Postprint: Association of Remnant Lipoprotein Cholesterol and Non-High-Density Lipoprotein Cholesterol Discordance with Coronary Artery Stenosis Severity

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Date: 2022-11-22T00:00:00+00:00

Abstract

Background: Previous studies have shown that discordance between blood lipids is associated with severe coronary events in patients with coronary heart disease, which may lead to overestimation or underestimation of their risk of coronary events. Currently, the clinical significance of discordance between remnant lipoprotein cholesterol (RLP-C) and non-high-density lipoprotein cholesterol (non-HDL-C) remains unclear. Objective: To determine the association between discordance of RLP-C and non-HDL-C and the severity of coronary artery stenosis in patients with coronary heart disease. Methods: A retrospective analysis was conducted on 421 patients from a previous prehypertension cohort study database who had complete coronary angiography records and complete Gensini score calculations. They were divided into 4 groups based on the median levels of RLP-C and non-HDL-C in the cohort: Group 1: RLP-C $<$ median RLP-C and non-HDL-C $<$ median non-HDL-C; Group 2: RLP-C $<$ median RLP-C and non-HDL-C $\geq$ median non-HDL-C (discordant low RLP-C group); Group 3: RLP-C $\geq$ median RLP-C and non-HDL-C

Full Text

Association between Discordance of Remnant Lipoprotein Cholesterol and Non-High-Density Lipoprotein Cholesterol with Severity of Coronary Artery Stenosis

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Funding: 1. National Key R&D Program of China "Active Health and Aging Technology Response" (Grant No. 2020YFC2004701) 2. Liaoning Province "Top Talent" Science and Technology Plan (Major) Project "Research and Application of Multi-modal Intelligent Assisted Diagnosis and Treatment Planning for Coronary Heart Disease in Elderly Population" (Grant No. 2022JH1/10400004)

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Abstract

Background: Previous studies have demonstrated that discordance between lipid parameters is associated with major coronary events in patients with coronary heart disease and may lead to overestimation or underestimation of coronary event risk. However, the clinical significance of discordance between remnant lipoprotein cholesterol (RLP-C) and non-high-density lipoprotein cholesterol (non-HDL-C) remains unclear.

Objective: To determine the association between RLP-C and non-HDL-C discordance and the severity of coronary artery stenosis in patients with coronary artery disease (CAD).

Methods: We retrospectively analyzed 421 patients from a previous high-normal blood pressure cohort study database who had complete coronary angiography records and complete Gensini score calculations. Based on the median RLP-C and non-HDL-C levels in the cohort, patients were divided into four groups: Group 1: RLP-C $<$ median RLP-C and non-HDL-C $<$ median non-HDL-C; Group 2: RLP-C $<$ median RLP-C and non-HDL-C $\geq$ median non-HDL-C (discordant low RLP-C group); Group 3: RLP-C $\geq$ median RLP-C and non-HDL-C $<$ median non-HDL-C (discordant high RLP-C group); Group 4: RLP-C $\geq$ median RLP-C and non-HDL-C $\geq$ median non-HDL-C. Groups 2 and 3 were discordant groups, while Groups 1 and 4 were concordant groups. The severity of coronary stenosis was determined using the Gensini scoring system. The median values of RLP-C and non-HDL-C were 0.72 mmol/L and 3.13 mmol/L, respectively.

Results: Lipid discordance was observed in 34% of patients. Severe CAD was present in 15%, 19%, 32%, and 25% of patients in subgroups 1, 2, 3, and 4, respectively (P = 0.033). In logistic regression models, there was no difference in CAD severity between discordant and concordant groups (OR = 1.451, 95% CI 0.867–2.429). However, when Group 2 (discordant low RLP-C) and Group 3 (discordant high RLP-C) were compared separately with the two concordant groups (reference), CAD severity was significantly higher in Group 3 (OR = 2.084, 95% CI 1.110–3.912) but not in Group 2 (OR = 0.958, 95% CI 0.473–1.939). Furthermore, after adjustment in multivariate logistic regression models, RLP-C remained a strong predictor of severe coronary artery disease risk (OR

= 1.911, 95% CI 1.253–2.914).

Conclusion: In our study, approximately one-third of patients exhibited discordance between RLP-C and non-HDL-C. The discordant pattern of high RLP-C with low non-HDL-C was associated with the degree of coronary stenosis and may be considered a novel risk factor for predicting severe coronary lesions in CAD patients, independent of age, sex, and other traditional risk factors.

Keywords: Coronary artery disease; Atherosclerosis; Remnant lipoprotein cholesterol; Non-high-density lipoprotein cholesterol; Discordance

Introduction

Remnant lipoprotein cholesterol (RLP-C) is a triglyceride-rich lipoprotein cholesterol that consists of very low-density lipoprotein cholesterol (VLDL-C) and intermediate-density lipoprotein cholesterol (IDL-C) in the fasting state, as well as remnants of these lipoproteins and chylomicrons in the non-fasting state [1]. RLP-C has been shown to be closely associated with ischemic heart disease (IHD) independent of traditional lipid parameters, including low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and total cholesterol (TC) [2-5]. The predictive and prognostic value of RLP-C in clinical practice is receiving increasing attention.

Non-HDL-C encompasses nearly all atherogenic factors, such as LDL-C, VLDL-C, and IDL-C. Several studies have demonstrated that non-HDL-C better predicts fatal cardiovascular disease events than LDL-C, and some national and international guidelines recommend non-HDL-C as a secondary target for lipid lowering [6,7]. Professor Mora from Brigham and Women' s Hospital, Harvard Medical School, first proposed that discordance between lipid patterns may have predictive value for coronary artery disease severity [8-10]. They found that when LDL-C levels are discordant with non-HDL-C levels, coronary risk may be underestimated or overestimated. In recent years, RLP-C has played an increasingly important role in atherosclerosis, yet no studies have investigated whether discordance between RLP-C and non-HDL-C is associated with the severity of coronary lesions in CAD patients. Therefore, this study explores this question.

Methods

1.1 General Data We retrospectively analyzed 421 patients from a previous high-normal blood pressure cohort study database who had complete coronary angiography records and complete Gensini score calculations. These patients underwent coronary angiography at the General Hospital of Northern Theater Command between January 2004 and December 2014. We further excluded 23

patients with incomplete baseline data. None of the included patients had systemic inflammation, renal or hepatic failure, hypothyroidism/hyperthyroidism, Cushing' s syndrome, familial hyperlipidemia, or other conditions causing secondary hypercholesterolemia. Finally, data from 398 patients were used for analysis. General patient information collected included age, sex, alcohol consumption, smoking status, and statin use. The patient screening and grouping flow chart is shown in [Figure 1: see original paper].

Note: RLP-C = remnant lipoprotein cholesterol; Non-HDL-C = non-high-density lipoprotein cholesterol

Figure 1 Flow Chart of Patient Screening and Grouping

1.2 Angiographic Assessment The Gensini scoring system [11] is an angiographic scoring method widely used to assess CAD severity. Each patient' s Gensini score was independently calculated by two experienced cardiologists (associate chief physician or higher) based on their angiographic results. The Gensini scoring principle assigns baseline scores of 1, 2, 4, 8, 16, and 32 for patients with luminal stenosis of 25%, 50%, 75%, 90%, 99%, and total occlusion, respectively. This score is then multiplied by a factor indicating the lesion location in the coronary tree (5 points for left main, 2.5 for proximal left anterior descending or circumflex, 1.5 for mid left anterior descending, 1 for distal left anterior descending, right coronary artery, and obtuse marginal, and 0.5 for other branches). Patients with a Gensini score $\geq$ 20 were considered to have severe CAD, approximately equivalent to $\geq$ 70% stenosis in the left anterior descending artery [11]. Coronary heart disease diagnosis used DSA examination as the gold standard, with CAD diagnosed when coronary stenosis involved major branches with $\geq$ 50% narrowing.

1.3 Measurement and Calculation of Lipid Parameters Fasting blood samples were collected before angiography to measure TC, LDL-C, HDL-C, and TG levels in the laboratory. RLP-C was calculated as TC - (LDL-C + HDL-C) [12]; non-HDL-C was calculated as TC - HDL-C [9].

1.4 Statistical Analysis Categorical variables were summarized as numbers and percentages, while continuous variables were summarized as mean $\pm$ standard deviation (SD) for normally distributed data and median (interquartile range, IQR) for skewed data. As there is no standard cutoff point for discordance, we selected median values to define discordance for easier application to our study population. Discordance was defined as RLP-C $\geq$ median RLP-C of the total sample and non-HDL-C $<$ median non-HDL-C of the total sample, or RLP-C $<$ median RLP-C and non-HDL-C $\geq$ median non-HDL-C. Concordance was defined as both RLP-C and non-HDL-C being either $\geq$ their respective medians or $<$ their respective medians. Based on this, patients were divided into four groups: Group 1: RLP-C $<$ median RLP-C and non-HDL-C $<$ median non-HDL-C; Group 2: RLP-C $<$ median RLP-C and non-HDL-C $\geq$ median

non-HDL-C (discordant low RLP-C group); Group 3: RLP-C ≥ median RLP-C and non-HDL-C < median non-HDL-C (discordant high RLP-C group); Group 4: RLP-C ≥ median RLP-C and non-HDL-C ≥ median non-HDL-C. Groups 2 and 3 were discordant groups, while Groups 1 and 4 were concordant groups. Baseline characteristics of the four subgroups were compared using chi-square tests for categorical variables and one-way ANOVA for continuous variables. To reduce the probability of Type I error, P-values for differences in categorical variables were adjusted using Bonferroni correction. Multivariate logistic regression analysis was used to determine whether discordance was a risk factor for severe coronary artery disease. Missing data (total missing < 20%) were imputed using multiple imputation. Data analysis was performed using SPSS for Windows version 26.0 (SPSS Inc., Chicago, IL, United States). A P-value < 0.05 was considered statistically significant.

Results

2.1 Baseline Characteristics and Prevalence of Discordant Groups The study population (n = 398) had a mean age of 58.86 (7.37) years, with 56.0% male. Baseline characteristics are shown in . Mean systolic blood pressure was 129.3 (7.5) mmHg. Approximately one-third of patients had diabetes; 24% had a family history of CAD; 14% consumed alcohol; nearly half were taking statins; and 16% had multivessel coronary artery disease. Mean levels (SD) of RLP-C, LDL-C, and non-HDL-C were 0.76 (0.54), 2.46 (0.81), and 1.23 (0.35) mmol/L, respectively. The median Gensini score was 4 (2, 15). RLP-C levels were positively correlated with non-HDL-C (r = 0.51, P < 0.001). Overall, discordance between RLP-C and non-HDL-C was observed in 34.2% of patients ([Figure 2: see original paper]).

Table 1 Baseline Characteristics of the Study Population

Figure 2 Scatter Plot and Incidence of Discordance and Concordance Defined by Median Values for RLP-C and Non-HDL-C

2.2 Baseline Characteristics of Four Subgroups Stratified by RLP-C and Non-HDL-C Discordance and Concordance There were no statistically significant differences among the four subgroups in age, body mass index (BMI), systolic blood pressure, fasting glucose, mean Gensini score, family history of CAD, family history of hypertension, statin use, or multivessel coronary disease. However, significant differences were observed in sex distribution and prevalence of severe CAD (both P < 0.05). Group 3 had a higher proportion of patients with severe coronary lesions compared to Group 1 (32% vs. 15%, respectively), as detailed in .

Table 2 Characteristics of Patients with Concordant and Discordant RLP-C and Non-HDL-C

2.3 Logistic Regression Analysis of Lipid Discordance and Severity of Coronary Lesions In both univariate and multivariate logistic models, there was no statistically significant difference in CAD severity between subjects with discordant versus concordant RLP-C and non-HDL-C (unadjusted OR = 1.333, 95% CI 0.811–2.276; age- and sex-adjusted OR = 1.370, 95% CI 0.831–2.258; age, sex, smoking, and alcohol-adjusted OR = 1.370, 95% CI 0.831–2.258; fully adjusted OR = 1.451, 95% CI 0.867–2.429) (all P > 0.05), as shown in . However, when comparing RLP-C < median RLP-C and non-HDL-C ≥ median non-HDL-C (discordant low RLP-C group) and RLP-C ≥ median RLP-C and non-HDL-C < median non-HDL-C (discordant high RLP-C group) separately against the two concordant groups (reference), CAD severity was significantly increased in Group 3 (OR = 2.084, 95% CI 1.110–3.912) but not in Group 2 (OR = 0.958, 95% CI 0.473–1.939), as detailed in .

Assignment specifications: Dependent variable: Gensini score ≥ 20 ($ $20 = 1, <20 = 0); Independent variables: age (assigned as actual measured value); sex (0 = female, 1 = male); smoking (0 = no, 1 = yes); alcohol consumption (0 = no, 1 = yes); statins (0 = no use, 1 = use); diabetes (0 = no, 1 = yes); discordant or concordant group (0 = concordant group, 1 = discordant group).

Table 3 Results of Multivariate Logistic Regression Analysis for CAD Severity Between Discordant and Concordant Groups

Table 4 Results of Multivariate Logistic Regression Analysis Between Cholesterol Discordant Subgroups and Risk of CAD Severity

2.4 Correlation Between RLP-C and Severity of Coronary Stenosis in CAD Patients Under Different Models Based on multivariate logistic regression analysis results, RLP-C remained an independent risk factor for severe coronary lesions in our study population, consistent with previous findings, as shown in .

Table 5 Correlation Between RLP-C and Severity of Coronary Artery Stenosis in Patients with Coronary Heart Disease Under Different Models

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Discussion

In this study, we evaluated the cross-sectional relationship between coronary stenosis severity and discordant RLP-C and non-HDL-C values. Discordance between RLP-C and non-HDL-C was present in 34.2% of patients, and differences in CAD severity were observed between discordant and concordant groups. Although the calculation formula for RLP-C partially overlaps with non-HDL-C, it is important to recognize that the clinical significance of RLP-C extends beyond its mathematical formula. Due to the high cost of directly measuring RLP-C with current technology, a more convenient calculation method is employed, but calculated RLP-C is not merely the difference between TC, LDL-C,

and HDL-C as shown in the formula. Based on single lipid measurement criteria, discordance between lipid patterns may lead to overestimation or underestimation of CAD risk.

Mora et al. [8] followed 27,533 healthy women for a median of 17.2 years, during which 1,070 coronary events occurred. Among 13,595 women with LDL-C below the median, those with discordant LDL-C and non-HDL-C levels had a threefold underestimation of coronary risk compared to women with concordant levels. Zhang et al. [9] also investigated discordance between LDL-C and non-HDL-C in patients not receiving lipid-lowering therapy. They found that cardiovascular risk was overestimated when LDL-C was $\geq$ median while non-HDL-C was $<$ median. Their study confirmed that coronary risk may be overestimated or underestimated when LDL-C levels are discordant with non-HDL-C levels. However, no studies have evaluated whether discordance between RLP-C and non-HDL-C may lead to potential overestimation or underestimation of CAD risk and severity.

Given the increasingly important role of RLP-C in CAD, we assessed whether discordance between RLP-C and non-HDL-C is associated with CAD severity. We found that patients with RLP-C $\geq$ median and non-HDL-C $<$ median had greater CAD severity than those with concordant RLP-C and non-HDL-C levels. However, compared to concordant subjects, the discordant pattern of RLP-C $<$ median RLP-C and non-HDL-C $\geq$ median non-HDL-C was not significantly associated with CAD severity. This may be because RLP-C is a better predictor of CAD severity than non-HDL-C. Unlike non-HDL-C, RLP-C represents the cholesterol content in triglyceride-rich lipoproteins, which are primary contributors to atherosclerotic heart disease as triglycerides are ultimately catabolized [13]. In the fasting state, RLP-C consists primarily of cholesterol content in VLDL and IDL. Abnormally elevated RLP-C levels are directly associated with acute myocardial infarction, ischemic stroke, peripheral artery disease, in-stent restenosis, aortic valve stenosis, and other unexpected cerebrovascular events [14-17]. Mechanistically, LDL particle cholesterol content may vary between individuals due to particle heterogeneity. However, intraparticle cholesterol mass can be regulated through exchange of cholesterol esters and TG, and these well-described processes explain discordance between non-HDL-C and RLP-C levels. For these reasons, patients with high RLP-C but acceptable non-HDL-C levels may require close monitoring and more intensive therapy to prevent recurrent coronary events, which is often overlooked in secondary prevention of CAD.

This study has several limitations. First, it is a retrospective observational study with inherent limitations. Second, there is no standard definition or cutoff value for RLP-C and non-HDL-C discordance; we used median values for our study population, which is a commonly used method in previous studies. Third, the sample size was relatively small, and larger studies are needed to confirm our findings.

In conclusion, approximately one-third of patients in our study exhibited discordance between RLP-C and non-HDL-C. We have shown that the discordant

pattern of high RLP-C with low non-HDL-C is associated with CAD severity and may be considered a risk factor for severe coronary artery disease, independent of age, sex, and other risk factors.

Author Contributions

Concept and design of academic research content and critical revision: CHEN Yan, LYU Zhibo, ZHAO Xin; **Statistical analysis and manuscript writing:** CHEN Yan; **Data analysis and interpretation:** CHEN Yan; **Statistical review:** CHEN Yan.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Varbo A, Benn M, Tybjaerg-Hansen A, et al. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation[J]. Circulation, 2013,128(12):1298-1309.
2. Wadstrom BN, Wulff AB, Pedersen KM, et al. Elevated remnant cholesterol increases the risk of peripheral artery disease, myocardial infarction, and ischaemic stroke: a cohort-based study[J]. Eur Heart J, 2022,43(34):3258-3269.
3. Wilson P, Remaley AT. Ischemic Heart Disease Risk and Remnant Cholesterol Levels[J]. J Am Coll Cardiol, 2022,79(24):2398-2400.
4. Doi T, Langsted A, Nordestgaard BG. Elevated Remnant Cholesterol Reclassifies Risk of Ischemic Heart Disease and Myocardial Infarction[J]. J Am Coll Cardiol, 2022,79(24):2383-2397.
5. Ginsberg HN, Packard CJ, Chapman MJ, et al. Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies-a consensus statement from the European Atherosclerosis Society[J]. Eur Heart J, 2021,42(47):4791-4806.
6. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias[J]. Eur Heart J, 2016,37(39):2999-3058.
7. Jacobson TA, Maki KC, Orringer CE, et al. National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2[J]. J Clin Lipidol, 2015,9(6 Suppl):S1-S122.

8. Mora S, Buring JE, Ridker PM. Discordance of low-density lipoprotein (LDL) cholesterol with alternative LDL-related measures and future coronary events[J]. Circulation, 2014,129(5):553-561.

9. Zhang Y, Wu NQ, Li S, et al. Non-HDL-C is a Better Predictor for the Severity of Coronary Atherosclerosis Compared with LDL-C[J]. Heart Lung Circ, 2016,25(10):975-981.

10. Kurmus O, Erkan AF, Ekici B, et al. Discordance of Low-Density Lipoprotein Cholestrol and Non-High-Density Lipoprotein Cholestrol and Coronary Artery Disease Severity[J]. Arq Bras Cardiol, 2020,114(3):469-475.

11. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease[J]. Am J Cardiol, 1983,51(3):606.

12. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk[J]. Eur Heart J, 2020,41(1):111-188.

13. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease[J]. Lancet, 2014,384(9943):626-635.

14. Lim GB. Inclusion of remnant cholesterol improves risk prediction for ischaemic heart disease[J]. Nat Rev Cardiol, 2022,19(8):504.

15. Xu X, Pandit RU, Han L, et al. Remnant Lipoprotein Cholesterol Independently Associates With In-Stent Restenosis After Drug-Eluting Stenting for Coronary Artery Disease[J]. Angiology, 2019,70(9):853-859.

16. Duran EK, Aday AW, Cook NR, et al. Triglyceride-Rich Lipoprotein Cholesterol, Small Dense LDL Cholesterol, and Incident Cardiovascular Disease[J]. J Am Coll Cardiol, 2020,75(17):2122-2135.

17. Kaltoft M, Langsted A, Nordestgaard BG. Triglycerides and remnant cholesterol associated with risk of aortic valve stenosis: Mendelian randomization in the Copenhagen General Population Study[J]. Eur Heart J, 2020,41(24):2288-2299.

Note: Figure translations are in progress. See original paper for figures.