IJPSR (2025), Volume 16, Issue 2 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 01 January 2025; received in revised form, 13 January 2025; accepted, 13 January 2025; published 01 February 2025

THE IMPACT OF REMNANT CHOLESTEROL AND LIPID PROFILE DISCORDANCE ON CAROTID INTIMA-MEDIA THICKNESS AMONG INDIAN PATIENTS WITH CORONARY ARTERY DISEASE: AN EXPLORATORY OBSERVATIONAL STUDY WITH ADVANCED REGRESSION ANALYSIS

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Keywords:

Remnant cholesterol, Lipid profile discordance, Carotid intima-media thickness, Coronary artery disease, Atherosclerosis

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ABSTRACT: Background: Residual cardiovascular risk persists despite optimal LDL-C lowering, suggesting that remnant cholesterol (RC) may contribute to atherosclerosis. **Objective:** To evaluate the association between RC, lipid profile discordance, and cIMT, and determine if RC and lipid discordance are independent predictors of increased cIMT after adjusting for traditional cardiovascular risk factors. **Methods:** In this cross-sectional study of 60 patients (mean age 56 ± 10 years, 63% male) with cardiovascular conditions, cIMT measurements and lipid profiles were obtained. RC was calculated as total cholesterol minus LDL-C minus HDL-C. Patients were grouped into four categories based on median LDL-C and RC levels. Statistical analyses assessed associations between RC, lipid discordance, cIMT, and cardiovascular risk factors. **Results:** RC showed a moderate positive correlation with cubed mean cIMT ($r = 0.36$, $p = 0.0047$). Patients with high discordant RC had significantly higher cubed mean cIMT compared to those with low concordant levels. In regression analysis, body mass index ($\beta = 0.337$, $p < 0.001$), smoking status ($\beta = 0.819$, $p = 0.002$), and LDL-C ($\beta = 0.010$, $p = 0.044$) were significant predictors of cubed cIMT, while RC showed a trend toward significance ($\beta = 0.129$, $p = 0.110$). **Conclusion:** Elevated RC and lipid discordance are associated with increased cIMT. Incorporating RC into cardiovascular risk models could help identify high-risk patients who might benefit from targeted therapies. Further research is needed to confirm these findings.

INTRODUCTION: Cardiovascular diseases, particularly coronary artery disease (CAD), remain the leading cause of death worldwide [1]. Despite advances in lipid-lowering therapies targeting low-density lipoprotein cholesterol (LDL-C), a substantial residual cardiovascular risk persists with elevated remnant cholesterol [2, 3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(2).565-83

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(2).565-83

This suggests that other lipid fractions and risk factors contribute to the development and progression of atherosclerosis.

Remnant Cholesterol and Atherosclerosis: Remnant cholesterol (RC) is the cholesterol content carried within triglyceride-rich lipoproteins (TRL), including very low-density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL), it contains up to 4 times as much cholesterol per particle as compared to Low-density lipoproteins (LDL) [3]. Unlike LDL-C, which has been extensively studied, the role of RC in atherogenesis has gained attention more recently.

Elevated RC levels have been associated with an increased risk of ischemic heart disease and all-cause mortality, regardless of LDL-C levels [3-5]. RC particles are considered highly atherogenic due to their direct ability to penetrate the subendothelial space and enter the arterial intima, promote endothelial dysfunction, and induce inflammatory responses. They are larger than LDL particles and can carry more cholesterol per particle, potentially leading to greater plaque formation [6].

Discordant Lipid Profiles: Discordant lipidology refers to the inconsistency between LDL-C levels and other lipid parameters such as non-HDL cholesterol (non-HDL-C), apolipoprotein B (ApoB) and RC [7]. Non-HDL-C includes all atherogenic lipoproteins, providing a more comprehensive risk assessment [3]. Patients with discordant lipid profiles may have normal LDL-C but elevated non-HDL-C or ApoB, indicating an increased number of atherogenic particles and a higher cardiovascular risk.

Carotid Intima Media Thickness as a Marker: Carotid intima-media thickness (cIMT) is a non-invasive measure of subclinical atherosclerosis. Increased cIMT is associated with a higher risk of myocardial infarction and stroke [8]. cIMT assessment can aid in early detection of atherosclerotic changes before clinical manifestations occur.

Rationale and Objectives: This study explores the relationship between remnant cholesterol, discordant lipid profiles, and mean carotid intima-media thickness in predicting the severity of coronary artery disease. Using advanced regression analyses, our objective is to determine whether RC and lipid discordance are independent predictors of increased cIMT and CAD severity after adjusting for traditional cardiovascular risk factors.

MATERIALS AND METHODS:

Study Design and Population: This cross-sectional, observational study was conducted at a tertiary care hospital over a six-month period (January to June 2024). A total of 60 patients with various cardiovascular conditions were enrolled. This study was designed as an exploratory analysis to generate hypotheses for future research with larger sample sizes.

Inclusion Criteria:

Patients were eligible for inclusion if they met the following criteria:

- Age ≥18 years.
- Diagnosed with one of the following cardiovascular conditions:
  - ST-elevation myocardial infarction (STEMI), confirmed by positive cardiac biomarkers and electrocardiography (ECG).
  - Non-ST-elevation myocardial infarction (NSTEMI), confirmed by positive cardiac biomarkers electrocardiography (ECG).
  - Unstable angina, confirmed by angiographically proven significant coronary artery disease.
  - Chronic stable angina, confirmed by angiographically proven significant coronary artery disease.
  - Intermediate- or high-risk atherosclerotic cardiovascular disease (ASCVD) (Framingham Risk Score >10%) with normal coronary arteries on angiography.
- Availability of carotid intima-media thickness (cIMT) measurements from high-resolution B-mode ultrasound.
- Complete lipid profile data, including direct measurement of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TG).
- Patients are taking at least moderate intensity statins.

Note: For patients diagnosed with STEMI or NSTEMI, CAD severity was inferred based on clinical presentation, electrocardiographic changes, and elevated cardiac biomarkers, consistent with established diagnostic criteria [9]. While CAG provides detailed anatomical information, it was not mandatory for these patients due to emergent clinical management priorities. In such cases, the presence of an acute coronary syndrome was considered indicative of significant obstructive CAD. However, detailed assessment of CAD

severity (e.g., number of vessels involved) was not available for these patients without CAG data.

Exclusion Criteria:

The following exclusion criteria were applied:

- Presence of acute or chronic inflammatory diseases (e.g., autoimmune disorders, active infections).
- Significant liver dysfunction, defined as transaminase levels exceeding three times the upper limit of normal.
- Known familial hypercholesterolemia or other primary lipid disorders.
- Chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m².
- History of malignancy or ongoing cancer treatment.
- Pregnancy or lactation.
- Ongoing treatment with systemic corticosteroids or immunosuppressants.
- Patients with incomplete or missing clinical or laboratory data (e.g., unavailable cIMT or lipid profile measurements).
- Patients with hemodynamic instability or cardiogenic shock requiring immediate intervention during the study period.

Ethical Considerations: The study was approved by the Institutional Ethics Committee and informed consent was obtained from all participants (IEC no. Dean/2024/EC/6953 dated 28/02/2023).

Data Collection:
Demographic and Clinical Data:

1. Age, sex, smoking status.
2. Medical history: hypertension, diabetes mellitus, previous stroke or transient ischemic attack (TIA), hypothyroidism, chronic kidney disease (CKD).
3. Anthropometric measurements: weight, height, body mass index (BMI).

Laboratory Investigations: Lipid profiles were obtained from serum samples collected irrespective of fasting status, in line with emerging guidelines supporting non-fasting lipid testing for cardiovascular risk assessment [10, 11]. Although triglyceride levels can be affected by recent food intake, studies have shown that the increase in remnant cholesterol concentrations after meals is minimal and not statistically significant [12]. The median levels of RC were 0.55 mmol/l during fasting and 0.67 mmol/l at 3 to 4 h after the last meal [13]. The highest and lowest levels were seen at 1 and 7 pm, respectively. Moreover, non-fasting samples may provide a more accurate representation of the usual metabolic conditions under which remnant lipoproteins contribute to atherosclerosis [10]. Total cholesterol was measured using the CHOD-PAP method triglycerides were measured using the GPO-PAP method, while the direct homogeneous enzyme method was used for measuring LDL-C and HDL-C.

Glycaemic Status: Hemoglobin A1c (HbA1c), random blood sugar (RBS).

Renal Function Tests: Urea, creatinine, estimated glomerular filtration rate (eGFR).

Liver Function Tests: Alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, direct bilirubin.

Thyroid Function Tests: Thyroid-stimulating hormone (TSH).

Lipid Calculations:
Remnant Cholesterol (RC): RC = TC - LDL-C - HDL-C.

Non-HDL Cholesterol (Non-HDL-C): Non-HDL-C = TC - HDL-C.

Definition of Lipid Profile Discordance: Patients were classified into four groups based on median LDL-C and RC splits, as described by [14]

Concordant Low: LDL-C < median and RC < median.

Discordant High RC: LDL-C < median and RC > median.

Concordant High: LDL-C > median and RC > median.

Discordant Low RC: LDL-C > median and RC < median.

Carotid Intima-Media Thickness Measurement: Carotid ultrasonography was conducted manually by certified sonographers who were blinded to the baseline characteristics of the participants and the laboratory findings. All examinations were performed according to the Mannheim consensus guidelines by [15] using high-resolution B-mode ultrasound machines (Vivid T8, GE Healthcare) equipped with a 7.5- to 15 MHz linear-array transducer.

Measurement Sites: Far wall of the bilateral common carotid arteries, in a plaque-free segment at least 10 mm proximal to the bifurcation.

Plaque Identification: Focal structures encroaching into the arterial lumen by at least 0.5 mm or 50% of the surrounding intima-media thickness, or with a thickness greater than 1.5 mm.

Data Analysis: Mean and maximum cIMT values calculated; an abnormal cIMT defined as a mean or maximum cIMT value of ≥1 mm [16, 17].

Data Transformation for Normality: The choice of transformation for each variable was based on the specific characteristics of its distribution and the goal of achieving an approximate normal distribution. For each variable, we assessed normality using graphical methods (histograms, Q-Q plots) and statistical tests (e.g., Shapiro-Wilk test). The transformation that most effectively normalized the distribution was selected. Variables showing significant deviations from normality were transformed to improve statistical analyses:

Diastolic Blood Pressure (mmHg): log transformation was applied due to slight positive skewness (4.014, p=0.024) ($\chi^2(2) = 1.14$, p = 0.566)

SGOT (U/L): inverse square root transformation was applied because of moderate positive skewness (7.41, p<0.001) and high kurtosis (56.57, p<.0001) ($\chi^2(2)=2.18$, p = 0.336).

SGPT (U/L): inverse square root transformation was applied because of moderate positive skewness (7.44, p<0.001) and high kurtosis (56.86, p<.0001) ($\chi^2(2)=2.50$, p = 0.287).

Creatinine (mg/dL): inverse transformation was applied because of moderate positive skewness (5.36, p<0.001) and high kurtosis (36.12, p<.0001) ($\chi^2(2)=1.12$, p = 0.572).

Triglycerides (mg/dL): Square root transformation was used to address slight positive skewness (0.72, p<0.02) (χ^2 (2) = 3.11, p = 0.211).

Remnant Cholesterol (mg / dL): Square root transformation was used to address slight positive skewness (0.88, p<0.006) ($\chi^2(2)=2.66$, p = 0.264).

LVEF (%): Log transformation was applied to correct for slight kurtosis (1.96, p<0.004) ($\chi^2(2)=6.46$, p = 0.040).

cIMT (Mean): Cubic transformation was employed after other transformations did not sufficiently normalize the data for mild kurtosis (4.0, p=0.001) ($\chi^2(2)=1.57$, p = 0.455).

Coronary Angiography: In patients with unstable angina and chronic stable angina, CAG was performed to assess CAD severity based on the number of vessels involved and the degree of luminal narrowing (defined as >70% narrowing for non-left main coronary artery lesions and >50% for left main coronary artery lesions). For patients presenting with STEMI or NSTEMI, CAD severity was inferred from clinical presentation, electrocardiographic changes, and elevated cardiac biomarkers, as immediate management took precedence over diagnostic angiography in some cases [9]. Although CAG provides detailed anatomical information, it was not mandatory for these patients due to emergent care considerations. As a result, while the presence of significant CAD was established, detailed anatomical severity assessment was not available for all patients.

Statistical Analysis: Data were analyzed using StataNow 18.5 BE (StataCorp LLC, USA). Continuous variables were presented as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. The Independent Samples t-test was used to compare mean cIMT values between groups (eg elevated vs normal RC levels). The Chi-square test was used for categorical variables (eg, presence of multivessel disease).

Pearson's correlation coefficient (r) was used to assess the relationship between RC levels, lipid parameters, and cIMT. Multiple linear regression with mean cIMT as dependent variable and independent variables, including RC, lipid discordance, LDL-C, HDL-C, TG, age, BMI, hypertension, diabetes, and smoking status, was performed. A p-value <0.05 was considered statistically significant.

Sample size Calculations: A power analysis using StataNow 18.5 was conducted to evaluate the sample size adequacy for the multiple linear regression analysis. With an expected R-squared of 0.25, four predictors, a significance level of 0.05, and a power of 80%, the required sample size was determined to be 41 participants. Our study included 60 participants, surpassing this threshold.

For an observed R-squared of 0.67 with 60 participants, the achieved power was approximately 100%. Furthermore, an additional power analysis for detecting an increase in R-squared from 0.6939 to 0.7902 with the addition of five predictors and 22 control variables indicated that 42 participants would suffice for 80% power at a 5% significance level. Even under more stringent criteria (alpha = 0.01, power = 90%), a sample size of 61 was required, closely approximated by our 60 participants.

RESULTS:

Baseline Characteristics: The study included 60 patients with a mean age of 55.6 ± 11.1 years, 40% (24/60) of whom were females. Demographic and clinical characteristics are summarized in **Table 1.** Significant age differences were observed across groups, with the Concordant Low LDL-C and RC group being the youngest (mean age 50.2 years), and the Concordant High LDL-C and RC group being the oldest (mean age 58.9 years). Smoking prevalence was highest in the Discordant High LDL-C and Low RC group (54.55%), which may have contributed to adverse cardiovascular outcomes. Hypertension was most prevalent in the Discordant Low LDL-C and High RC group (50%), suggesting a potential link between elevated RC and hypertension. Similarly, the highest diabetes prevalence was also observed in the Discordant Low LDL-C and High RC group (56.25%), reinforcing the hypothesis that elevated RC is associated with metabolic conditions. Coronary angiography revealed that the Concordant Low LDL-C and RC group had the highest proportion of single-vessel disease (50%), while the Concordant High LDL-C and RC group had a greater prevalence of multi-vessel disease and a higher rate of left main coronary artery (LMCA) stenosis (21.05%), indicating a potentially higher risk for severe coronary artery disease.

TABLE 1: BASELINE CHARACTERISTICS OF THE STUDY POPULATION STRATIFIED BY LIPID AND REMNANT CHOLESTEROL CONCORDANCE/DISCORDANCE

Variable	Total Sample (n=60)	Concordant Low LDL-C and RC (n=14)	Discordant Low LDL-C and High RC (n=16)	Concordant High LDL-C and RC (n=19)	Discordant High LDL-C and Low RC (n=11)
Number of patients (%)	60 (100%)	14 (23.3%)	16 (26.7%)	19 (31.7%)	11 (18.3%)
Age (years)	55.6 ± 11.2	50.2 ± 11.6	54.7 ± 10.3	58.9 ± 10.7	57.8 ± 11.1
Female (%)	24 (40%)	8 (57.14%)	6 (37.50%)	7 (36.84%)	3 (27.27%)
Smoker (%)	22 (36.67%)	3 (21.43%)	6 (37.50%)	7 (36.84%)	6 (54.55%)
Hypertensive (%)	23 (38.33%)	6 (42.86%)	8 (50.00%)	5 (26.32%)	4 (36.36%)
Diabetic (%)	22 (36.67%)	6 (42.86%)	9 (56.25%)	4 (21.05%)	3 (27.27%)
Prior TIA/Stroke (%)	2 (3.33%)	0	1 (6.25%)	1 (5.26%)	0
CKD (%)	4 (6.67%)	2 (14.29%)	2 (12.50%)	0	0
Weight (kg)	66.5 ± 9.2	67.4 ± 10.1	71.4 ± 8.4	62.9 ± 8.8	64.5 ± 7.0
Height (cm)	163.7 ± 8.8	160.9 ± 8.8	166.0 ± 10.0	163.6 ± 8.4	163.8 ± 7.4
BMI (kg/m²)	25.5 ± 2.8	23.4 ± 1.3	25.7 ± 2.6	26.7 ± 3.0	25.6 ± 3.3
Heart Rate (bpm)	82.8 ± 14.0	80.7 ± 13.2	82.3 ± 10.2	86.3 ± 16.7	80.0 ± 15.3
Systolic BP (mmHg)	125.3 ± 20.4	124.0 ± 17.5	122.8 ± 21.1	123.7 ± 23.4	133.6 ± 17.3
Diastolic BP (mmHg)	77.1 ± 13.1	77.7 ± 10.0	77.1 ± 15.3	78.1 ± 14.1	74.7 ± 12.8
Laboratory Parameters					
Haemoglobin (g/dL)	11.7 ± 2.2	10.8 ± 2.6	11.5 ± 2.2	12.2 ± 2.0	12.0 ± 2.0
Urea (mg/dL)	35.1 ± 23.4	37.0 ± 33.4	45.8 ± 25.9	30.8 ± 14.8	24.5 ± 6.1
Creatinine (mg/dL)	1.14 ± 0.37	1.31 ± 0.58	1.16 ± 0.29	1.07 ± 0.28	1.03 ± 0.23
Total Bilirubin (mg/dL)	0.69 ± 0.39	0.75 ± 0.53	0.67 ± 0.28	0.68 ± 0.39	0.67 ± 0.35

Direct Bilirubin (mg/dL)	0.29 ± 0.16	0.29 ± 0.13	0.29 ± 0.10	0.30 ± 0.19	0.27 ± 0.22
SGOT (U/L)	174.6 ± 762.8	477.2 ± 1,575.9	99.9 ± 95.9	82.7 ± 107.5	56.8 ± 35.2
SGPT (U/L)	122.2 ± 521.2	329.3 ± 1,077.5	59.0 ± 49.7	67.0 ± 74.4	45.7 ± 29.6
2D Echocardiography					
LVEF (%)	49.6 ± 12.9	49.9 ± 13.7	48.7 ± 11.5	46.7 ± 15.2	55.5 ± 8.6
Carotid Doppler					
cIMT (Right) (mm)	1.47 ± 0.29	1.26 ± 0.25	1.45 ± 0.32	1.64 ± 0.16	1.48 ± 0.30
cIMT (Left) (mm)	1.48 ± 0.30	1.34 ± 0.29	1.41 ± 0.35	1.64 ± 0.16	1.49 ± 0.34
Mean cIMT (mm)	1.48 ± 0.28	1.30 ± 0.26	1.43 ± 0.32	1.64 ± 0.14	1.48 ± 0.31
Max cIMT (mm)	1.55 ± 0.29	1.37 ± 0.29	1.51 ± 0.33	1.72 ± 0.13	1.54 ± 0.31
Diagnosis					
Acute Coronary Syndrome	32 (53.34%)	4 (28.58%)	10 (62.5%)	11 (57.89%)	7 (63.63%)
Chronic stable angina	28 (46.67%)	10 (71.43%)	6 (37.5%)	8 (42.1%)	4 (36.36%)
Coronary Angiography					
Normal Coronaries (%)	5 (8.33%)	2 (14.29%)	2 (12.50%)	2 (10.53%)	1 (9.09%)
Single Vessel Disease (%)	13 (21.67%)	7 (50.00%)	3 (18.75%)	8 (42.11%)	1 (9.09%)
Double Vessel Disease (%)	16 (26.67%)	1 (7.14%)	4 (25.00%)	5 (26.32%)	3 (27.27%)
Triple Vessel Disease (%)	15 (25.00%)	1 (7.14%)	5 (31.25%)	4 (21.05%)	
LMCA >50% stenosis	8 (13.33%)	1 (7.14%)	2 (12.50%)	4 (21.05%)	1 (9.09%)
CAG not done (%)	11 (18.33%)	3 (21.43%)	2 (12.50%)	4 (21.05%)	2 (18.18%)

This table presents the baseline clinical, laboratory, echocardiographic, and carotid Doppler characteristics of the study population (N=60), stratified by groups based on the concordance/discordance of LDL-C and remnant cholesterol levels. The variables are shown for the total sample and for four groups: Concordant Low LDL-C and Remnant Cholesterol (RC), Discordant Low LDL-C and High RC, Concordant High LDL-C and RC, and Discordant High LDL-C and Low RC. Continuous variables are presented as mean ± standard deviation (SD), and categorical variables as number (percentage). LDL-C = Low-density lipoprotein cholesterol; RC = Remnant cholesterol; BMI = Body mass index; BP = Blood pressure; CKD = chronic kidney disease; cIMT = Carotid intima-media thickness; LVEF = Left ventricular ejection fraction; ACS = Acute coronary syndrome; TIA = Transient ischemic attack; SGOT = Serum glutamic oxaloacetic transaminase (Aspartate transaminase); SGPT = Serum glutamic pyruvic transaminase (Alanine transaminase).

Lipid Profile and Remnant Cholesterol Levels: The mean lipid levels and calculated remnant cholesterol are presented in Table 2. Overall mean of total cholesterol was 171.1 ± 29.2 mg/dL, mean LDL cholesterol levels were 109.9 ± 26.1 mg/dL, mean HDL cholesterol was 42.9 ± 8.8 mg/dL, calculated mean Remnant cholesterol was 19.0 ± 13.0 mg/dL and the mean triglycerides were 159.7 ± 57.2 mg/dL. The median LDL was 108.8 mg/dL and the median median remnant cholesterol was 16 mg/dL. The analysis reveals distinct lipid profiles across the stratified groups. Total cholesterol levels were highest in the Concordant High LDL-C and RC group (194.5 mg/dL) and the Discordant High LDL-C group (180.7 mg/dL), suggesting more pronounced dyslipidemia in these populations. Conversely, the Concordant Low LDL-C and RC group had the lowest total cholesterol levels (147.4 mg/dL), indicating a more favorable lipid profile. LDL-C levels followed a similar trend, with the highest values in the Concordant High LDL-C and RC group (127.1 mg/dL) and the Discordant High LDL-C group (133.6 mg/dL). Remnant cholesterol showed significant variation, with the highest levels in the Discordant High RC group (27.3 mg/dL), pointing to potential metabolic disturbances even in the presence of lower LDL-C levels. These findings highlight that discordance between LDL-C and RC may define distinct cardiovascular risk profiles, with some groups potentially requiring targeted therapies.

TABLE 2: LIPID PROFILE PARAMETERS IN STUDY POPULATION STRATIFIED BY LDL-C AND REMNANT CHOLESTEROL CONCORDANCE AND DISCORDANCE

Variable	Total sample (n = 60)	Concordant low LDL and RC(n=14)	Discordant high RC (n=16)	Concordant high LDL and RC (n=19)	Discordant high LDL (n=11)
Total cholesterol, mg / dL	171.1 ± 29.2	147.4 ± 17.0	157.6 ± 30.0	194.5 ± 18.8	180.7 ± 21.2
LDL Cholesterol, mg/dL	109.9 ± 26.1	92.3 ± 14.3	88.6 ± 20.4	127.1 ± 14.8	133.6 ± 19.8
HDL cholesterol, mg / dL	42.9 ± 8.8	46.4 ± 6.5	41.7 ± 10.4	42.0 ± 9.4	41.7 ± 7.4

Triglycerides, mg/dL	159.7 ± 57.2	151.4 ± 43.4	152.2 ± 71.8	171.9 ± 61.3	160.2 ± 43.6
Remnant cholesterol, mg / dL	19.0 ± 13.0	9.2 ± 5.1	27.3 ± 13.5	26.6 ± 8.3	6.3 ± 5.1

The table presents lipid parameters, including total cholesterol, LDL-C, HDL-C, triglycerides, and remnant cholesterol, for the total study population (N=60) and stratified by concordance and discordance of LDL-C and remnant cholesterol levels. Mean values ± standard deviation (SD) are provided for each group: Concordant Low LDL-C and RC, Discordant High RC, Concordant High LDL-C and RC, and Discordant High LDL-C and Low RC. The variation in lipid profiles across groups highlights potential metabolic and cardiovascular risk factors. Further statistical analysis is warranted to confirm the clinical significance of these differences. LDL-C = Low-density lipoprotein cholesterol; RC = Remnant cholesterol; HDL-C = High-density lipoprotein cholesterol; SD = Standard deviation. mg/dL" refers to milligrams per deciliter.

Classification Based on Lipid Discordance: Classification of the study population was based on lipid discordance, utilizing the median values for low-density lipoprotein cholesterol (LDL-C) and remnant cholesterol (RC). The median LDL-C was 108.8 mg/dL, and the median RC was 16 mg/dL. Patients were then categorized into four groups according to their lipid profiles, following the method described previously [14] (refer to **Fig. 1** for details):

Group 1 (Concordant Low): 14 patients (23%) with both LDL-C and RC levels below the respective median values.

Group 2 (Discordant High RC): 16 patients (27%) with LDL-C levels below the median but RC levels above the median.

Group 3 (Concordant High): 19 patients (32%) with both LDL-C and RC levels above the median.

Group 4 (Discordant High LDL): 11 patients (18%) with LDL-C levels above the median and RC levels below the median.

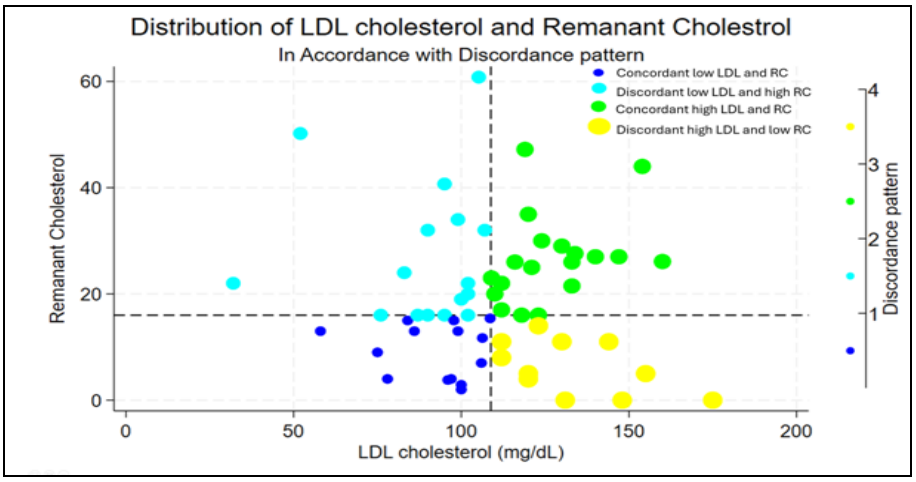

FIG. 1: SCATTER PLOT SHOWING DISTRIBUTION OF LDL CHOLESTEROL AND REMNANT CHOLESTEROL IN ACCORDANCE WITH DISCORDANCE PATTERN. DARK BLUE AND GREEN DOTS ARE LOW AND HIGH CONCORDANT PATTERN RESPECTIVELY, WHILE LIGHT BLUE IS DISCORDANT HIGH RC PATTERN, AND YELLOW DOTS ARE DISCORDANT HIGH LDL PATTERN. DASHED Y(LINE) REPRESENTS MEDIAN OF REMNANT CHOLESTEROL (16 MG/DL). DASHED X(LINE) REPRESENTS MEDIAN OF LDL CHOLESTEROL (108.8 MG/DL).

Carotid Intima-Media Thickness

- Mean cIMT: 1.48 ± 0.28mm.
- Mean of cIMT cubed: 3.54 ± 1.57mm^3 (done to normalize mean cIMT data).
- Mean of cIMT cubed was lower in group with LDL cholesterol values below median compared to those who have above median (2.9mm^3 vs 4.18mm^3, t=-3.45, p=0.0005). Similarly, the cube ofcIMT was lower in the group with RC values below the median compared to those who have above the median (2.96 vs 3.95mm3, t=-2.54, p=0.007).

Correlation Analysis: A Pearson correlation analysis was performed (see also **Table 3 and Fig. 2-8**) to evaluate the relationships between key clinical parameters and the cube of cIMT.

The following significant correlations were observed:

BMI: Strong positive correlation with the cube of cIMT (r = 0.7716, p < 0.001), indicating a strong association between increased body mass and carotid intima-media thickness.

LDL Cholesterol: moderate positive correlation (r = 0.3830, p = 0.0025), supporting its role in atherosclerotic progression (see **Fig. 8**).

Square Root of Remnant Cholesterol: Moderate positive correlation with the cube of cIMT (r = 0.3605, p = 0.0047), highlighting its potential role as an emerging cardiovascular risk factor (see **Fig. 7**).

Total Cholesterol: moderate positive correlation (r = 0.5103, p < 0.001), consistent with its established role in the stratification of cardiovascular risk.

Creatinine Inverse: moderate positive correlation (r = 0.3779, p = 0.0029), linking renal function with carotid intima-media thickness.

Non-significant correlations were observed for HDL cholesterol (r = -0.0199, p = 0.8800) and triglycerides (r = 0.1989, p = 0.1275), suggesting a limited impact on cIMTcube in this cohort. There was no correlation between square root of Remnant Cholesterol and square root of Triglycerides (r=0.1274, p=0.3321).

TABLE 3: PEARSON'S CORRELATION COEFFICIENTS BETWEEN KEY CLINICAL PARAMETERS AND THE CUBE OF CIMT

Variable	Correlation coefficient (r) with the cube of cIMT	p-value
Total Cholesterol	0.5103	<0.001
HDL Cholesterol	-0.0199	0.8800
LDL Cholesterol	0.3830	0.0025
Square Root of Remnant Cholesterol	0.3605	0.0047
Square Root of Triglycerides	0.1989	0.1275
Creatinine Inverse	0.3779	0.0029
BMI (Kg/m^2)	0.7716	<0.001

Table 3 Pearson's correlation coefficients between key clinical parameters and the cube of cIMT. Statistically significant correlations were observed for BMI, LDL cholesterol, remnant cholesterol, total cholesterol, and creatinine inverse, indicating theirpotential role in predicting carotid intima-media thickness. Triglycerides and HDL cholesterol did not show statistically significant associations with the cube of cIMT.

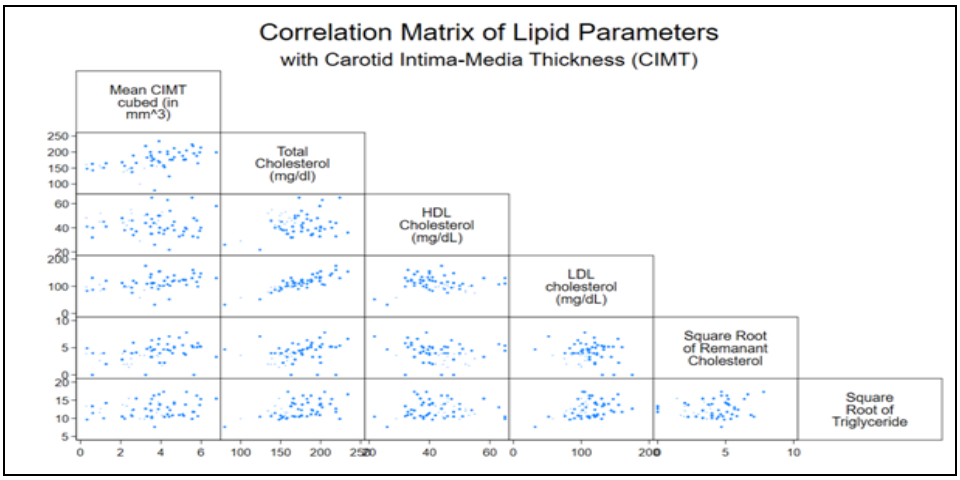

FIG. 2: CORRELATION MATRIX OF LIPID PARAMETERS WITH CAROTID INTIMA-MEDIA THICKNESS (CIMT). THIS FIGURE SHOWS THE CORRELATION COEFFICIENTS BETWEEN VARIOUS LIPID PARAMETERS, INCLUDING LDL CHOLESTEROL, HDL CHOLESTEROL, TOTAL CHOLESTEROL, SQUARE ROOT OF REMNANT CHOLESTEROL, SQUARE ROOT OF TRIGLYCERIDES, AND MEAN CIMT CUBED (A MARKER OF ATHEROSCLEROTIC BURDEN). THE POSITIVE CORRELATION BETWEEN LDL CHOLESTEROL AND MEAN CIMT CUBED (R = 0.3830, P = 0.0025) INDICATES AN ASSOCIATION BETWEEN ELEVATED LDL LEVELS AND INCREASED ARTERIAL WALL THICKNESS. TOTAL CHOLESTEROL ALSO DEMONSTRATES A STRONG CORRELATION WITH MEAN CIMT CUBED (R = 0.5103, P < 0.001), SUGGESTING ITS ROLE IN ATHEROSCLEROSIS. SIMILARLY, REMNANT CHOLESTEROL ALSO SHOWS MODERATE POSITIVE CORRELATION WITH CUBE OF CIMT (R=0.3605, P=0.0047) CONVERSELY, HDL CHOLESTEROL SHOWS NO SIGNIFICANT ASSOCIATION WITH CIMT OR OTHER LIPID PARAMETERS IN THIS MATRIX.

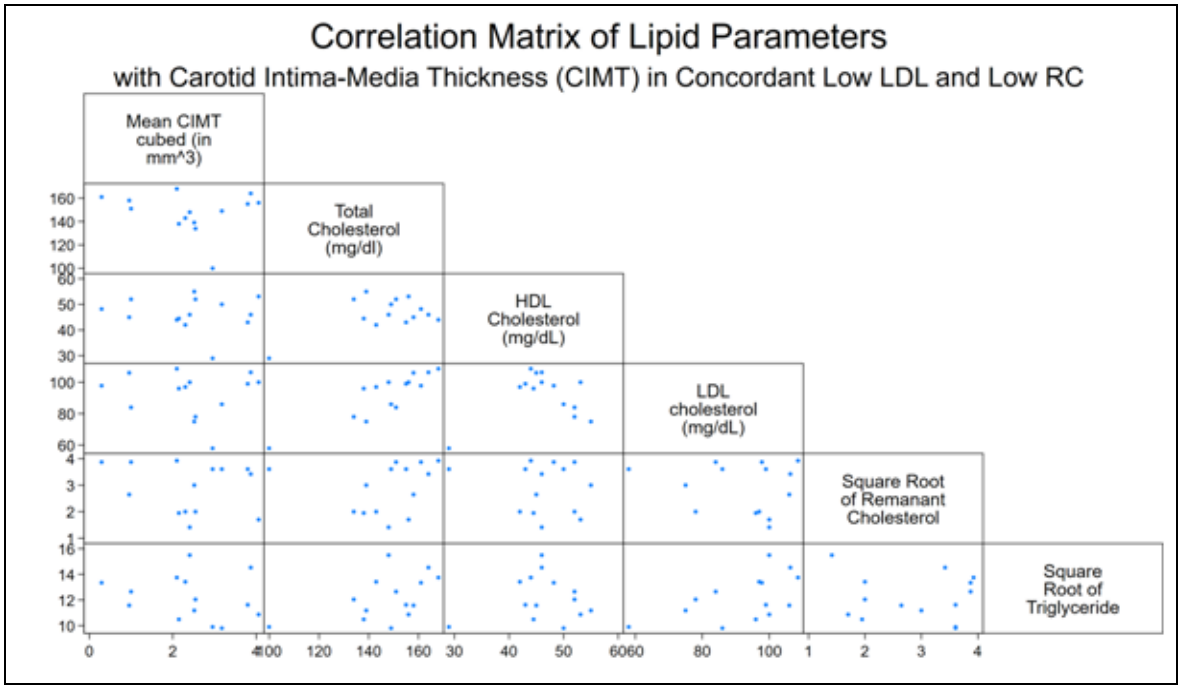

FIG. 3: THIS SCATTERPLOT MATRIX DISPLAYS THE RELATIONSHIPS BETWEEN SEVERAL LIPID PARAMETERS (TOTAL CHOLESTEROL, HDL CHOLESTEROL, LDL CHOLESTEROL, SQUARE ROOT OF REMNANT CHOLESTEROL, AND SQUARE ROOT OF TRIGLYCERIDES) AND MEAN CUBED CAROTID INTIMA-MEDIA THICKNESS (CIMT) FOR PATIENTS WITH CONCORDANT LOW LDL AND LOW REMNANT CHOLESTEROL (RC). THE MATRIX ALLOWS FOR A VISUAL EXPLORATION OF THE LINEARITY AND POTENTIAL ASSOCIATIONS AMONG THESE VARIABLES.

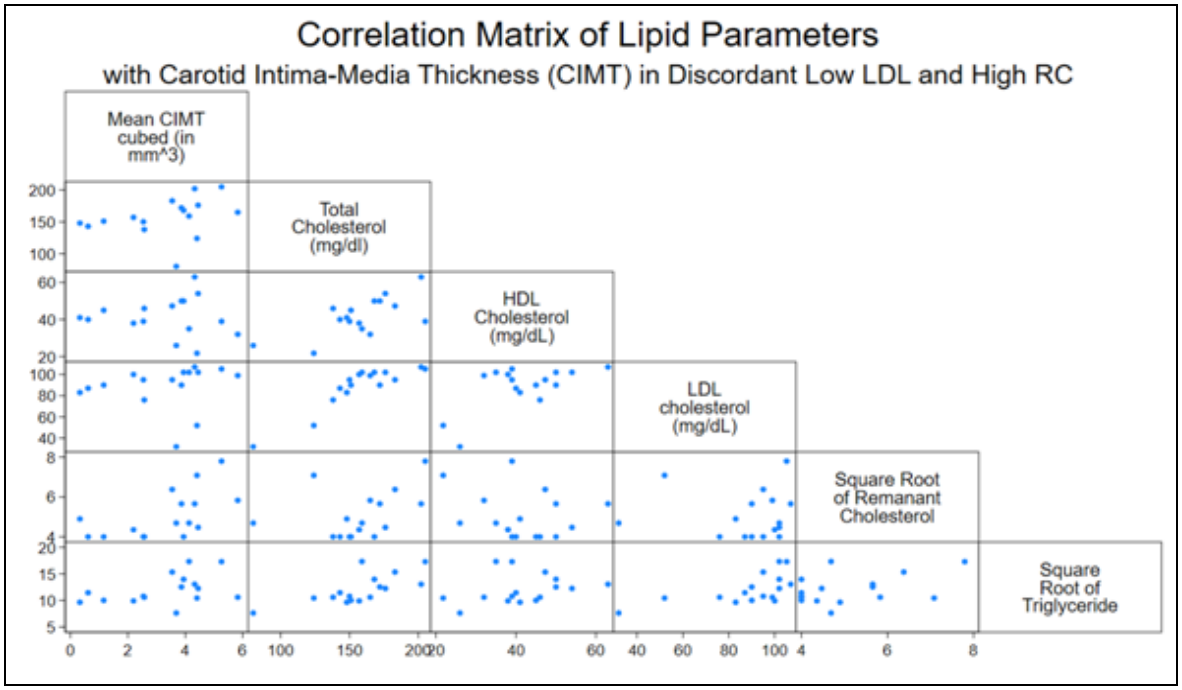

FIG. 4: CORRELATION MATRIX OF LIPID PARAMETERS WITH CAROTID INTIMA-MEDIA THICKNESS (CIMT) IN DISCORDANT LOW LDL AND HIGH REMNANT CHOLESTEROL (RC) GROUP. THIS MATRIX DISPLAYS THE RELATIONSHIPS BETWEEN VARIOUS LIPID PARAMETERS (TOTAL CHOLESTEROL, HDL CHOLESTEROL, LDL CHOLESTEROL, SQUARE ROOT OF REMNANT CHOLESTEROL, AND SQUARE ROOT OF TRIGLYCERIDES) AND MEAN CIMT CUBED (A MARKER OF SUBCLINICAL ATHEROSCLEROSIS). NOTABLY, REMNANT CHOLESTEROL SHOWS A POSITIVE CORRELATION WITH MEAN CIMT, INDICATING ITS POTENTIAL CONTRIBUTION TO ATHEROSCLEROSIS PROGRESSION IN THIS DISCORDANT LIPID PROFILE GROUP.

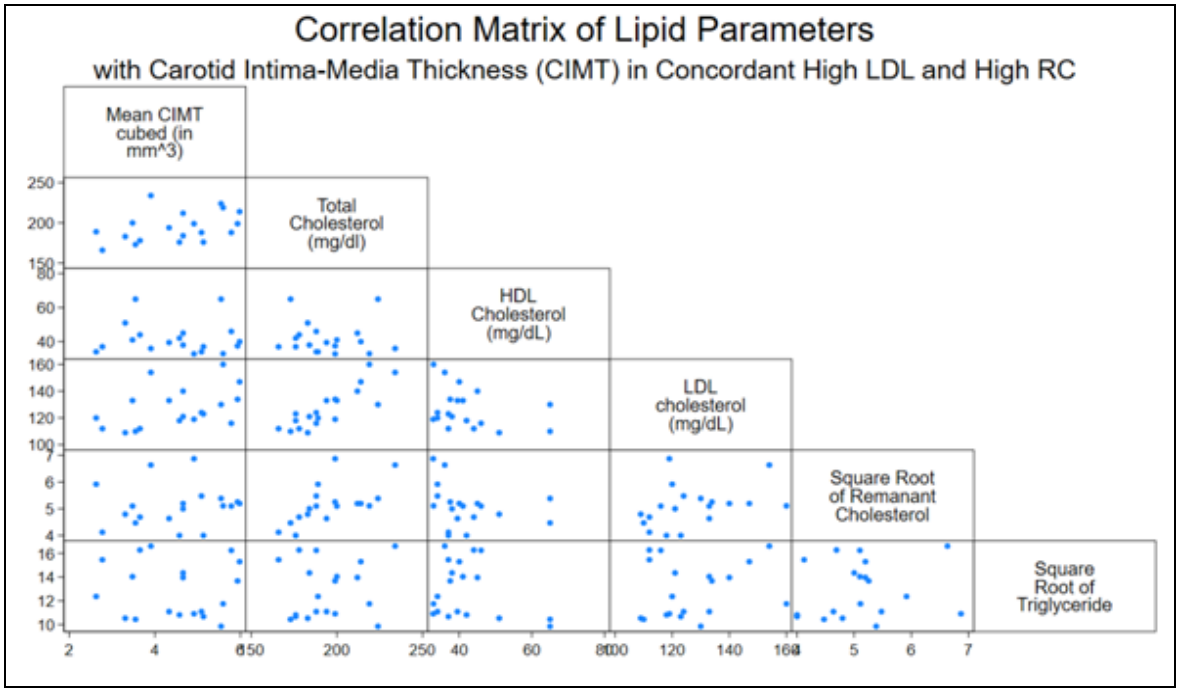

FIG. 5: CORRELATION MATRIX OF LIPID PARAMETERS WITH CAROTID INTIMA-MEDIA THICKNESS (CIMT) IN CONCORDANT HIGH LDL AND HIGH REMNANT CHOLESTEROL (RC) GROUP. THIS MATRIX SHOWS THE ASSOCIATIONS BETWEEN LIPID VARIABLES (TOTAL CHOLESTEROL, HDL CHOLESTEROL, LDL CHOLESTEROL, SQUARE ROOT OF REMNANT CHOLESTEROL, AND SQUARE ROOT OF TRIGLYCERIDES) AND MEAN CIMT CUBED, WHICH REFLECTS ATHEROSCLEROTIC BURDEN. THE POSITIVE CORRELATION BETWEEN LDL CHOLESTEROL AND MEAN CIMT SUGGESTS THAT ELEVATED LDL CHOLESTEROL MIGHT BE A CONTRIBUTING FACTOR TO INCREASED ATHEROSCLEROSIS IN INDIVIDUALS WITH BOTH HIGH LDL AND HIGH REMNANT CHOLESTEROL.

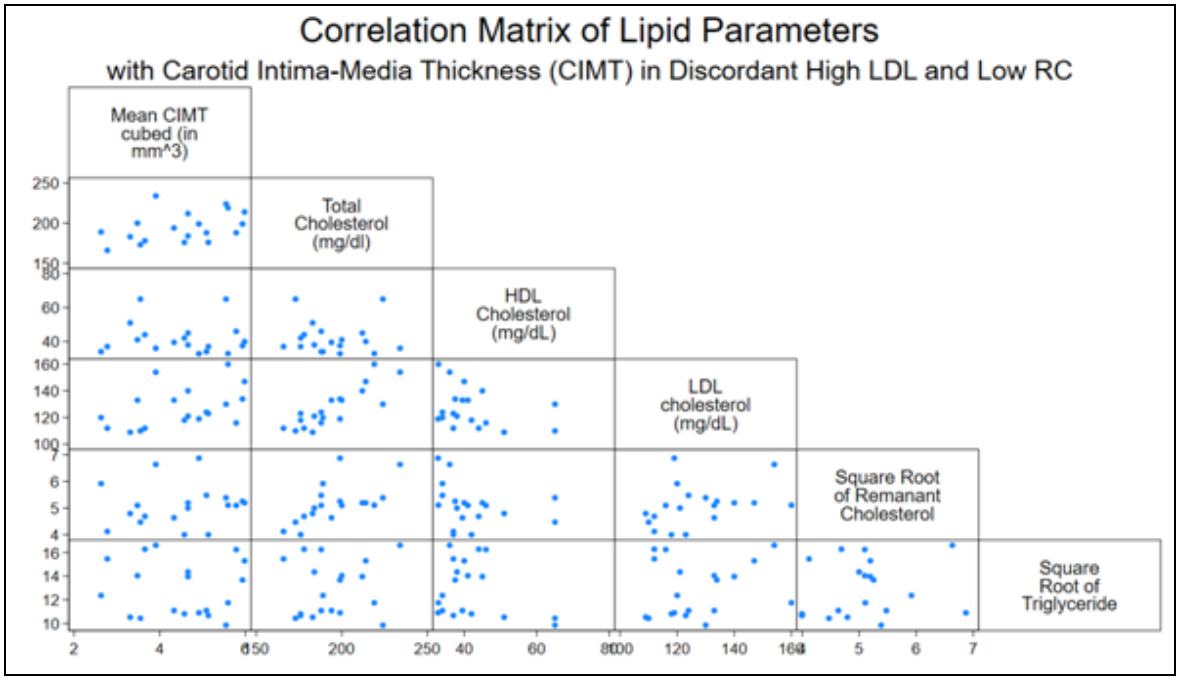

FIG. 6: CORRELATION MATRIX OF LIPID PARAMETERS WITH CAROTID INTIMA-MEDIA THICKNESS (CIMT) IN DISCORDANT HIGH LDL AND LOW REMNANT CHOLESTEROL (RC) GROUP. THIS MATRIX ILLUSTRATES THE CORRELATIONS BETWEEN VARIOUS LIPID PARAMETERS (LDL CHOLESTEROL, HDL CHOLESTEROL, TOTAL CHOLESTEROL, SQUARE ROOT OF REMNANT CHOLESTEROL, SQUARE ROOT OF TRIGLYCERIDES) AND MEAN CIMT CUBED, A MEASURE OF ATHEROSCLEROTIC BURDEN. THE POSITIVE CORRELATION BETWEEN LDL CHOLESTEROL AND MEAN CIMT SUGGESTS A POTENTIAL ROLE OF ELEVATED LDL CHOLESTEROL IN ATHEROSCLEROSIS PROGRESSION, EVEN IN THE PRESENCE OF LOW REMNANT CHOLESTEROL LEVELS.

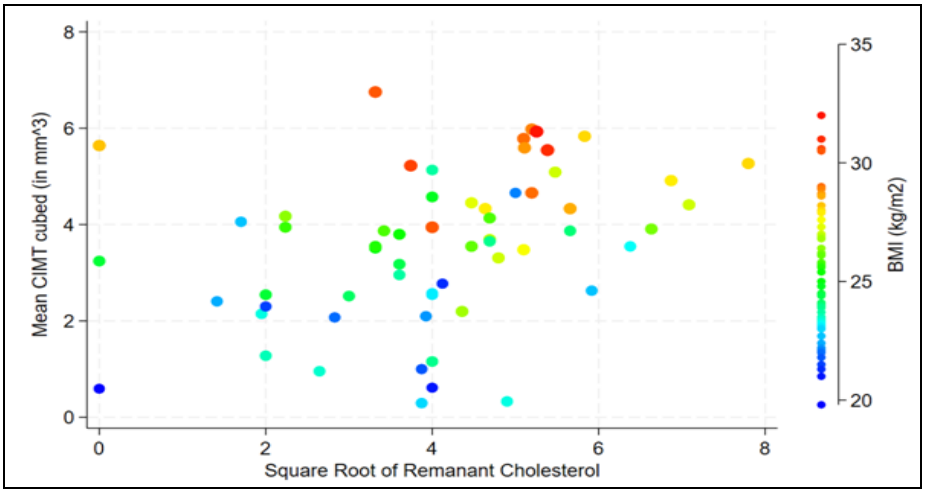

FIG. 7: SCATTER PLOT SHOWING THE MODERATE POSITIVE CORRELATION BETWEEN REMNANT CHOLESTEROL AND THE CUBE OF CIMT (R = 0.3605, P = 0.0047), WITH POINT COLORS REPRESENTING BODY MASS INDEX (BMI). THE COLOR GRADIENT FROM BLUE TO RED CORRESPONDS TO INCREASING BMI, INDICATING THAT HIGHER REMNANT CHOLESTEROL IS ASSOCIATED WITH INCREASED CIMT, PARTICULARLY IN INDIVIDUALS WITH LOWER BMI. HOWEVER, IN INDIVIDUALS WITH HIGHER BMI, CIMT APPEARS TO INCREASE REGARDLESS OF REMNANT CHOLESTEROL LEVELS, SUGGESTING A POTENTIAL GREATER CONTRIBUTION OF OBESITY-RELATED FACTORS.

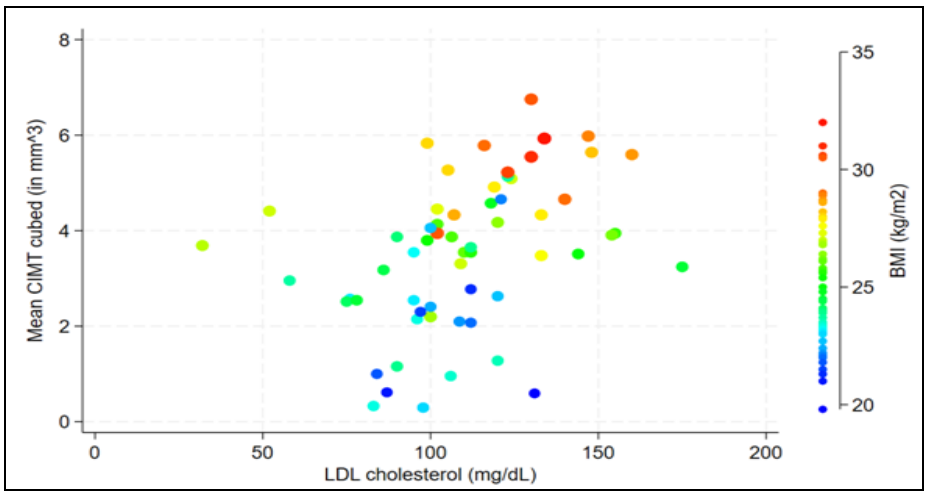

FIG. 8: SCATTER PLOT DEPICTING THE MODERATE POSITIVE CORRELATION (R = 0.3830, P = 0.0025) BETWEEN LDL CHOLESTEROL (MG/DL) AND MEAN CUBED CAROTID INTIMA-MEDIA THICKNESS (CIMT), WITH POINT COLORS REPRESENTING BODY MASS INDEX (BMI). THE GRADIENT FROM BLUE TO RED INDICATES INCREASING BMI, WITH BLUE CORRESPONDING TO LOWER BMI AND RED TO HIGHER BMI. THE PLOT SHOWS THAT HIGHER LDL CHOLESTEROL TENDS TO BE ASSOCIATED WITH INCREASED CIMT, ESPECIALLY IN INDIVIDUALS WITH ELEVATED BMI, HIGHLIGHTING THE COMBINED INFLUENCE OF LDL CHOLESTEROL AND OBESITY ON ARTERIAL WALL THICKNESS.

Subgroup Analysis Based on LDL-C and RC Concordance: Participants were stratified into four groups based on concordance or discordance of LDL cholesterol and remnant cholesterol levels:

Group 1 (Concordant low LDL-C and RC): BMI positively correlated with cube of cIMT (r = 0.5271, p = 0.0528). Creatinine inverse significantly correlated with cube of cIMT (r = 0.5489, p = 0.0421). LDL-C, remnant cholesterol, and triglycerides showed no significant correlations with cube of cIMT see **Fig. 3.**

Group 2(Discordant low LDL-C, high RC): BMI strongly correlated with cube of cIMT (r = 0.7149, p = 0.0019). Remnant cholesterol positively correlated with cube of cIMT (r = 0.5925, p = 0.0156) see **Fig. 9.** Triglycerides, LDL-C and creatinine inverse showed moderate, non-significant correlations **Fig. 4.**

Group 3 (Concordant high LDL-C and RC): BMI positively correlated with cube of cIMT (r = 0.6636, p = 0.0019). LDL-C showed moderate correlation with cube of cIMT (r = 0.4383, p = 0.0605) see **Fig. 10.** No significant correlations with remnant cholesterol or triglycerides see **Fig. 5.**

Group 4 (Discordant high LDL-C, low RC): BMI strongly correlated with cube of cIMT (r = 0.9454, p < 0.0001). Creatinine inverse positively correlated with cube of cIMT (r = 0.7066, p = 0.0151). No significant correlations with LDL-C, remnant cholesterol, or triglycerides see **Fig. 6.**

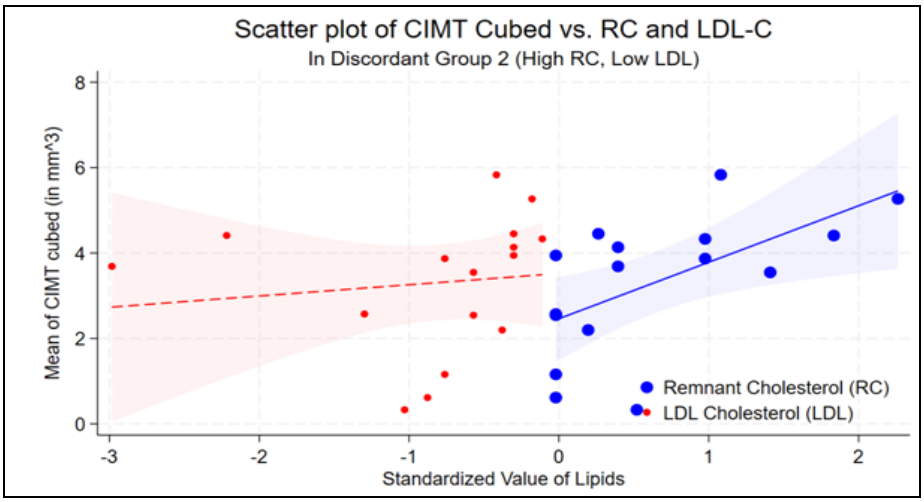

FIG. 9: SCATTER PLOT SHOWING THE RELATIONSHIP BETWEEN THE MEAN OF CIMT CUBED (IN MM^3) AND STANDARDIZED VALUES OF SQUARE ROOT OF REMNANT CHOLESTEROL (RC) (BLUE) AND LDL CHOLESTEROL (LDL-C) (RED) IN DISCORDANT GROUP 2 (HIGH RC, LOW LDL). THE SHADED REGIONS REPRESENT 95% CONFIDENCE INTERVALS FOR THE LINEAR FIT OF EACH VARIABLE. RC SHOWS A STRONG, SIGNIFICANT POSITIVE CORRELATION WITH CIMT CUBED (R=0.59, P=0.0156), WHILE LDL-C SHOWS A WEAK AND NON-SIGNIFICANT CORRELATION (R=0.13, P=0.64).

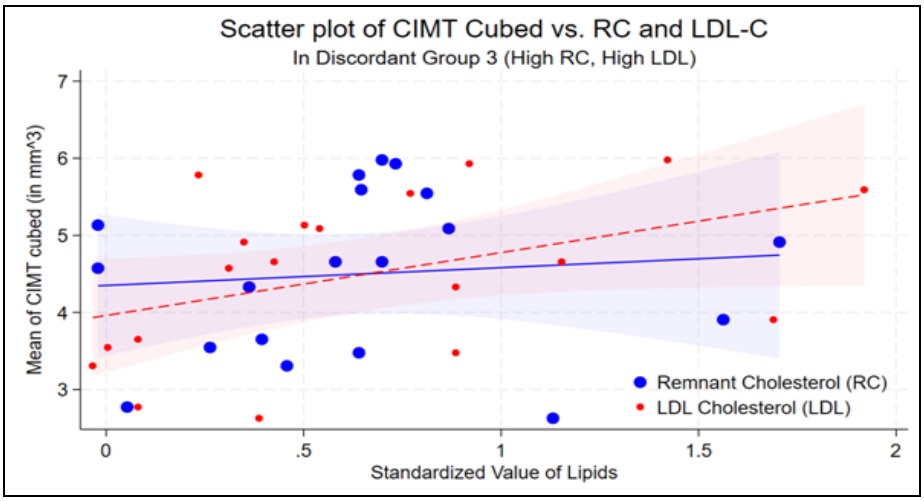

FIG. 10: SCATTER PLOT SHOWING THE RELATIONSHIP BETWEEN THE MEAN OF CIMT CUBED (IN MM^3) AND STANDARDIZED VALUES OF SQUARE ROOT OF REMNANT CHOLESTEROL (RC) (BLUE) AND LDL CHOLESTEROL (LDL-C) (RED) IN DISCORDANT GROUP 3 (HIGH RC, HIGH LDL). THE SHADED REGIONS REPRESENT 95% CONFIDENCE INTERVALS FOR THE LINEAR FIT OF EACH VARIABLE. RC SHOWS A WEAK AND STATISTICALLY INSIGNIFICANT CORRELATION WITH CIMT CUBED (R=0.10, P=0.68), WHILE LDL-C SHOWS A MODERATE POSITIVE CORRELATION (R=0.44, P=0.06), APPROACHING STATISTICAL SIGNIFICANCE.

Multiple Linear Regression with cIMT as Dependent Variable:

Initial Full Model (Model 1): The initial regression model included 22 variables (clinical, biochemical, and cardiovascular risk factors), explaining 79% of the variance in cubed carotid intima-media thickness (cIMT cubed) (R-squared = 0.7902, adjusted R-squared = 0.6654). BMI was the most significant predictor (coefficient = 0.3329, p < 0.001), followed by smoking status (coefficient =

0.852, p = 0.024). Multicollinearity was observed, particularly among lipid variables. Total cholesterol exhibited a high variance inflation factor (VIF > 50), largely due to its correlation with LDL cholesterol (r = 0.8785). As LDL cholesterol is more directly associated with atherogenic potential, total cholesterol was excluded to address multicollinearity.

Model Refinement (Model 2): In Model 2, total cholesterol was removed and the model retained 21 variables, maintaining similar predictive power (R-squared = 0.7878, adjusted R-squared = 0.6705). BMI remained the most significant predictor (coefficient = 0.3329, p < 0.001), with smoking status also showing significance (coefficient = 0.894, p = 0.015). Other variables such as SBP, HDL, and creatinine contributed less to the variance of cIMT. Total cholesterol removal improved the model's AIC (174.04) and BIC (220.11), enhancing parsimony without compromising fit.

Stepwise Regression (Model 3): Stepwise regression further simplified the model, retaining only BMI (coefficient = 0.3929, p < 0.001) and smoking status (coefficient = 0.863, p = 0.001). This model explained 66% of the variance (R-squared = 0.6637, adjusted R-squared = 0.6519). AIC (163.65) and BIC (169.94) were lower, reflecting a more efficient model.

Reintroduction of Lipid Profile Variables (Model 4): Reintroducing LDL cholesterol, remnant cholesterol, and triglycerides resulted in BMI (coefficient = 0.340, p < 0.001) and smoking status (coefficient = 0.807, p = 0.002) remaining significant. LDL cholesterol approached significance (coefficient = 0.0093, p = 0.095). The R-squared was 0.6948 (adjusted R-squared = 0.6665), with AIC (163.84) and BIC (176.41).

Final Model (Model 5): The final model, which removed triglycerides, retained BMI, smoking status, LDL cholesterol, and remnant cholesterol, explaining 69% of the variance (R-squared = 0.6939, adjusted R-squared = 0.6716). BMI remained the strongest predictor (coefficient = 0.3367, p < 0.001), followed by smoking status (coefficient = 0.819, p = 0.002), and LDL cholesterol (coefficient = 0.0102, p = 0.044) (see **Table 4**). Although remnant cholesterol did not reach significance (coefficient = 0.1293, p = 0.110), it showed a trend toward relevance. The final model had the lowest AIC (162.02) and BIC (172.49), with no signs of multicollinearity (mean VIF = 1.25), heteroskedasticity (p = 0.1101), or omitted variable bias (RESET test, p = 0.8251).

TABLE 1 RESULTS OF THE FINAL REGRESSION MODEL (MODEL 5)

Variable	Coefficient β	Std. Error (p-value)	95% CI
BMI (kg/m2)	0.3367	0.0490 (< 0.001)	[0.2384, 0.4350]
Smoking Status	0.819	0.2477 (0.002)	[0.3221, 1.3151]
LDL Cholesterol (mg/dL)	0.0102	0.0049 (0.044)	[0.0003, 0.0201]
Remnant Cholesterol (sqrt-transformed)	0.1293	0.0795 (0.110)	[-0.0300, 0.2886]
Constant	-6.9752	1.0827 (< 0.001)	[-9.1449, -4.8055]

This table displays the results of the final regression model (Model 5), which predicts the cubed mean carotid intima-media thickness (cube of cIMT) based on four key predictors: body mass index (BMI), smoking status, LDL cholesterol, and remnant cholesterol. BMI and smoking status are the strongest predictors, with LDL cholesterol showing significant contribution. Remnant cholesterol, though not statistically significant, shows a trend toward relevance. The model explains approximately 67% of the variance in cIMT.

Sensitivity Analysis:

Comparison of Model with Restricted Cubic Spline: A comparison between two models to assess their ability to predict cubed carotid intima-media thickness (cube of cIMT). The first model utilized restricted cubic spline (RCS) terms for LDL cholesterol and the square root of remnant cholesterol, while the second model used these variables directly without transformations. Model 1, which used RCS terms, had an R-squared value of 0.3370, an adjusted R-squared of 0.2887, an AIC of 208.39, and a BIC of 218.86. Moderate multicollinearity was observed with variance inflation factor (VIF) values around 3.65. Additionally, the Ramsey RESET test indicated potential model misspecification with a p-value of 0.0594, suggesting that Model 1 may not fully capture all variable relationships. In contrast, Model 2, which used direct predictors, had an R-squared of 0.3212 and an adjusted R-squared of

0.2974. Model 2 also had lower AIC (205.79) and BIC (212.08) values, indicating a more parsimonious fit. VIF values were lower at 1.02, suggesting minimal multicollinearity. However, the Ramsey RESET test showed significant omitted variables in Model 2 ($p = 0.0172$), indicating that some predictors might have been excluded (See model details in Supplementary material).

In conclusion, while Model 2 demonstrated better simplicity and lower multicollinearity, the presence of omitted variable bias suggested the need for further refinement. Model 1, despite its complexity, better captured non-linear relationships. However, given the goal of clinical application and interpretability, Model 2's direct predictor approach is favoured for its generalizability and ease of use in a practical setting.

Modelling with Transformed vs. Untransformed Variables: In this comparison, we evaluated models using both transformed and untransformed predictors of cubed cIMT. The untransformed model, Model 1, had an R-squared of 0.7509 and an adjusted R-squared of 0.5677. The AIC and BIC for this model were -14.64 and 39.81, respectively. Significant predictors in this model included BMI ($p = 0.002$) and smoking status ($p = 0.032$). However, the Breusch-Pagan test indicated the presence of heteroskedasticity in the residuals ($p = 0.0017$), suggesting that the variability in the error terms was not constant across observations. Additionally, VIF for LDL cholesterol in this model was extremely high (121.88), indicating severe multicollinearity, which could distort the accuracy of the coefficient estimates.

In contrast, the transformed model, Model 2, had a higher R-squared value of 0.8240 and an adjusted R-squared of 0.6946, with AIC and BIC values of 170.81 and 225.27, respectively. In this model, BMI ($p < 0.0001$) and smoking status ($p = 0.009$) remained significant predictors, and the transformation helped resolve issues with heteroskedasticity, as no heteroskedasticity was detected ($p = 0.7173$). Furthermore, multicollinearity was reduced, with the VIF for LDL cholesterol lowered to 58.60, although still somewhat elevated (See model details in Supplementary material). In conclusion, Model 2, with transformed variables, explained more variance in cIMT and better addressed residual issues, making it the preferred model for inference. While Model 1 offered a simpler fit, it struggled with issues of multicollinearity and heteroskedasticity. BMI and smoking status remained consistent predictors across both models, underscoring their significance in predicting cIMT.

Sensitivity Analysis for Final Model (Model 5 of section 6.7.5): A sensitivity analysis was conducted to compare the performance of the final model using both untransformed and transformed variables. The untransformed model had an R-squared value of 0.5906 and an adjusted R-squared of 0.5608. In this model, BMI ($p < 0.001$) and smoking status ($p = 0.006$) were significant predictors. However, the Breusch-Pagan test detected heteroskedasticity ($p = 0.0001$), indicating that the variance of the residuals was not constant, which could affect the reliability of the model's estimates.

In the transformed model, the R-squared increased to 0.6939, with an adjusted R-squared of 0.6716. The significant predictors in this model included BMI ($p < 0.001$), smoking status ($p = 0.002$), and LDL cholesterol ($p = 0.044$). Importantly, no heteroskedasticity was detected in this model ($p = 0.1008$), meaning that the model met the assumption of constant variance in the residuals, thus enhancing its reliability (See model details in Supplementary material).

In conclusion, the transformed model provided better explanatory power and more robust model diagnostics. Although the untransformed model offered a simpler fit, the transformed model proved more reliable and suitable for making precise inferences. The significance of LDL cholesterol in the transformed model further highlights its role in predicting atherosclerotic burden and cardiovascular risk, aligning with established clinical knowledge.

DISCUSSION: This exploratory study aimed to investigate the relationship between remnant cholesterol (RC), discordance in the lipid profile, and carotid intima-media thickness (cIMT) in predicting the severity of coronary artery disease (CAD). Our results highlight several key findings

with potential implications for the assessment and management of cardiovascular risk.

Remnant Cholesterol and Atherosclerosis: Recently, the National Lipid Association has recommended the use of Apo(B) as a better marker of ASCVD in statin-treated patients [18]. Similarly, remnant cholesterol (RC) has gained increasing attention as an emerging risk factor for atherosclerosis, independent of traditional markers such as low-density lipoprotein cholesterol (LDL-C) [2]. The reason for choosing RC in this study is due to its ease of calculation and the availability of direct enzymatic assays of LDL-C at a relatively low cost in India. Although Apo(B) is a robust marker, it remains expensive. Moreover, as noted by [12] and [13], fasting states do not significantly alter RC values, making it a practical marker for large-scale clinical use.

RC is carried within triglyceride-rich lipoproteins (TRLs), including very-low-density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL), both of which can penetrate the arterial wall and contribute to plaque formation and inflammation [6]. Our study demonstrated a moderate positive correlation between RC and cubed mean cIMT ($r = 0.3605$, $p = 0.0047$), reinforcing RC's role as a predictor of subclinical atherosclerosis. Similar findings were reported in a study by [19], where RC positively correlated with mean cIMT in ischemic stroke patients.

Although RC did not achieve statistical significance in the final regression model ($p = 0.110$), the trend toward significance suggests that RC could be a valuable marker in specific subgroups, such as non-obese individuals, where traditional markers like LDL-C may not fully capture atherogenic risk. Future studies with larger sample sizes and better statistical power are necessary to explore this trend further. Including RC in risk stratification models may offer a more comprehensive assessment of cardiovascular risk, particularly for patients with discordant lipid profiles. Clinicians often question why remnant cholesterol is calculated rather than relying solely on triglyceride measurements, which are readily available. Triglycerides are present in all lipoprotein particles at varying concentrations, yet multiple studies have demonstrated no direct correlation between triglyceride levels and atherosclerosis. In our own investigations, we similarly observed no significant association between carotid intima-media thickness (CIMT) and triglycerides ($p = NS$).

A plausible explanation for this discrepancy is that the atherogenic component is not the triglyceride molecule itself but rather the cholesterol contained in triglyceride-rich lipoproteins, commonly referred to as remnant cholesterol. Our findings indicated a direct correlation between remnant cholesterol and CIMT ($p < 0.05$). To achieve this result, we employed direct LDL cholesterol measurements instead of relying on calculated LDL-C values derived from triglyceride levels.

Lipid Profile Discordance and Cardiovascular Risk: Lipid profile discordance, characterized by a mismatch between LDL-C and other lipid parameters like non-HDL cholesterol and RC, has emerged as an important contributor to residual cardiovascular risk [2, 7, 20-24].

Our study identified that patients with discordant high RC (i.e., high RC and low LDL-C) had significantly higher mean cubed cIMT compared to those with concordant low RC and LDL-C levels. This finding underscores the limitations of relying solely on LDL-C for risk assessment, as it may overlook individuals with elevated TRLs and atherogenic dyslipidemia, who remain at higher risk for cardiovascular events. The clinical implications of lipid discordance are significant. Patients with elevated RC but normal LDL-C may benefit from therapies targeting TRLs and RC, such as fibrates, omega-3 fatty acids, or newer agents like angiopoietin-like protein 3 (ANGPTL3) inhibitors. These treatments could reduce residual cardiovascular risk, which persists despite optimal LDL-C lowering.

Body Mass Index (BMI) and Smoking Status as Strong Predictors: In our final regression model, BMI and smoking status emerged as the strongest predictors of cubed mean cIMT, consistent with existing research [25, 26] linking obesity and smoking to increased cardiovascular risk. The strong correlation between BMI and cIMT ($r = 0.7716$, $p < 0.001$) emphasizes the critical role of weight management in reducing atherosclerotic burden.

Similarly, smoking cessation remains a cornerstone of cardiovascular risk reduction, as smokers had significantly higher cIMT than non-smokers. With the rising global prevalence of obesity and smoking, our findings stress the importance of aggressive lifestyle interventions to mitigate these modifiable risk factors. Public health campaigns targeting smoking cessation and promoting healthy weight could significantly curb the progression of subclinical atherosclerosis and prevent future cardiovascular events.

Limitations of the Study: While our exploratory study offers novel insights, several limitations should be acknowledged. First, the relatively small sample size of 60 patients may reduce the generalizability of our findings and limit the statistical power to detect subtle associations between remnant cholesterol (RC), lipid discordance, and carotid intima-media thickness (cIMT). Although the sample size was deemed sufficient based on power analysis, the combination of a small cohort with numerous predictors could affect the robustness of the results. Future studies with larger cohorts and a refined set of predictors are necessary to validate these associations.

Additionally, remnant cholesterol was calculated using directly measured LDL-C values, which is particularly advantageous in populations with elevated triglycerides. However, variability in LDL-C assays, whether through direct measurement or the Friedewald formula, may have impacted the accuracy of RC calculations [27]. To reduce assay-related variability, future research should employ standardized methods or alternative approaches for LDL-C and RC measurements.

Due to the small sample size, data transformations were required to meet assumptions of normality and homoscedasticity. While these transformations enhanced model fit, they complicated the interpretation of the regression coefficients, as these reflect relationships between transformed variables. Although back-transformations were applied where feasible, caution is warranted, as they can introduce bias. Nonetheless, sensitivity analyses demonstrated that transformations did not alter the direction or significance of key associations. The lack of coronary angiography (CAG) data for certain patients, particularly those with STEMI or NSTEMI, represents another limitation. This absence prevented a full assessment of the anatomical severity of coronary artery disease (CAD), which may have influenced the observed relationships between cIMT and CAD severity. Future studies should ensure comprehensive angiographic data collection for all participants to strengthen the understanding of these associations.

Furthermore, the exclusion of ApoB measurements is a significant limitation, as ApoB provides a more precise measure of atherogenic particle count compared to RC. Future studies should incorporate ApoB to improve cardiovascular risk stratification.

Finally, the cross-sectional nature of this study restricts our ability to infer causality. Although associations between RC, lipid discordance, and cIMT were identified, longitudinal studies are essential to establish the temporal relationship between these factors and cardiovascular outcomes.

Future Directions: Our study highlights several important avenues for future research. Longitudinal studies, similar to those conducted in Western populations [5], are needed to determine whether elevated remnant cholesterol (RC) and lipid discordance predict long-term cardiovascular events, such as myocardial infarction or stroke, in the Indian population. These studies should incorporate robust statistical methods, such as multivariable regression models and machine learning algorithms, to better capture the complex interactions between RC, lipid discordance, and cardiovascular risk factors. Leveraging large datasets and advanced data analytics will enhance the development of more accurate risk prediction models for cardiovascular diseases.

Interventional trials targeting RC and lipid discordance could provide direct evidence for the role of these lipid markers in reducing cardiovascular risk. The emerging role of triglyceride-rich lipoproteins (TRLs) in atherosclerosis, particularly through mechanisms like endothelial dysfunction and foam cell formation, supports the potential benefit of therapies that specifically target RC. Promising treatments, such as ANGPTL3 [28-31] and ApoC-III inhibitors [32-35], have the potential to reduce residual

cardiovascular risk in patients with discordant lipid profiles. Additionally, incorporating advanced lipid biomarkers, such as ApoB [22], into future research will provide a more comprehensive understanding of atherogenic risk posed by RC and lipid discordance, improving precision in cardiovascular risk stratification.

Future studies should utilize advanced imaging techniques, such as coronary computed tomography angiography (CCTA) and magnetic resonance imaging (MRI), to evaluate the relationship between RC and plaque characteristics. These imaging modalities, as explored by [36], offer insights into plaque composition and burden, aiding in understanding RC's role in atherosclerosis progression. Mendelian randomization studies [3, 37] could further establish causal relationships between RC and cardiovascular risk, while population-specific studies [20] will elucidate genetic and environmental influences on RC levels.

Future research should address the limitations of our study through several key strategies. Large-scale longitudinal cohort studies with diverse populations are essential to confirm causal relationships between RC, lipid discordance, and cardiovascular outcomes. Randomized controlled trials focusing on RC reduction can provide definitive evidence of its role in mitigating carotid intima-media thickness (cIMT) progression and reducing cardiovascular events. Moreover, Mendelian randomization studies will strengthen causal inferences, and advanced imaging techniques will further elucidate the mechanisms underlying RC's association with atherosclerosis. Multi-center studies involving diverse populations will enhance the generalizability of findings, and incorporating advanced biomarkers, such as ApoB, will refine cardiovascular risk assessment. Lastly, mechanistic studies exploring the biological pathways linking RC to atherosclerosis will be vital for identifying new therapeutic targets for cardiovascular disease prevention and management.

CONCLUSION: This exploratory study suggests that elevated remnant cholesterol (RC) and lipid profile discordance may be associated with increased carotid intima-media thickness (cIMT), a marker of subclinical atherosclerosis, among Indian patients with coronary artery disease. Body mass index (BMI) and smoking status emerged as significant predictors of cIMT, while RC showed a trend towards being an independent predictor. However, given the cross-sectional design and the relatively small sample size of our study, these findings are preliminary and should be interpreted with caution.

Our results highlight the potential importance of incorporating RC and lipid discordance into cardiovascular risk assessment models to better identify patients at higher risk for atherosclerotic cardiovascular disease. Such an approach could inform more personalized strategies for risk reduction, including lifestyle interventions and targeted therapies aimed at lowering triglyceride-rich lipoproteins.

Nevertheless, further research is warranted to confirm these associations and to elucidate the underlying mechanisms. Large-scale, longitudinal studies are needed to establish causal relationships and to determine whether interventions targeting RC and lipid discordance can effectively reduce cIMT progression and subsequent cardiovascular events. Future studies should also consider including apolipoprotein B measurements and exploring genetic and mechanistic pathways to provide a more comprehensive understanding of the role of RC in atherosclerosis.

In conclusion, while our study adds to the growing body of evidence on the role of remnant cholesterol in cardiovascular risk, the findings are preliminary. They underscore the need for continued research in this area to validate our observations and to translate them into clinical practice effectively.

Data Availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

ACKNOWLEDGMENT: We extend our gratitude to the staff of the cardiology departments for their assistance in data collection and patient care. We also thank the patients who participated in this study.

Funding: No external funding was received for this research.

Use of AI and AI-assisted Technologies Statement: During the preparation of this work, the author(s) utilized paid versions of large language models provided by OpenAI for tasks such as proofreading and generating suggestions to improve clarity and coherence. Following the use of these AI tools, the author(s) carefully reviewed and edited the manuscript to ensure its accuracy and appropriateness for publication. All final content decisions were made independently, and the author(s) take full responsibility for the integrity and accuracy of the manuscript. The use of AI tools adhered to ethical guidelines for transparency and responsible use of AI in academic publishing.

Credit Authorship Contribution Statement: Tripathi S. - Conceptualization, formal analysis, Software, Visualization; Pandey U.K.- Writing-review and editing; Kulshestra S-data curation; Jain D.-Project administration.

CONFLICTS OF INTEREST: The authors declare no conflicts of interest related to this study.

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How to cite this article:
Tripathi S, Pandey UK, Jain D and Kulshrestha S: The impact of remnant cholesterol and lipid profile discordance on carotid intima-media thickness among indian patients with coronary artery disease: an exploratory observational study with advanced regression analysis. Int J Pharm Sci & Res 2025; 16(2): 565-83. doi: 10.13040/IJPSR.0975-8232.16(2).565-83.