipoprotein(a) [Lp(a)] is a cardiovascular risk factor, but its relationship with coronary imaging phenotypes remains incompletely characterized. **Methods:** We performed a retrospective secondary analysis of previously collected data from 106 clinically referred adults who underwent coronary computed tomography angiography (CCTA). Analyses included a 30 mg/dL Lp(a) categorization, continuous logistic and ordinal regression, nonlinear splines, and bootstrap-based internal assessment. Clinical covariates were available only as group summaries. **Results:** Coronary artery disease (CAD) was present in 60.4%. CAD prevalence did not differ significantly between Lp(a) groups (odds ratio 1.82, 95% confidence interval 0.79–4.20). Continuous Lp(a) showed an unadjusted nonlinear association with Coronary Artery Disease Reporting and Data System (CAD-RADS) severity (nonlinearity $p < 0.001$). Coronary artery calcium (CAC) distributions were similar. The apparent area under the receiver operating characteristic curve was 0.801 (95% confidence interval 0.709–0.894). **Conclusions:** Lp(a) showed an exploratory nonlinear association with CCTA-defined disease in this referral-enriched cohort. Independence from confounding and clinical diagnostic utility remain unestablished.

Keywords: lipoprotein(a); coronary computed tomography angiography; CAD-RADS; coronary plaque; coronary artery calcium; receiver operating characteristic curve

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1. Introduction

Ischemic coronary heart disease remains a leading cause of morbidity and mortality worldwide and imposes a substantial socioeconomic burden on health systems [1,2]. Despite the widespread implementation of cardiovascular prevention guidelines and intensive lipid-lowering therapy, a considerable proportion of patients continue to experience atherosclerotic disease progression or recurrent events [3–7]. This residual cardiovascular risk reflects persistent inflammatory, metabolic, and genetically determined atherogenic pathways that are not fully addressed by conventional treatment. Identifying circulating

biomarkers that add biologically and clinically relevant information may improve individualized risk assessment.

Lipoprotein(a) [Lp(a)] is a liver-synthesized particle composed of a low-density lipoprotein (LDL)-like apolipoprotein B-100-containing a core covalently linked to apolipoprotein(a), a highly polymorphic glycoprotein [8,9]. More than 80–90% of circulating Lp(a) variation is genetically determined by the apolipoprotein(a)-encoding LPA locus; concentrations are generally stable throughout adult life and respond little to lifestyle change [9–11]. Statins do not meaningfully lower Lp(a), although they reduce LDL cholesterol and cardiovascular risk [11,12]. Lp(a) may promote atherosclerosis through its cholesterol cargo and oxidized phospholipids, amplify vascular inflammation, and exert potential prothrombotic or antifibrinolytic effects through the structural homology of apolipoprotein(a) with plasminogen [13–17].

Coronary computed tomography angiography (CCTA) characterizes coronary artery disease (CAD), including stenosis and plaque composition [18–20]. Coronary artery calcium (CAC) scoring quantifies calcified burden but does not capture noncalcified plaque [21]. The Coronary Artery Disease Reporting and Data System (CAD-RADS) 2.0 classifies maximal stenosis severity [22]. Previous studies link Lp(a) to low-attenuation plaque progression and suggest complementary risk information from Lp(a) and CAC [23–25]. Their relationship with cross-sectional imaging findings in clinically referred patients remains less clear.

We examined Lp(a) across four complementary CCTA domains: plaque presence, qualitative composition, calcified burden, and stenosis severity. Continuous and categorical analyses assessed whether these relationships were concordant within a clinically referred cohort; the study was not designed to establish screening or treatment utility.

2. Materials and Methods

2.1. Study Design and Population

We conducted a retrospective, single-center, cross-sectional secondary analysis of previously collected clinical, laboratory, and CCTA data from 106 consecutive adults referred for clinically indicated CCTA because of suspected stable coronary artery disease or reassessment of cardiovascular risk. Data were collected between January 2022 and December 2024 at the Center for Advanced Research in Multimodality Cardiac Imaging, part of CardioMed Medical Center in Târgu Mureș, Romania. The present analysis used these existing data without additional participant recruitment or study-specific procedures.

Selection was restricted to clinically referred adults with an available Lp(a) result and diagnostic-quality CCTA. Screening and exclusion counts and indications for Lp(a) test-ing were unavailable, limiting assessment of selection bias.

Inclusion criteria were age > 18 years, an available serum Lp(a) measurement, and diagnostic-quality CCTA. Exclusion criteria were previous coronary artery bypass grafting or percutaneous coronary intervention that precluded native-vessel CAD-RADS assessment, acute coronary syndrome within the preceding 3 months, severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m^2), documented allergy to iodinated contrast, or motion artifact that prevented reliable coronary analysis.

The original analytical threshold divided participants into Lp(a) < 30 mg/dL ($n = 67$) and >30 mg/dL ($n = 39$); none had exactly 30 mg/dL. This boundary separates lower concentrations from the 30–50 mg/dL grey zone and higher values [12], rather than defining uniformly high risk. The 2025 European Society of Cardiology (ESC)/European Atherosclerosis Society update identifies > 50 mg/dL as risk enhancing [26]. Continuous analyses therefore supplement this categorization. Values remain in mg/dL without molar conversion.

The original data collection was approved by the institutional ethics committee (Approval No. 26884, 10 November 2021) and the Scientific Research Ethics Committee of the

"George Emil Palade" University of Medicine, Pharmacy, Science and Technology of Târgu Mureș (Approval No. 1513, 9 December 2021), before data collection began in January 2022. The present study is a retrospective secondary analysis of those data. The research was conducted in accordance with the Declaration of Helsinki.

2.2. Clinical and Laboratory Assessment

Hypertension was defined by systolic pressure ≥ 140 mmHg, diastolic pressure ≥ 90 mmHg, or antihypertensive treatment; dyslipidemia by elevated total/LDL cholesterol under contemporaneous ESC recommendations or lipid-lowering treatment; and diabetes by fasting glucose ≥ 126 mg/dL, glycated hemoglobin ≥ 6.5%, or glucose-lowering treatment. Body mass index and active smoking were recorded. Clinical characteristics were available only as group summaries. Linked age, sex, risk factors, lipid concentrations, renal function, and medication type, dose, intensity, duration, and timing were unavailable for adjustment.

Clinical covariates were available only as aggregate summaries and could not be linked to individual outcomes. Multivariable adjustment was therefore not feasible, and no assumption of random missingness or absence of treatment was made.

Fasting venous blood samples were obtained before imaging. Serum lipoprotein(a) [Lp(a)] concentrations were measured using an immunoturbidimetric method on a BS-600M automated chemistry analyzer (Mindray, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China) and reported in mg/dL. Calibration and internal quality control were performed according to the manufacturer's instructions.

2.3. CCTA Acquisition and Image Analysis

Examinations were performed using a 128-slice multidetector CT system (SOMATOM Definition AS, Siemens Healthineers, Erlangen, Germany) at the Center for Advanced Research in Multimodality Cardiac Imaging, Cardio-Med Medical Center. A retrospectively electrocardiographically gated acquisition protocol was used, with heart-rate optimization before scanning; oral or intravenous beta-blockers were administered when clinically appropriate to achieve a target heart rate below 65 beats/min. The imaging protocol included an initial non-contrast scan for CAC scoring, followed by contrast-enhanced CCTA. Iodinated contrast medium (80–100 mL) was administered intravenously, followed by a 50 mL saline chaser, at an injection rate of 5.5–6.0 mL/s during a single breath-hold. Acquisition parameters included a tube voltage of 120 kV, gantry rotation time of 0.33 s, and detector collimation of 128 × 0.6 mm. All image datasets were digitally stored for subsequent reconstruction, analysis, and post-processing.

CAC was measured using the Agatston method and summarized as median/interquartile range, CAC = 0 prevalence, and categories < 10, 10–100, and >100. CAD comprised any coronary plaque. Recorded composition was noncalcified (NCP), mixed (MP), or predominantly calcified (CP); these labels describe visible composition, not validated vulnerability. CAD-RADS 2.0 grades 0–5 were modeled ordinally [22]; separate 4A/4B codes were unavailable. Collapsed grades 0–1, 2–3, and 4–5 were retained descriptively.

CAD-RADS categories represent maximal stenosis: 0, no plaque; 1, 1–24%; 2, 25–49%; 3, 50–69%; 4, 70–99% stenosis or qualifying left-main/three-vessel disease; and 5, total oc-clusion [22]. Noncalcified, mixed, and calcified labels describe the absence, coexistence, or predominance of visible calcium. A single composition label may not capture coexisting plaque phenotypes; comparisons are descriptive and subject to classification uncertainty.

Experienced readers, blinded to laboratory results, assessed images using syngo.via Frontier (Siemens Healthineers, Erlangen, Germany); non-evaluable segments were excluded and disagreements resolved by consensus. Analysis used one recorded composition label per CAD-positive patient. The original allocation hierarchy, lesion-level measure-

ments, quantitative plaque burden, and high-risk features were unavailable. Independent pre-consensus or repeat readings were also unavailable; consensus labels alone cannot support inter- or intraobserver agreement estimates.

2.4. Statistical Analysis

All 106 records had complete Lp(a) and imaging variables; CAD status agreed with CAD-RADS 0 versus >0. Continuous variables are summarized as median (interquartile range) or mean ± standard deviation, and categories as *n* (%). Original baseline summaries and tests were retained because individual clinical values were unavailable. Reanalyzed comparisons used two-sided Fisher's exact, Pearson chi-square, or tie-corrected Mann–Whitney U tests, as appropriate. Binary comparisons include odds ratios (ORs) and 95% confidence intervals (CIs). No patient values were imputed.

Unadjusted logistic regression modeled CAD, and cumulative-logit proportional-odds regression modeled CAD-RADS 0–5. Restricted cubic splines of log2 Lp(a) used four knots at the 5th, 35th, 65th, and 95th percentiles. Likelihood-ratio tests compared spline and log-linear models (two additional degrees of freedom). The ordinal spline was the primary severity model; log-linear ORs per doubling and Spearman correlation were secondary summaries. The proportional odds was assessed by a joint Wald comparison across five cumulative binary logits, accounting for shared participants through individual-score covariance [27]. Models developed during revision are exploratory; linked confounders were unavailable.

Sensitivity analyses varied the ordinal spline specification: three knots (10th, 50th, 90th percentiles), shifted four knots (10th, 35th, 65th, 90th), merging CAD-RADS 4–5, and excluding Lp(a) values outside the 5th–95th percentiles. Knots were recalculated in the trimmed sample. Each spline was compared with the corresponding log-linear model by likelihood-ratio testing. These checks assess dependence on specification, not external validity.

Receiver operating characteristic (ROC) analysis evaluated continuous Lp(a), with a DeLong normal-approximation CI for the area under the curve (AUC). The Youden index selected the lowest maximizing observed threshold using a strict "greater than" rule. Internal assessment repeated selection in 2000 outcome-stratified bootstrap samples (seed 20261022); mean differences between resample and original-sample performance were subtracted from apparent sensitivity, specificity, accuracy, and Youden index [28]. A bootstrap percentile AUC interval was also calculated. Tests used nominal two-sided $p < 0.05$ without multiplicity adjustment. Original summaries used GraphPad Prism 10.3.1 and MedCalc 20.2.18; reanalysis used Python 3.11.9, withNumPy, SciPy, pandas and scikit-learn with maximum-likelihood logistic and ordinal routines.

3. Results

3.1. Cohort Characteristics

Among 106 participants, mean age was 58.49 ± 9.54 years and 61.3% were men (Table 1). Nonsignificant baseline comparisons do not establish covariate balance. Median Lp(a) was 19.55 mg/dL (interquartile range 10.03–82.10) overall, 11.90 (6.00–18.45) below 30 mg/dL, and 97.90 (77.75–128.55) above 30 mg/dL. Clinical referral and the observed risk-factor burden preclude describing this cohort as uniformly low risk.

Table 1. Baseline characteristics according to Lp(a) group.

Characteristic [1]	Overall ($n = 106$)	Lp(a) < 30 ($n = 67$)	Lp(a) > 30 ($n = 39$)	p Value
Age, years	58.49 ± 9.54	57.73 ± 9.77	59.79 ± 9.10	0.2767
Male sex, n (%)	65 (61.3)	40 (59.7)	25 (64.1)	0.6845
BMI, kg/m^2	27.8 (25.4–30.5)	28.1 (25.4–31.6)	27.4 (25.6–30.0)	0.3618
Hypertension, n (%)	59 (55.7)	36 (53.7)	23 (59.0)	0.6866
Dyslipidemia, n (%)	71 (67.0)	43 (64.2)	28 (71.8)	0.5219
Type 2 diabetes, n (%)	19 (17.9)	13 (19.4)	6 (15.4)	0.7937
Active smoking, n (%)	36 (34.0)	24 (35.8)	12 (30.8)	0.6734

[1] Values are mean ± SD, median (IQR), or n (%). BMI, body mass index; Lp(a), lipoprotein(a). Original clinical summaries and p values are retained. Individual clinical covariates, lipid/renal measurements, and treatment histories were unavailable for linkage; omission does not imply normal values or absence of treatment.

3.2. Coronary Atherosclerosis and Plaque Phenotype

CAD occurred in 37/67 participants below 30 mg/dL and 27/39 above 30 mg/dL (55.2% vs. 69.2%; OR 1.82, 95% CI 0.79–4.20; $p = 0.2166$). Among CAD-positive patients, non-calcified and mixed labels were numerically more frequent in the higher-Lp(a) group, but the overall composition distribution did not differ significantly ($p = 0.1747$; Table 2).

Table 2. CCTA findings according to Lp(a) group.

CCTA Finding [1]	Overall	Lp(a) < 30	Lp(a) > 30	Global p Value
Any coronary plaque	64 (60.4)	37 (55.2)	27 (69.2)	0.2166
Plaque phenotype among CAD-positive participants	$n = 64$	$n = 37$	$n = 27$	0.1747
Noncalcified	21 (32.8)	10 (27.0)	11 (40.7)	-
Mixed	26 (40.6)	14 (37.8)	12 (44.4)	-
Calcified	17 (26.6)	13 (35.1)	4 (14.8)	-
CAC median (IQR)	0 (0–34.8)	0 (0–32.4)	0 (0–37.2)	0.9912
CAC = 0	63 (59.4)	40 (59.7)	23 (59.0)	1.000
CAC categories	$n = 106$	$n = 67$	$n = 39$	0.3003
<10	66 (62.3)	42 (62.7)	24 (61.5)	-
10–100	26 (24.5)	14 (20.9)	12 (30.8)	-
>100	14 (13.2)	11 (16.4)	3 (7.7)	-
CAD-RADS grades	$n = 106$	$n = 67$	$n = 39$	-
0	42 (39.6)	30 (44.8)	12 (30.8)	-
1	16 (15.1)	9 (13.4)	7 (17.9)	-
2	14 (13.2)	8 (11.9)	6 (15.4)	-
3	16 (15.1)	10 (14.9)	6 (15.4)	-
4	2 (1.9)	2 (3.0)	0 (0.0)	-
5	16 (15.1)	8 (11.9)	8 (20.5)	-
Collapsed CAD-RADS	$n = 106$	$n = 67$	$n = 39$	0.6090
0–1	58 (54.7)	39 (58.2)	19 (48.7)	-
2–3	30 (28.3)	18 (26.9)	12 (30.8)	-
4–5	18 (17.0)	10 (14.9)	8 (20.5)	-

[1] Values are median (IQR) or n (%). Composition percentages use CAD-positive patients; CAC and CAD-RADS use all 106. CAC = 0 is included in <10. Global p values compare composition, CAC categories, or collapsed CAD-RADS; exact grades are descriptive. CAC, coronary artery calcium; CAD, coronary artery disease; CCTA, coronary computed tomography angiography.

3.3. Coronary Calcium and CAD-RADS

Median CAC was 0 (IQR 0–32.4) below 30 mg/dL and 0 (0–37.2) above 30 mg/dL (Mann–Whitney $p = 0.9912$). CAC = 0 occurred in 59.7% and 59.0%, respectively ($p = 1.000$). Three low positive scores had been omitted from the original category totals; all 106 CAC

measurements were available. Corrected < 10 counts were 42/67 and 24/39 (category comparison $p = 0.3003$). Full CAD-RADS counts appear in Table 2; collapsed grades did not differ significantly ($p = 0.6090$).

3.4. Exploratory ROC Analysis

Apparent AUC was 0.801 (95% CI 0.709–0.894; Figure 1); its bootstrap percentile interval was 0.700–0.891. At the exploratory > 10.7 mg/dL operating point, sensitivity and specificity were 93.8% and 64.3%. Bootstrap correction reduced these to 92.8% and 62.0%, with accuracy 80.6% (Table 3). Selected thresholds had descriptive 2.5th–97.5th percentiles of 8.7–14.2 mg/dL.

Table 3. Exploratory operating-point classification and bootstrap internal assessment.

Metric [1]	Apparent	Optimism Corrected	Basis
Sensitivity	93.8%	92.8%	60/64
Specificity	64.3%	62.0%	27/42
Accuracy	82.1%	80.6%	87/106
Youden index	0.580	0.548	Sensitivity + specificity − 1
Positive predictive value	80.0%	Not estimated	60/75
Negative predictive value	87.1%	Not estimated	27/31

[1] Apparent estimates use >10.7 mg/dL. Corrected estimates subtract mean optimism after threshold reselection in 2000 stratified bootstrap samples; they assess the selection procedure, not an externally validated cutoff. Predictive values are apparent and prevalence-dependent.

Internal resampling evaluates optimism in the threshold-selection procedure, not external validity of a fixed cutoff. The >10.7 mg/dL operating point remains strictly exploratory and must not be used to exclude CAD, guide treatment, or select patients for CCTA.

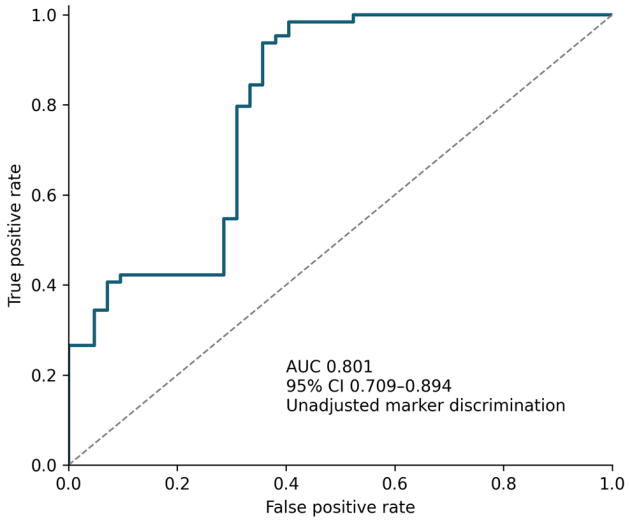


Figure 1. ROC curve of continuous Lp(a) for CCTA-defined CAD ($n = 106$). AUC, area under the curve; ROC, receiver operating characteristic. Marker discrimination is unadjusted and does not establish clinical utility.

3.5. Continuous Lp(a) and CAD-RADS Severity

Continuous Lp(a) was associated with CAD and ordinal CAD-RADS in unadjusted models (Table 4). Splines improved fit over log-linear models for both outcomes (nonlinearity $p < 0.001$). The ordinal spline showed an overall association ($\chi^2 = 73.20$, 3 df; $p < 0.001$); its proportional-odds diagnostic was nonsignificant ($\chi^2 = 14.80$, 12 df; $p = 0.252$). The non-

monotonic fit (Figure 2) limits interpretation of a single per-doubling OR. No observations fell between 25.6 and 42.8 mg/dL, and only two patients had CAD-RADS 4, limiting the assessment of shape and assumptions.

Table 4. Unadjusted patient-level models and functional-form assessment.

Outcome [1]	Estimate	95% CI	*p* Value
Any CAD, >30 versus <30 mg/dL	OR 1.82	0.79–4.20	0.2166
CAD, log-linear model per doubling	OR 1.93	1.44–2.59	<0.001
Full CAD-RADS, log-linear model per doubling	Common OR 1.65	1.33–2.04	<0.001
Full CAD-RADS, spline overall association	LR $\chi^2 = 73.20$; df = 3	—	<0.001
Full CAD-RADS, spline nonlinearity	LR $\chi^2 = 50.78$; df = 2	—	<0.001
CAD presence, spline nonlinearity	LR $\chi^2 = 48.41$; df = 2	—	<0.001
Spline proportional-odds diagnostic	Wald $\chi^2 = 14.80$; df = 12	—	0.252
Lp(a) and CAD-RADS, Spearman	$\rho = 0.489$	—	<0.001

[1] All models are exploratory and unadjusted. The ordinal spline is the primary severity model; log-linear ORs are secondary because of nonlinearity. OR, odds ratio; CI, confidence interval; LR, likelihood ratio; df, degrees of freedom. The proportional-odds test compares three spline coefficients across five cumulative logits.

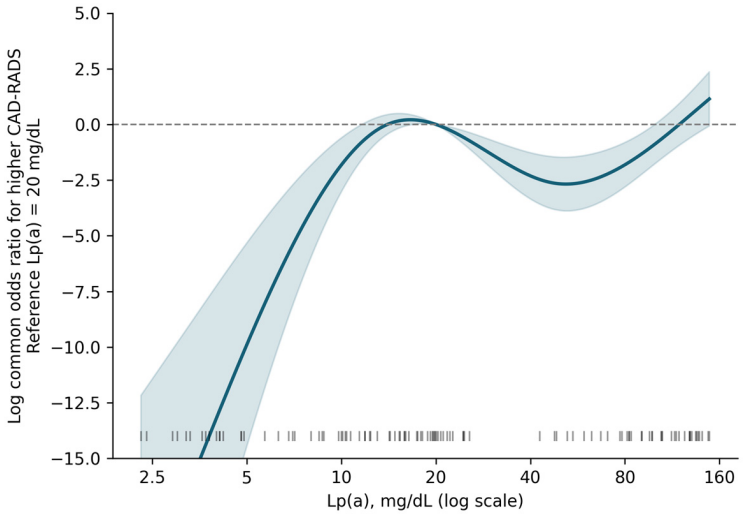


Figure 2. Unadjusted ordinal restricted cubic spline. The log common OR is relative to 20 mg/dL; the Lp(a) axis is logarithmic. Shading shows pointwise 95% Wald CIs; rug marks show observations. Sparse exposure regions limit interpretation; the curve does not establish a causal dose response.

Nonlinearity persisted with three knots ($\chi^2 = 17.61$, 1 df; $p < 0.001$), shifted four knots ($\chi^2 = 50.98$, 2 df; $p < 0.001$), merged grades 4–5 ($\chi^2 = 51.21$, 2 df; $p < 0.001$), and exclusion of ex-treme Lp(a) values ($n = 94$; $\chi^2 = 42.76$, 2 df; $p < 0.001$). All models converged. Lp(a) intervals ≤ 10, >10–20, >20–30, >30–50, >50–75, >75–100, and >100 mg/dL contained 27, 29, 11, 3, 6, 11, and 19 participants, respectively; corresponding CAD counts were 2, 25, 10, 0, 1, 9, and 17. These uneven distributions support reporting nonlinearity but do not establish a reproducible curve shape.

4. Discussion

Continuous Lp(a) showed an unadjusted nonlinear association with CAD and CAD-RADS, whereas comparisons at 30 mg/dL were nonsignificant. The contribution is a joint assessment of complementary CCTA domains in a clinically referred cohort, rather than a new diagnostic threshold or first demonstration of Lp(a)-related atherosclerosis.

Epidemiological and genetic studies support an association between Lp(a) and cardiovascular risk [10,11,29]. This biological evidence supports studying Lp(a) but does not eliminate confounding or referral bias in the present imaging cohort.

Lp(a)-associated inflammation provides a plausible link to plaque biology [14,15]. Kaiser et al. studied advanced stable CAD with serial CCTA and found greater 12-month low-attenuation plaque progression at Lp(a) $\geq$ 70 mg/dL (26.2 versus −0.7 mm^3; $p = 0.020$) [24]. Our nonsignificant composition comparison concerns a single qualitative patient-level label at one examination, using a lower analytical boundary. Differences in population, exposure definition, and longitudinal quantitative versus cross-sectional qualitative endpoints prevent direct replication or contradiction of their result. Our labels cannot establish plaque vulnerability.

Mehta et al. assessed incident cardiovascular risk in 4512 MESA and 2078 Dallas Heart Study participants, evaluating Lp(a) jointly with CAC [23,25]. Their outcome-based analysis differs from our comparison of contemporaneous CAC distributions. Thus, the absence of a significant CAC difference in 106 referred patients does not refute complementary prognostic information from these markers. CAC = 0 also does not exclude non-calcified plaque [21], as observed here; our sample cannot establish equivalence between groups.

Ordinal modeling respects CAD-RADS ordering without assuming equal distances between grades. Sensitivity analyses retained evidence of nonlinearity across knot choices, merged severe grades, and tail exclusion. However, these are repeated analyses of the same small cohort: they do not establish stability of turning points, exclude overfitting, or resolve the exposure gap. The fitted downturn must not be interpreted as a protective Lp(a) range. A nonsignificant proportional-odds diagnostic does not prove the assumption; independent replication remains necessary.

The apparent AUC and bootstrap-corrected classification remain conditional on this referred cohort. CAD prevalence (60.4%) affects predictive values, while case mix can affect discrimination. Without an independent cohort or clinical comparator, neither transportability nor incremental utility is established; Lp(a)-based CCTA referral is unsupported.

Consensus supports Lp(a) measurement within cardiovascular risk assessment [12,26]. Dimitriadis et al. discuss residual lipid risk and therapies targeting LDL cholesterol, Lp(a), apolipoprotein C-III, and angiopoietin-like protein 3 [30]. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition modestly lowers Lp(a) [31]; antisense and small-interfering ribonucleic acid approaches produce larger reductions [32–34]. Our missing treatment histories preclude assessment of these effects. Dyslipidemia status cannot be a substitute for cumulative LDL exposure or treatment intensity, so residual confounding remains.

5. Strengths and Limitations

Strengths include complementary CCTA measures, blinded image reading, complete Lp(a)/imaging data, ordinal modeling with diagnostic checks, and bootstrap internal assessment.

This retrospective, single-center, cross-sectional study is susceptible to referral bias and cannot establish causality. Group-level clinical summaries lack the joint patient-level information required for adjustment; imputing entirely absent covariates would impose unverifiable assumptions. Nonsignificant baseline tests do not exclude confounding. The exploratory models are limited by sample size, exposure gaps, sparse grades, and unadjusted multiple testing. Unavailable lesion-level data and independent reader ratings limit phenotype interpretation and reproducibility assessment. External validation, clinical comparators, and longitudinal outcomes are absent.

6. Conclusions

Lp(a) showed an exploratory nonlinear association with CCTA-defined disease in this referral-enriched cohort. Unmeasured confounding and limited validation preclude an independent-effect claim or clinical cutoff. Studies with complete covariates and independent validation are required.

Author Contributions: Conceptualization, A.I.R., B.B.M., I.K. and T.B.; methodology, A.I.R., B.B.M., I.K. and N.R.; software, B.B.M. and N.R.; validation, B.B.M., I.K. and T.B.; formal analysis, A.I.R. and B.B.M.; investigation, A.I.R., B.B.M., N.R. and I.S.B.; resources, I.K., I.S.B. and T.B.; data curation, A.I.R. and B.B.M.; writing—original draft preparation, A.I.R. and B.B.M.; writing—review and editing, B.B.M., I.K., N.R., I.S.B. and T.B.; visualization, A.I.R. and B.B.M.; supervision, I.K. and T.B.; project administration, I.K. and T.B. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study is a retrospective secondary analysis of previously collected clinical, laboratory, and coronary CT angiography data. The original data collection was approved by the institutional ethics committee (Approval No. 26884, 10 November 2021) and the Scientific Research Ethics Committee of the "G. E. Palade" University of Medicine, Pharmacy, Science and Technology of Târgu Mureș (Approval No. 1513, 9 December 2021). These approvals preceded the January 2022–December 2024 data-collection period. The present secondary analysis involved no additional participant recruitment or study-specific procedures. The research was conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement: Written informed consent has been obtained from the patients to publish this paper.

Data Availability Statement: The data presented in this study are available upon request from the corresponding author. The data are not publicly available due to privacy reasons.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AUC	Area under the curve
BMI	Body mass index
CAC	Coronary artery calcium
CAD	Coronary artery disease
CAD-RADS	Coronary Artery Disease Reporting and Data System
CCTA	Coronary computed tomography angiography
CI	Confidence interval
CP	Calcified plaque
df	Degrees of freedom
ECG	Electrocardiography

ESC	European Society of Cardiology
HDL	High-density lipoprotein
HU	Hounsfield units
IQR	Interquartile range
LDL	Low-density lipoprotein
Lp(a)	Lipoprotein(a)
LPA	Lipoprotein(a) gene
LR	Likelihood ratio
MESA	Multi-Ethnic Study of Atherosclerosis
MP	Mixed plaque
NCP	Noncalcified plaque
OR	Odds ratio
PCSK9	Proprotein convertase subtilisin/kexin type 9
RNA	Ribonucleic acid
ROC	Receiver operating characteristic
SD	Standard deviation

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