Association of Increased Remnant Cholesterol and The Risk of Coronary Artery Disease: A Retrospective Study

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Abstract

Background and Aims

Low-density lipoprotein cholesterol (LDL-C) is the primary target in lipid-lowering therapy in coronary artery disease (CAD). But some patients with normal levels of LDL-C still suffer from CAD progression and malignant outcomes (e.g., MACEs), and the mechanism is unclear. Previous prospective studies demonstrated that remnant cholesterol (RC) and non-HDL-C were capable to predict the risk of CAD. This study evaluated the association between RC and non-HDL-C with the risk of CAD.

Methods

12,563 patients were enrolled in our study. We categorized patients into four concordance/discordance groups according to the median of RC, LDL-C and non-HDL-C. Then we performed a propensity score matching (PSM) strategy. Unadjusted and adjusted multivariate logistic regression models were used to evaluate the relationship between lipid concentrations.

Results

8,658 (68.9%) patients were male with a median age of 61 (54,67) years. The multivariate logistic regression showed the OR of RC was 1.952 (CI=1.276-2.988, p=0.002). The OR of low RC/high LDL-C group was 0.574 (CI=0.462-0.714, p=0.001) and the OR of low RC/high non-HDL-C group was 0.574 (CI=0.462-0.714, p=0.001). The p for interaction between RC and hypertension, diabetes were both <0.001.

Conclusions

Our study showed a significant association between RC and CAD. The level of RC was more capable to reflect the risk of CAD than LDL-C and non-HDL-C. There was an interaction relationship between remnant cholesterol and age, gender, hypertension, diabetes in CAD. But we didn't find whether there was a relationship between non-HDL-C and CAD.

1 Introduction

Over the past years, coronary artery disease (CAD) has become the leading cause of morbidity and mortality worldwide [1, 2]. Great progress has been made in the research of its pathophysiology, and it has been demonstrated that low-density lipoprotein cholesterol (LDL-C) plays an important role in the process of atherosclerosis, which made it the primary target in lipid-lowering therapy [3–5], such as statins or non-statin agent (e.g, ezetimibe, evolocumab) [6, 7]. However, there are still a great number of patients, which have received the treatment above, suffering from disease progression and malignant outcomes (e.g., MACEs).

- Meanwhile, remnant cholesterol (RC) has drawn increasing attention from cardiologists. Remnant cholesterol, defined as the cholesterol content of triglyceride-rich lipoproteins, is consist of very low-density lipoproteins and intermediate-density lipoproteins (VLDL and IDL) in fasting state, and chylomicron remnants in non-fasting state [8–10]. Recently, several studies have demonstrated that the elevated level of remnant cholesterol in serum is a significant risk factor for atherosclerosis, and it is remnant cholesterol and non-HDL-C, but not LDL-C, which better reflect the outcome of CAD, independently [10–14]. Therefore, in this clinical retrospective study, we aimed to test the hypothesis that elevated RC and non-HDL-C index had strong associations with CAD, and to explore whether the level of RC is more capable to predict the risk of CAD than LDL-C and non-HDL-C.

2 Patients And Methods

Study design and population

- This retrospective study enrolled 12,563 patients, which once underwent coronary angiography from January 1, 2019, to January 21, 2020, at Beijing Anzhen Hospital, Capital Medical University. Our major exclusion criteria included extreme age (patients<18 or>80 years old), valvular heart disease, cardiomyopathy, severe hepatic or renal dysfunction, the history of stroke or myocardial infarction (MI), malignant tumor, leukopenia or thrombocytopenia, any ongoing inflammatory, in-stent restenosis (ISR), chronic total occlusion (CTO) and patients whose date of LDL-C was not available. This study was approved by the Beijing Anzhen Hospital Ethics Committee of Capital Medical University, and all patients gave their advance consent to participate in this study.

Measurements

- Patient demographics data including gender, age, body mass index (BMI), smoking status, clinical characteristics such as hypertension, hypercholesterolemia, diabetes mellitus, and laboratory results were obtained from the original electronic medical records. We took the serum sample from patients after an overnight fasting (> 8 h) and stored it at − 70°C for laboratory analysis. Fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), and lipid level including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) were measured by standard laboratory techniques. The level of LDL-C was determined by the Friedewald equation. Furthermore, non-HDL-C was

estimated as TC minus HDL-C while RC was calculated as TC minus LDL-C minus HDL-C. All blood samples were tested in triplicate under the guidance of the manufacturer's instructions.

Diagnostic criteria

- CAD was diagnosed according to the guideline of European Society of Cardiology (ESC) in 2019 [15]. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, or previously diagnosed hypertension [16]. Hypercholesterolemia was defined as TC > 5.18mmol/L (200mg/dl) or TG > 1.72 mmol/L (150 mg/dL). Diabetes mellitus was defined as a fasting serum glucose ≥ 7.0 mmol/L or a non-fasting glucose ≥ 11.10 mmol/L according to WHO guidelines on diabetes [17].

Statistical analysis

- We calculated the medians of the RC, LDL-C and non-HDL-C index to divide all patients into two different groups: low (less than the medians) and high (equal to or greater than the medians). Then we categorized patients into four groups according to having a low or high RC index and LDL-C, RC and non-HDL-C, non-HDL-C and LDL-C as follows: low/low, low/high, high/low, and high/high. Categorical variables were presented as absolute numbers and percentages while analyzed by the $\chi 2$ test or Fisher's exact test. Continuous variables were presented as medians and interquartile range (Q25, and Q75) while analyzed by the Kruskal-Wallis test because of skewed distribution. Spearman ρ test correlation analyses were also adopted to investigate the correlation between RC and other CAD risk factors.
- Furthermore, the receiver operating characteristic (ROC) curve was used to identify the cut-off point of RC and divided 12,563 patients into two groups (less than the medians and equal to or greater than the medians). Then we performed a propensity score matching (PSM) strategy according to the RC group to reduce the influence of observed imbalances in clinical baseline characteristics, which adopted a multivariable logistic regression model based on: age, gender, hypertension, hypercholesterolemia, smoking status, diabetes mellitus, BMI, DBP, SBP, WBC, RBC, PLT, Hb, PT, APTT, Hcy, CR, UA, FBG, HbA1C, hs-CRP, BNP, and the matching ratio is 1:1. Multivariate logistic regression analyses were used to adjust confounders and calculate odds ratios (OR) and 95% confidence intervals (CI). Finally, subgroup analyses were carried out to examine the *p* value for interaction between RC and other risk factors after PSM.
- All statistical data analyses were conducted by IBM SPSS software version 26.0. A two-tailed *p* value of < 0.05 was considered statistically significant in our analyses.

3 Results

Baseline clinical characteristics (total population)

Among 21,980 patients who underwent CTA before, 12,563 patients were enrolled in the final analyses, with 10,236 in CAD group and 2,327 in non-CAD group. The flowchart is shown in Fig. 1. The baseline clinical characteristics of all patients are shown in Table 1. Among the patients enrolled, 8,658 (68.9%) were male with a median age of 61 (54,67) years and BMI of 25.86 (23.87,28.02) kg/m2, 62.9% (7906) and 31.2% (3920) of whom had hypertension and diabetes. The median values which defined concordance/discordance groups for RC, LDL-C, and non-HDL-C were 0.51 mmol/l, 2.26 mmol/l and 2.83 mmol/l, respectively. Moreover, in clinical presentation, most of the participants were unstable angina (72.1%), while a small part of patients showed non-CAD (16.6%), stable CAD (1.9%), non-ST segment elevation myocardial infarction (5.3%) and ST segment elevation myocardial infarction (4.0%).

Table 1
Baseline clinical characteristics and laboratory parameters of patients according to RC and LDL-C index categories

Variables	All Participants (N = 12563)	RC＜Median LDL-C < Median group (n = 3596)	RC＜Median LDL-C ≥ Median group (n = 2612)	RC ≥ Median LDL-C＜Median group (n = 2684)	RC ≥ Median LDL-C ≥ Median group (n = 3671)	*p* value
Clinical Characteristics						
Man(%)	8658(68.9%)	2693(74.9%)	1777(68.0%)	1845(68.7%)	2343(63.8%)	＜0.001
Age (yrs)	61(54,67)	62(55,67)	61(54,67)	61(54,67)	60(53,66)	＜0.001
BMI (kg/m^2)	25.86(23.87,28.02)	25.55(23.52,27.68)	25.47(23.51,27.68)	26.19(24.22,28.27)	26.09(24.16,28.40)	＜0.001
Hypertension, n (%)	7906(62.9%)	2259(62.8%)	1500(57.4%)	1844(68.7%)	2303(62.7%)	＜0.001
Hypercholesterolemia,n (%)	9894(78.8%)	2727(75.8%)	2113(80.9%)	2077(77.4%)	2977(81.1%)	＜0.001
Smoking ,n (%)	5801(46.2%)	1716(47.7%)	1202(46.0%)	1228(45.8%)	1655(45.1%)	0.143
Diabetes,n (%)	3920(31.2%)	1178(32.8%)	644(24.7%)	1000(37.3%)	1098(29.9%)	＜0.001
Laboratory parameters						
SBP (mmHg)	130(120,140)	128(119,138)	130(120,140)	129(120,139)	130(120,140)	＜0.001
DBP (mmHg)	77(70,84)	76(70,82)	78(70,85)	77(70.84)	78(70,85)	＜0.001
FBG (mmol/L)	6.58(5.39,13.61)	6.44(5.35,12.36)	6.13(5.28,10.42)	7.10(5.52,16.91)	6.75(5.47,16.42)	＜0.001
HbA1C (%)	6.1(5.6,6.9)	6.0(5.6,6.8)	5.9(5.6,6.6)	6.2(5.7,7.2)	6.1(5.7,7.1)	＜0.001
TC (mmol/L)	3.97(3.35,4.74)	3.18(2.86,3.49)	4.42(4.03,4.94)	3.59(3.25,3.91)	4.91(4.43,5.52)	＜0.001
TG (mmol/L)	1.38(0.99,2.00)	0.99(0.78,1.25)	1.12(0.88,1.41)	1.92(1.43,2.65)	1.92(1.47,2.56)	＜0.001
LDL-C(mmol/L)	2.26(1.76,2.91)	1.72(1.44,1.97)	2.83(2.50,3.31)	1.81(1.55,2.04)	2.97(2.58,3.51)	＜0.001
HDL-C(mmol/L)	1.08(0.93,1.27)	1.10(0.94,1.28)	1.18(1.02,1.38)	0.97(0.84,1.15)	1.06(0.93,1.24)	＜0.001
RC(mmol/L)	0.51(0.37,0.71)	0.37(0.29,0.43)	0.37(0.28,0.44)	0.67(0.57,0.88)	0.73(0.60,0.94)	＜0.001
Non-HDL-C(mmol/L)	2.83(2.26,3.58)	2.07(1.78,2.33)	3.18(2.85,3.67)	2.56(2.27,2.81)	3.79(3.36,4.39)	＜0.001
Triglycerides > 1.69 mmol/l＆ HDL-C < 1.03/1.29 mmol/l (in men/women)	11214(89.3%)	3217(89.5%)	2348(89.9%)	2398(89.3%)	3251(88.6%)	0.370
WBC (×10^9/L)	6.72(5.73,7.97)	6.58(5.63,7.78)	6.73(6.57,7.94)	6.75(5.76,8.01)	6.83(5.86,8.18)	＜0.001
RBC (×10^12/L)	4.63(4.33,4.93)	4.59(4.29,4.88)	4.65(4.35,4.95)	4.60(4.30,4.89)	4.68(4.38,4.99)	＜0.001
PLT (×10^9/L)	221(188,260)	213(180,249)	227(194,265)	214(184,256)	231(196,270)	＜0.001
Hb(g/L)	143(133,154)	142(132,152)	145(134,155)	142(131,152)	145(134,156)	＜0.001
PT(Sec)	11.4(10.9,11.9)	11.6(11.1,12.1)	11.4(11.0,11.9)	11.3(10.8,11.8)	11.2(10.8,11.7)	＜0.001
ATPP(Sec)	32.5(30.3,34.8)	32.6(30.4,34.9)	32.6(30.3,34.7)	32.3(30.3,34.7)	32.4(30.3,34.8)	0.157
BNP(pg/ml)	28(15,58)	30(16,59)	27(15,57)	27(14,55)	28(14,61)	0.008
Hs-CRP(mg/L)	1.10(0.52,2.74)	0.75(0.39,1.87)	1.18(0.56,3.02)	1.10(0.54,2.60)	1.51(0.72,3.53)	＜0.001
Homocysteine (umol/L)	12.3(9.9,15.3)	12.3(10.0,15.3)	12.7(10.4,15.7)	12.1(9.7,15.0)	12.1(9.8,15.4)	＜0.001
Uric acid(umol/L)	333.3(280.4,393.3)	322.5(271.1,376.0)	322.8(273.1,379.3)	342.9(289.1,408.0)	346.3(290.0,406.8)	＜0.001

[a]. Values are median or n (%).

[b]. Abbreviations: BMI, body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FBG, Fasting blood glucose; HbA1C, Glycosylated hemoglobin A1C; TC, total cholesterol; TG, triglyceride; LDL-C, Low density lipoprotein cholesterol; HDL-C, High density lipoprotein cholesterol; WBC, white blood cell; RBC, red blood cell; PLT, Platelets; PT, Prothrombin time; ATPP, Aqueous two-phase partitioning; BNP, Brain Natriuretic Peptide; Hs-CRP, hyper-sensitive C-reactive protein; CAD, Coronary artery disease; ACS, Acute Coronary Syndrome; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction

Variables	All Participants (N = 12563)	RC＜Median LDL-C < Median group (n = 3596)	RC＜Median LDL-C ≥ Median group (n = 2612)	RC ≥ Median LDL-C＜Median group (n = 2684)	RC ≥ Median LDL-C ≥ Median group (n = 3671)	*p* value
Creatinine (umol/L)	70.2(60.9,80.5)	70.7(62.1,80.0)	68.9(59.7,79.2)	71.7(61.8,82.1)	69.9(60.1,80.5)	＜0.001
Clinical presentation,n (%)						
Non-CAD	2086(16.6%)	485(13.5%)	608(23.3%)	386(14.4%)	607(16.5%)	＜0.001
Stable CAD	241(1.9%)	101(2.8%)	47(1.8%)	37(1.4%)	56(1.5%)	＜0.001
ACS	10236(81.5%)	3010(83.7%)	1957(74.9%)	2261(84.2%)	3008(81.9%)	＜0.001
Unstable angina	9063(72.1%)	2783(77.4%)	1684(64.5%)	2061(76.8%)	2535(69.1%)	＜0.001
NSTEMI	666(5.3%)	121(3.4%)	156(6.0%)	107(4.0%)	282(7.7%)	＜0.001
STEMI	507(4.0%)	106(2.9%)	117(4.5%)	93(3.5%)	191(5.2%)	＜0.001

[a]. Values are median or n (%).

[b]. Abbreviations: BMI, body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FBG, Fasting blood glucose; HbA1C, Glycosylated hemoglobin A1C; TC, total cholesterol; TG, triglyceride; LDL-C, Low density lipoprotein cholesterol; HDL-C, High density lipoprotein cholesterol; WBC, white blood cell; RBC, red blood cell; PLT, Platelets; PT, Prothrombin time; ATPP, Aqueous two-phase partitioning; BNP, Brain Natriuretic Peptide; Hs-CRP, hyper-sensitive C-reactive protein; CAD, Coronary artery disease; ACS, Acute Coronary Syndrome; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction

The baseline clinical characteristics of patients compared by groups with concordant and discordant values of RC versus LDL-C are shown in Table 1. There were significant differences in age, gender, hypertension, smoking, diabetes and other laboratory parameters across the four groups. Furthermore, patients with a high RC index were more likely to have a higher FBG and WBC, while patients with a high LDL-C index were more possible to get a higher hs-CRP. Similar patterns were also observed in non-HDL-C versus LDL-C and RC versus non-HDL-C groups, which are separately shown in Supplemental Table 1 and Supplemental Table 2.

Correlation analyses and multivariable logistic regression analyses (before and after PSM)

As spearman correlation analyses before PSM showed (Supplemental Table 3, the RC index was positively related to FBG, HbA1C and hs-CRP (r = 0.098, 0.122 and 0.172 respectively, with all $p < 0.001$).

The ROC curve showed the cut-off point of RC for PSM was 0.415 mmol/l. After PSM, there were 5,252 patients being enrolled, with 4,298 in CAD group and 954 in non-CAD group. The new median values of RC, LDL-C, and non-HDL-C were 0.42 mmol/l, 2.13 mmol/l and 2.63 mmol/l. Then multivariate logistic regression analyses were performed to investigate the associations between independent confounders and CAD, before and after PSM. The model of analyses were as followed: model 1: age, gender, hypertension, hypercholesterolemia, smoking, diabetes, BMI; model 2: model 1, SBP, DBP, FBG, HbA1C, HDL-C, TG; model 3: model 2, creatinine, uric acid, hs-CRP, BNP, WBC, homocysteine. After adjustment for traditional predictors, the results illustrated that after PSM, the level of RC (OR = 1.952, CI = 1.276–2.988, $p = 0.002$) was an independent risk factor for CAD. While the OR of TC was 0.880 (CI = 0.808–0.958, $p = 0.003$), the OR of LDL-C was 0.847 (CI = 0.776–0.925, p＜0.001) and the OR of non-HDL-D was 0.880 (CI = 0.808–0.958, $p = 0.003$) (Table 2, Fig. 2, Fig. 3). Furthermore, according to the concordance/discordance groups analyses, the OR of low RC/high LDL-C group was 0.574 (CI = 0.462–0.714, p＜0.001) and the OR of low RC/high non-HDL-C group was 0.574 (CI = 0.462–0.714, p＜0.001), while the OR of high non-HDL-C/high LDL-C group was 0.712 (CI = 0.603–0.841, p＜0.001).

Table 2
Multivariate logistic regression analyses of the risk of CAD

Variable	OR (95% CI)					
	Before PSM			After PSM		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
RC	1.306 (1.136–1.502) †	1.879 (1.409–2.506) †	1.777 (1.292–2.444) †	1.268 (1.003–1.603) §	1.940 (1.270–2.963) ‡	1.952 (1.276–2.988) ‡
TC	0.905 (0.864–0.948) †	0.933 (0.879–0.991) §	0.902 (0.843–0.966) ‡	0.871 (0.810–0.937) †	0.889 (0.817–0.967) ‡	0.880 (0.808–0.958) ‡
LDL-C	0.870 (0.824–0.919) †	0.899 (0.845–0.957) ‡	0.868 (0.809–0.932) †	0.850 (0.781–0.924) †	0.857 (0.786–0.935) †	0.847 (0.776–0.925) †
Non-HDL-C	0.933 (0.889–0.980) ‡	0.933 (0.879–0.991) §	0.902 (0.843–0.966) ‡	0.901 (0.836–0.972) ‡	0.889 (0.817–0.967) ‡	0.880 (0.808–0.958) ‡
Variable	**OR (95% CI)**					
	Before PSM			**After PSM**		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
RC/LDL						
Low/low (referent)	-	-	-	-	-	-
Low/high	1.758 (1.531–2.020) †	1.535 (1.313–1.795) †	1.568 (1.314–1.870) †	0.618 (0.505–0.757) †	0.640 (0.517–0.793) †	0.626 (0.504–0.778) †
High/low	1.039 (0.895–1.207)	1.013 (0.843–1.218)	1.072 (0.875–1.314)	1.119 (0.894–1.401)	1.171 (0.915–1.498)	1.171 (0.915–1.498)
High/high	0.902 (0.787–1.034)	0.986 (0.822–1.182)	0.925 (0.754–1.135)	0.968 (0.791–1.184)	1.022 (0.803–1.302)	1.004 (0.786–1.281)
Variable	**OR (95% CI)**					
	Before PSM			**After PSM**		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
RC/Non-HDLC						
Low/low (referent)	-	-	-	-	-	-
Low/high	0.585 (0.508–0.673) †	0.662 (0.564–0.776) †	0.640 (0.534–0.767) †	0.577 (0.471–0.707) †	0.590 (0.476–0.730) †	0.574 (0.462–0.714) †
High/low	1.054 (0.901–1.233)	1.091 (0.882–1.350)	0.973 (0.769–1.230)	1.152 (0.912–1.455)	1.133 (0.865–1.482)	1.134 (0.866–1.485)

[a.] † P < 0.001

‡ P < 0.01

§ P < 0.05

[b]. Model1: Age + gender + Hypertension + Hypercholesterolemia + Smoking + Diabetes + BMI

Model2:Model1 + SBP + DBP + FBG + HbA1C + HDL + TG

Modle3: Model2 + CR + UA + HsCRP + BNP + WBC + Homocysteine

[c]. Abbreviations: TC, total cholesterol; TG, triglyceride; LDL-C, Low density lipoprotein cholesterol; HDL-C, High density lipoprotein cholesterol; RC, Remnant cholesterol

Variable	OR (95% CI)					
	Before PSM			After PSM		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
High/high	0.959	0.979	0.922	0.994	1.021	1.009
	(0.847–1.087)	(0.838–1.144)	(0.773–1.099)	(0.824–1.199)	(0.825–1.264)	(0.815–1.251)
Variable	**OR (95% CI)**					
	Before PSM			**After PSM**		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
Non-HDLC/LDL						
Low/low (referent)	-	-	-	-	-	-
Low/high	0.650	0.698	0.732	0.895	0.941	0.950
	(0.520–0.813) †	(0.542–0.898) ‡	(0.550–0.974) §	(0.628–1.274)	(0.657–1.348)	(0.663–1.362)
High/low	0.867	0.852	0.867	1.017	1.113	1.122
	(0.686–1.096)	(0.624–1.163)	(0.615–1.223)	(0.689–1.501)	(0.699–1.774)	(0.704–1.788)
High/high	0.753	0.789	0.767	0.742	0.729	0.712
	(0.678–0.837) †	(0.699–0.891) †	(0.669–0.880) †	(0.635–0.867) †	(0.618–0.860) †	(0.603–0.841) †
a. † P < 0.001						
‡ P < 0.01						
§ P < 0.05						
b. Model1: Age + gender + Hypertension + Hypercholesterolemia + Smoking + Diabetes + BMI						
Model2:Model1 + SBP + DBP + FBG + HbA1C + HDL + TG						
Modle3: Model2 + CR + UA + HsCRP + BNP + WBC + Homocysteine						
c. Abbreviations: TC, total cholesterol; TG, triglyceride; LDL-C, Low density lipoprotein cholesterol; HDL-C, High density lipoprotein cholesterol; RC, Remnant cholesterol						

Subgroup analyses (after PSM)

Subgroup analyses were performed to explore the P value for interaction between RC and other risk factors (Supplemental Table 4). The results indicated that there was an interconnection between RC and age, gender, hypertension, diabetes as different risk factors for CAD (with all *p* for interaction < 0.001, respectively).

Discussion

Compared with the studies before, our study has got a large sample to get much closer to the real world. In this study, we elicited three major findings. At first, the elevated level of RC was positively correlated with CAD. Secondly multivariate logistic regression analyses indicated that RC was a risk factor for CAD, independently. Furthermore, the level of RC was more capable to reflect the risk of CAD than LDL-C or non-HDL-C. Finally, there was an interaction relationship between RC and age, gender, hypertension, diabetes in CAD progression.

The relationship between remnant cholesterol and coronary artery disease

As far as we know, hypercholesterolemia is a common lipid disorder related to the increasing incidence of CAD [5]. Because of the residual risk in statin-treated patients with a seemingly optimal low level of LDL-C [18], more and more studies raised the hypothesis that there was a strong association between remnant cholesterol and CAD risk [8, 19, 20]. Triglyceride-rich lipoproteins (TRLs), also known as VLDL, IDL and their remnants, have always been considered harmful for cardiovascular health [21, 22]. Nordestgaard et al demonstrated that it was cholesterol, but not triglycerides may cause atherosclerosis in TRLs. Furthermore, healthy participants with a high remnant-C level were more likely to have a greater risk of incident CAD, independently [23]. In-vitro and animal studies indicated the potential mechanism for this phenomenon may be that the remnant-C content could enter and get trapped in the arterial wall, and have an influence as same as LDL-C [24–26]. It could be taken up by macrophages or smooth muscle cells (SMC), then further induces inflammation, which plays an important role in the process of plaque initiation, progression and rupture [27, 28].

Moreover, in addition to LDL-C, non-HDL cholesterol also includes TRLs. Therefore, it's not surprising to find RC and non-HDL-C play an important role in the process of CAD.

Several cohort studies [11, 12, 29] and randomized clinical trials [10] investigating the relationship between RC, non-HDL-C and the outcomes of CAD have been conducted over recent years. Castañer et al enrolled 6,901 patients from the PREDIMED (Prevención con Dieta Mediterránea) study [10], while Langsted et al enrolled patients from the Copenhagen General Population Study (CGPS), a cohort study consisting of 109,574 individuals [29]. Both studies showed that the high level of RC was associated with major adverse cardiovascular events (MACEs). In addition to CGPS, Varbo et al also included patients from the CCHS (Copenhagen City Heart Study) and the CIHDS (Copenhagen Ischemic Heart Disease Study), a total of 73,513 subjects. It showed that a 1 mmol/l (39 mg/dl) non-fasting RC increased may lead to a 2.8-fold causal risk for ischemic heart disease [12]. Moreover, Johannesen et al suggested that non-HDL-C, but not LDL-C, was related to an increasing risk of all-cause mortality of CAD [11]. Similarly, with different models of multivariate logistic regression analyses, our study concluded that remnant cholesterol was an independent causal risk for CAD, which was consistent with the results of former studies.

RC, LDL-C and non-HDL-C

Furthermore, the concordance/ discordance groups analyses were adopted to compare the capacity of predicting the CAD risk between RC and LDL-C or non-HDL-C, because of the tight correlation in those indexes and the hypothesis that RC could induct the elevated levels of other atherogenic lipoproteins [30]. By comparing the disagreements between RC and LDL-C or non-HDL-C, these analyses could show us the final consequences of the RC index. After PSM, the results illustrated that low RC groups had less possibility to suffer from CAD. What's more, as one of the predictors, the level of RC was more capable to reflect the risk of CAD than LDL-C and non-HDL-C.

RC and other CAD risk factors

Previous studies confirmed the potential mechanism of RC could be that it inducted the migration of mononuclear cells and macrophage in endothelial cells and promoted the occurrence of inflammation [31, 32]. The spearman correlation analyses of our study indicated that the level of RC in serum was positively related to hs-CRP. This phenomenon was consistent with the results of previous studies. Meanwhile, we performed subgroup analyses to examine the relationship between RC and other risk factors in the incident and progression of CAD, such as age, gender, hypertension, and diabetes status. To our knowledge, hypertension and insulin resistance (IR) have a strong relationship with inflammation or dyslipidemia, both been generally recognized that could promote the CAD progression [33]. As the results showed, there was an interaction between RC and other risk factors. But the exact physiological mechanisms that how they affect others influences in CAD progression remain unknown.

Analyses of conflict results in our study

Our study showed that non-HDL-C, TC and LDL-C were protective factors for CAD, and the disease incidence of the high non-HDL-C/high LDL-C group was less than the low non-HDL-C/low LDL-C group, which were inconsistent with the clinical phenomenon and the results of existing research. All the conflict results in our study mentioned above may be attributed to: (1) Our study was a retrospective study, while a cohort study or a randomized clinical trial could get much closer to the real-world scenarios and draw conclusions in line with the clinical phenomenon. (2) Most participation in this study were unstable angina patients (72.1%), which may cause a deviation from the average value of all populations.

4 Limitations

Our present study also has several limitations: (1) This study was a single-center, retrospective study. (2) The study was also conducted with a nonrandomized sample, which probably restricted the generalizability of our results. Thus, there must be more multicenter randomized-controlled trials done to explore the relationship between RC and CAD in the future. (3) Our study only enrolled a Chinese population at a single hospital. (4) The study did not take the use of drugs or socioeconomic status into consideration. (5) Finally, the detailed interaction relationship between RC and age, gender, hypertension, and diabetes needs further exploration.

5 Conclusions

Hypercholesterolemia is a common lipid disorder related to the increasing incidence of CAD. Besides LDL-C, our study illustrated a significant association between RC and CAD. Furthermore, the level of RC was more capable to reflect the risk of CAD than LDL-C or non-HDL-C. Moreover, there was an interaction relationship between remnant cholesterol and age, gender, hypertension, diabetes in CAD progression. But whether non-HDL-C could be an independent risk factor for CAD was not reflected in this study. And the exact interaction between RC and other CAD risk factors remains unclear. Further studies of RC and its exact mechanisms in the incident and progression of CAD need to be conducted to promote the development of lipid-lowering therapy for CAD patients.

Abbreviations

CAD, Coronary artery disease; RC, remnant cholesterol; BMI, body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FBG , Fasting blood glucose; HbA1C, Glycosylated hemoglobin A1C; TC, total cholesterol; TG, triglyceride; LDL-C, Low density lipoprotein cholesterol; HDL-C,

High density lipoprotein cholesterol; WBC, white blood cell; RBC, red blood cell; PLT, Platelets; PT, Prothrombin time; ATPP, Aqueous two-phase partitioning; BNP, Brain Natriuretic Peptide; hs-CRP, hyper-sensitive C-reactive protein; ACS, Acute Coronary Syndrome; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; ROC: Receiver-operating characteristic curve

Declarations

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

Wang kexin carried out the experiments, acquired the data and wrote the first draft of the paper; Ding yaodong carried out the experiments and wrote sections of the manuscript; Gao wen, Wang rui, Yang jiaxin, Liu xiaoli and Shen hua recruited the subjects, performed the patients assessments and critically reviewed the paper for intellectual content. Wang kexin, Ding yaodong, Wang rui, and Yang jiaxin performed the statistical analyses; Ge hailong conceived and designed the study and handled funding and supervision.

All authors read and approved the final manuscript.

Acknowledgments

Not applicable.

Data Availability Statement

The data and materials can be used with permission.

Ethics approval and consent to participate

The study was approved by the Beijing Anzhen Hospital Ethics Committee of Capital Medical University, and all participants signed an informed consent form.

Consent for publication

All participants provided written informed consent before enrollment in this study.

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Figures

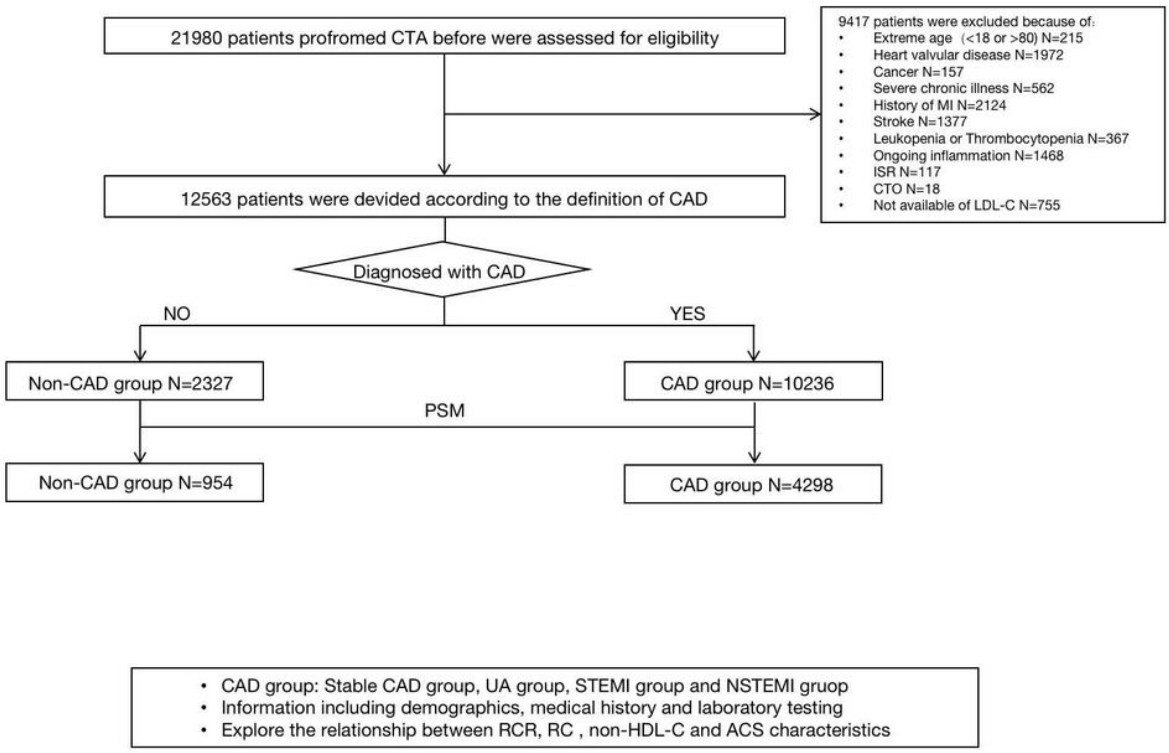

Figure 1

A flow chart

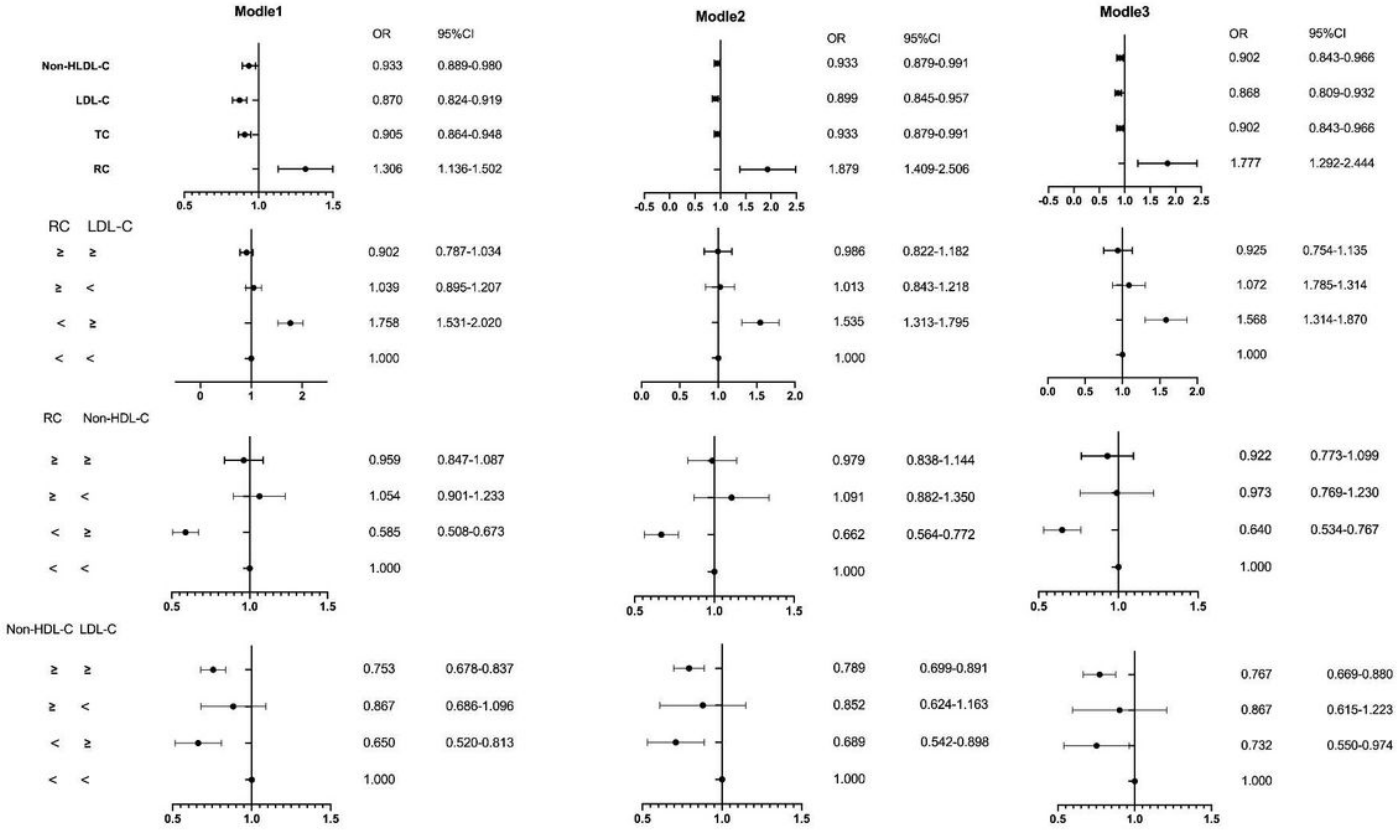

Figure 2

Multivariate logistic regression analyses before PSM

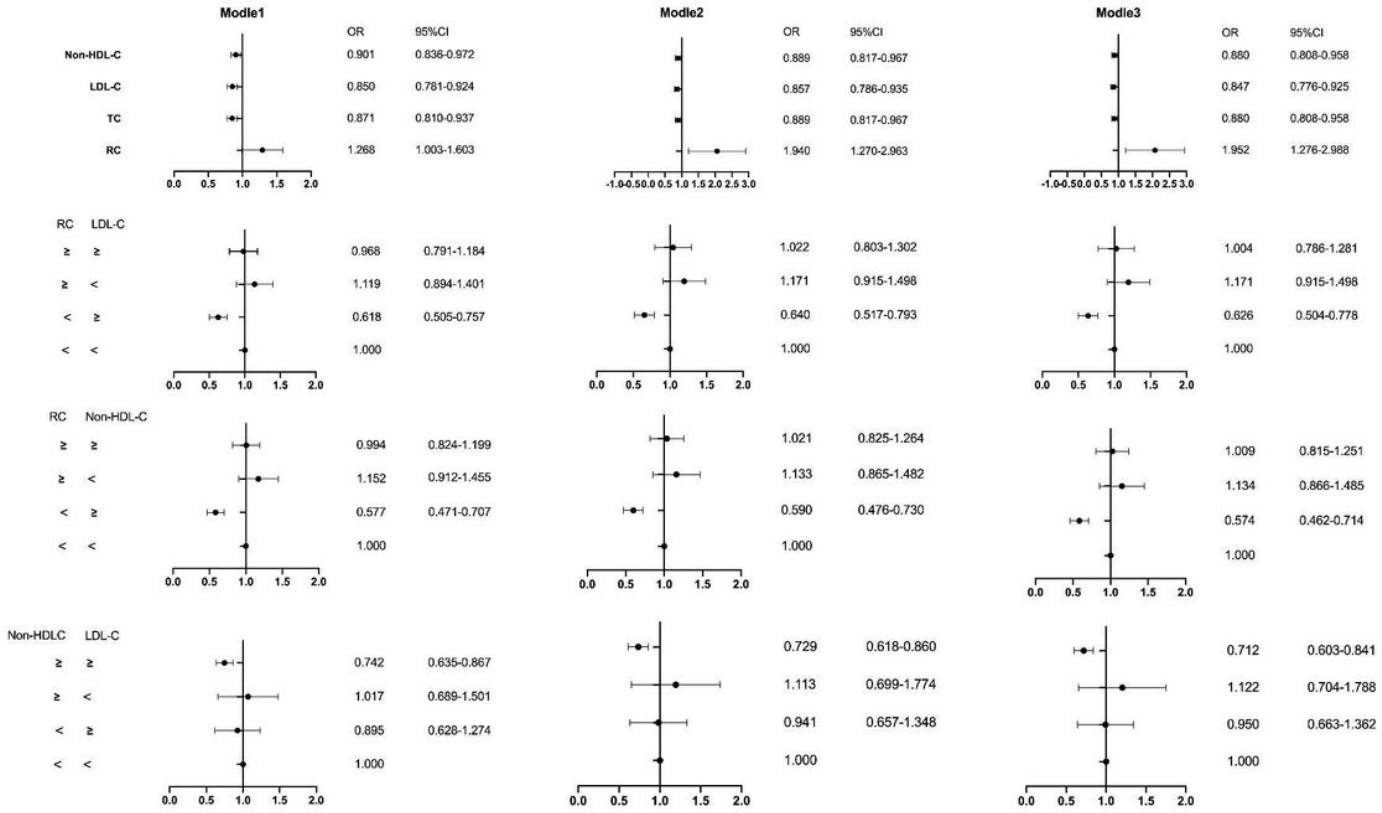

Figure 3

Multivariate logistic regression analyses after PSM

Supplementary Files

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- SupplementalTable1.docx
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