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A Synergistic Effect of Remnant Cholesterol and C-Reactive Protein on Predicting the Severity of Coronary Artery Disease

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Background: Increased levels of remnant cholesterol (RC) and inflammation are linked to higher risks of atherosclerotic cardiovascular disease. Whether a combination of C-reactive protein (CRP) and RC improves the predictive ability for evaluating the severity of coronary artery lesions remains unknown.

Methods: A total of 1675 patients with coronary artery disease were stratified according to the Synergy Between Percutaneous Coronary Intervention (SYNTAX) score (SYNTAX score ≤22 versus SYNTAX score >22). Logistic regression and restricted cubic spline models were used to evaluate the relationship between RC, CRP and the severity of coronary artery lesions. Multivariate logistic regression was used to identify predictors of a mid/high SYNTAX score (SYNTAX score >22). The predictive value of RC combined with CRP was estimated by the ROC curve, continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

Results: The multivariable-adjusted odds ratios (95% CIs) for the highest versus lowest quartile of RC were 2.143 (1.450–3.166) for a mid/high SYNTAX score (SYNTAX score >22). The association of RC with severity of coronary artery lesions was maintained significant in the subsample of patients, regardless of traditional cardiovascular risk factors like LDL-C levels and glycemic metabolism status. Moreover, the addition of CRP and RC to the baseline risk model had an incremental effect on the predictive value for a mid/high SYNTAX score (increase in C-statistic value from 0.650 to 0.698; IDI 0.03; NRI 0.306; all $P < 0.01$).

Conclusion: Elevated RC levels were significantly associated with the severity of coronary artery lesions even in patients with optimal low-density lipoprotein cholesterol levels. Adjustment of the RC by CRP further improved the predictive ability for the severity of coronary artery lesions. The combination of RC and CRP might serve as a noninvasive predictor of CAD complexity and could potentially influence the management and therapeutic approach.

Keywords: coronary artery disease, coronary angiography, remnant cholesterols, C-reactive protein, inflammation, SYNTAX score

Introduction

Elevated remnant cholesterol (RC) and low-grade inflammation are both observed and causally linked to an increased risk of atherosclerotic cardiovascular diseases.[1] Meanwhile, the results of Mendelian randomization studies have established a causal link from elevated RC to systemic low-grade inflammation.[2,3] The Synergy Between Percutaneous Coronary Intervention (SYNTAX) score is a comprehensive angiographic tool that evaluates anatomic risk factors to grade the complexity of coronary artery disease (CAD).[4] Patients with higher SYNTAX scores indicate more complex

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disease and have an increased potential risk of major adverse cardiovascular events.[5,6] However, the individual and synergistic effects of RC and low-grade inflammation, as indicated by elevated C-reactive protein (CRP), on the complexity of coronary artery disease (CAD) remain unknown.

RC is the plasma cholesterol content of triglyceride-rich lipoproteins (TRLs), comprised of very low-density lipoproteins and intermediate-density lipoproteins in the fasting state and chylomicron remnants in the nonfasting states.[7–9] RC could penetrate the arterial wall and is more easily absorbed by macrophage cells to promote endothelial dysfunction, low-grade inflammation, foam cell formation, and the accumulation of cholesterol in the arterial wall, leading to the progression of atherosclerosis and in consequence atherosclerotic cardiovascular diseases (ASCVD).[10–12] Emerging evidence from epidemiology and Mendelian randomization studies has established a causal association between RC levels and ASCVD, including peripheral artery disease,[13] ischemic heart disease,[14–16] myocardial infarction (MI),[13,14,16–18] and ischemic stroke.[13,16–20] However, whether RC is independently associated with the complexity of coronary artery lesions is yet to be determined.

Similarly, low-grade inflammation is both observationally and causally linked to an increased risk of MI, ASCVD, and all-cause mortality.[2,21] Despite the causal link between elevated RC and increased CRP levels,[2,3] it remains uncertain whether the simultaneous elevation of both factors contributes to an increased risk of greater complexity in the angiographic severity of CAD. Therefore, the aim of this study was to examine the combined effect of RC and CRP on the complexity of CAD in patients undergoing coronary angiography.

Methods

We enrolled 1675 patients hospitalized at the Third People's Hospital of Chengdu (Sichuan, China) undergoing coronary angiography who were diagnosed with CAD from July 2018 to June 2021. Individuals who had a history of coronary artery bypass grafting and incomplete key variables such as CRP, SYNTAX score, and RC variables were excluded. This retrospective observational study received institutional review board approval and was conducted in accordance with the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study. We confirmed that all the data were anonymized to ensure confidentiality.

Data Collection

This study collected sociodemographic information, medical history, smoking status, laboratory findings, and procedural details of the participants through electronic medical records. The medical history information included the following conditions: percutaneous coronary intervention (PCI), hypertension, diabetes mellitus, atrial fibrillation, stroke, and chronic obstructive pulmonary disease.

Peripheral venous blood samples were collected after an overnight fast (>8 h). Laboratory parameters, including triglycerides, total cholesterol, LDL-C, high-density lipoprotein cholesterols (HDL-C), fasting blood glucose (FBG), cardiac troponin T (cTnT), serum creatinine (Scr), brain natriuretic peptide (BNP), uric acids, and CRP were measured by standard biochemical techniques in the Clinical Laboratory of the Third People's Hospital of Chengdu. The two-dimensional modified Simpson's method was applied to determine the left ventricular ejection fraction (LVEF).

Definitions

Premature CAD is defined as the occurrence of coronary artery disease in individuals under the age of 55 for men and under the age of 65 for women.[22] Diabetes mellitus was defined according to one of the following criteria: (1) self-reported diabetes diagnosed by a physician, or the usage of antidiabetic medication, such as diet, oral agents, and/or insulin, prior to hospitalization; and (2) the presence of classic symptoms of diabetes accompanied by a random blood glucose level of ≥11.1 mmol/L, fasting blood glucose level ≥7.0 mmol/L, a hemoglobin A1c (HbA1c) level of ≥6.5%, and/or a 2-hour blood glucose level of ≥11.1 mmol/L during the 75-g oral glucose tolerance test.[23] Patients with prediabetes were defined by the presence of impaired fasting glucose and/or impaired glucose tolerance and/or HbA1c 5.7–6.4%.[23] Hypertension was defined as a physician-diagnosed condition that was self-reported, current treatment with anti-hypertensive medication, and/or resting systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg over three measurements.[24] Self-reported medical history of previous conditions such as percutaneous

coronary intervention, stroke, atrial fibrillation, and chronic obstructive pulmonary disease was retrieved, and subsequently confirmed by relevant medical records. RC was estimated as total cholesterol minus LDL-C minus HDL-C.[25] Using the web-based calculation tool (http://syntaxscore.com/), the SYNTAX score was calculated from the preprocedural angiograms by two independent cardiologists who were blinded to the study protocol and baseline clinical characteristics.[26,27]

Statistical Analysis

Categorical data are described as counts and percentages (%) and were compared using either the chi-square or Fisher's exact test as appropriate. Continuous data are described as either the mean with standard deviation or median with interquartile range and were compared using the Student's *t* test or the Mann–Whitney *U*-test, respectively. For comparisons across the quartiles of RC, the One-Way Analysis of Variance and Kruskal–Wallis test were utilized for parametric and non-parametric continuous variables respectively, while the chi-square test was employed for categorical data.

A logistic regression analysis was performed to assess the correlation between RC and the severity of angiographic coronary artery lesions (SYNTAX score ≤22 versus SYNTAX score >22). Univariate and multivariate models adjusted for age, body mass index (BMI), diabetes mellitus, heart rate (HR), cTnT, BNP, Scr, uric acids, FBG, and CRP were performed. After evaluating collinearity, variables with an unadjusted P value of <0.05 were included in the multivariate model, and results presented as odds ratios (ORs) with 95% confidence intervals (CIs). Restricted cubic splines were employed to evaluate the dose-response relationship between RC and the severity of angiographic coronary artery lesions. In addition, we performed sensitivity analyses by including LDL-C and HDL-C, respectively, in the above fully adjusted model. We further conducted a subgroup analysis stratifying participants by premature CAD, sex, smoking habits, BMI, glucose metabolism status, hypertension, and LDL-C levels. The C-statistic, along with continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI), were utilized to assess the discriminatory ability of RC and CRP in predicting the severity of angiographic coronary artery lesions.

All statistical analyses were conducted using R version 4.0.2 software (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 26.0 software (IBM Corporation, New York, NY, USA). A P-value <0.05 was considered statistically significant.

Results

Baseline Characteristics

The average age of the 1675 patients (28.8% were female) with confirmed CAD who underwent coronary angiography was 67.08 ± 11.19 years. The baseline characteristics based on quartiles of RC (Q1, RC≤ 13.93 mg/dL; Q2, 13.93< RC≤ 20.51 mg/dL; Q3, 20.51< RC≤ 29.03 mg/dL; Q4, RC >29.03 mg/dL) are shown in Table 1.

Table 1 The Baseline Characteristics Based on Quartiles of Remnant Cholesterol

Variable	Q1 (n=418)	Q2 (n=419)	Q3 (n=420)	Q4 (n=418)	P value
Age, years	69.19±10.08	68.59±10.69	66.46±11.72	64.07±11.50	<0.001
Female, n (%)	88 (21.1)	116 (27.7)	128 (30.5)	150 (35.9)	<0.001
Premature CAD, n (%)	45 (10.8)	64 (15.3)	87 (20.7)	127 (30.4)	<0.001
BMI, kg/m^2	23.91±3.28	24.34±3.04	24.40±2.83	24.89±2.95	<0.001
Smoking, n (%)	214 (51.2)	212 (50.6)	223 (53.1)	210 (50.2)	0.846
Previous PCI, n (%)	65 (15.6)	33 (7.9)	36 (8.6)	22 (5.3)	<0.001
COPD, n (%)	27 (6.5)	23 (5.5)	27 (6.4)	16 (3.8)	0.302
Hypertension, n (%)	301 (72.0)	279 (66.6)	280 (66.7)	281 (67.2)	0.269
Diabetes mellitus, n (%)	142 (34.0)	164 (39.1)	159 (37.9)	177 (42.3)	0.095
AF, n (%)	42 (10.0)	42 (10.0)	28 (6.7)	22 (5.3)	0.019

(*Continued*)

Table 1 (Continued).

Variable	Q1 (n=418)	Q2 (n=419)	Q3 (n=420)	Q4 (n=418)	P value
Previous stroke, n (%)	46 (11.0)	37 (8.8)	37 (8.8)	23 (5.5)	0.041
SBP, mmHg	131.14±19.07	131.72±21.61	134.46±22.43	133.78±21.26	0.067
HR, bpm	75.68±13.70	75.77±14.10	76.77±13.81	78.96±15.03	0.002
cTnT, pg/mL	20.45 (10.15, 299.85)	34.25 (10.15, 596.10)	29.76 (10.15, 759.88)	47.85 (11.08, 1011.75)	0.007
BNP, pg/mL	110.90 (44.15, 333.41)	141.60 (46.3, 374.10)	121.35 (37.75, 333.41)	97.40 (32.98, 333.41)	0.011
Scr, mg/dL	0.90 (0.77,1.07)	0.89 (0.75,1.07)	0.88 (0.75,1.04)	0.83 (0.71,1.01)	0.001
Uric acids, mg/dL	62.06±16.62	63.04±19.33	64.88±19.14	65.50±18.53	0.025
FBG, mg/dL	116.16±50.59	120.78±51.36	125.10±53.62	135.88±68.58	<0.001
Triglyceride, mg/dL	104.76±56.66	130.12±63.89	168.66±85.18	255.53±171.32	<0.001
Total cholesterol, mg/dL	132.65±31.65	155.77±27.80	181.80±30.73	219.36±43.71	<0.001
LDL-C, mg/dL	77.48±24.42	93.94±22.36	112.44±24.57	135.24±35.50	<0.001
HDL-C, mg/dL	45.60±12.93	44.20±10.55	44.32±10.75	44.51±12.22	0.280
Non-HDL-C, mg/dL	87.05±25.53	111.57±22.76	137.48±25.38	174.85±38.58	<0.001
Lp (a), mg/L	123.20 (61.20, 274.46)	149.70 (69.70, 335.40)	139.05 (67.20, 351.43)	167.55 (69.25, 346.45)	0.072
C-reactive protein, mg/L	1.81 (0.60,6.38)	1.70 (0.60,6.88)	2.34 (0.60,10.36)	2.32 (0.60,9.60)	0.100
Diagnosis, n (%)					<0.001
CCS	56 (13.4)	27 (6.4)	29 (6.9)	24 (5.7)	
UA	189 (45.2)	182 (43.4)	201 (47.9)	167 (40.0)	
NSTEMI	75 (17.9)	96 (22.9)	81 (19.3)	101 (24.2)	
STEMI	98 (23.4)	114 (27.2)	109 (26.0)	126 (30.1)	
Number of stents	1.31±0.83	1.41±0.87	1.42±0.88	1.44±0.88	0.138
Length of stents, mm	33.69±24.23	36.47±26.76	38.02±26.15	38.46±27.39	0.037
SYNTAX score	13.22±7.99	14.98±9.06	14.80±8.94	15.08±8.56	0.005
Remnant cholesterol, mg/dL	9.57±3.24	17.63±1.86	25.03±2.46	39.62±10.48	<0.001

Notes: The groups were stratified by the quartiles of RC (Q1, RC≤ 13.93 mg/dL; Q2, 13.93< RC≤ 20.51 mg/dL; Q3, 20.51< RC≤ 29.03 mg/dL; Q4, RC >29.03 mg/dL). Data are presented as mean ± SD, median (IQR) or n (%).

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; SBP, systolic blood pressure; HR, heart rate; cTnT, cardiac troponin T; BNP, brain natriuretic peptide; Scr, serum creatinine; FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterols; HDL-C, high-density lipoprotein cholesterols; RC, remnant cholesterol; CCS, chronic coronary syndrome; UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Compared to patients in the Q1 group, individuals with higher levels of RC showed increased incidence of females, a greater incidence of premature CAD, an elevation in various cardiovascular risk factors, including BMI, HR, uric acids, FBG, triglycerides, total cholesterol, LDL-C, non-HDL-C, SYNTAX score, and an increase in stent length, while the frequency of the previous conditions including percutaneous coronary intervention, atrial fibrillation, and stroke was comparatively lower. The risk of a higher level of SYNTAX score increased with increasing quartiles of RC levels.

Patients were classified into low-risk (SYNTAX score ≤22) and mid/high-risk (SYNTAX score >22) groups according to the SYNTAX score, as illustrated in Table 2. Patients with a SYNTAX score >22 were older, had a higher prevalence of premature CAD and diabetes mellitus, and had elevated levels of HR, cTnT, BNP, Scr, uric acids, FBG, triglycerides, total cholesterol, LDL-C, non-HDL-C, CRP, SYNTAX score, RC, and a higher number and length of stents. The proportion of patients with a SYNTAX score >22 was significantly higher in the higher quartiles of RC than in the lowest quartile (Figure 1).

Association Between RC and Severity of CAD

After fully adjustment for covariates in Model I that RC levels were measured as a continuous variable, a 1-mg/dL increase in RC levels was associated with a 3% higher risk for a mid/high SYNTAX score (SYNTAX score >22, OR 1.030 [95% CI, 1.020–1.041], P <0.0001; Table 3). Results were similar when we categorized individuals by RC quartiles in unadjusted and adjusted models (all P<0.05; Table 3). The ORs (95% CIs) for a mid/high SYNTAX score

Table 2 The Baseline Characteristics Based on SYNTAX Score

Variable	All Subjects (n=1675)	SYNTAX Score ≤ 22 (n=1367)	SYNTAX Score > 22 (n=308)	*p* value
Age, years	67.08±11.19	66.48±11.15	69.74±11.01	<0.001
Female, n (%)	482 (28.8)	394 (28.8)	88 (28.6)	0.930
Premature CAD, n (%)	323 (19.3)	285 (20.8)	38 (12.3)	0.001
BMI, kg/m2	24.39±3.05	24.47±3.05	24.00±2.99	0.013
Smoking, n (%)	859 (51.3)	703 (51.4)	156 (50.6)	0.805
Previous PCI, n (%)	156 (9.3)	133 (9.7)	23 (7.5)	0.217
COPD, n (%)	93 (5.6)	75 (5.5)	18 (5.8)	0.804
Hypertension, n (%)	1141 (68.1)	924 (67.6)	217 (70.5)	0.330
Diabetes mellitus, n (%)	642 (38.3)	494 (36.1)	148 (48.1)	<0.001
AF, n (%)	134 (8.0)	105 (7.7)	29 (9.4)	0.311
Previous Stroke, n (%)	143 (8.5)	113 (8.3)	30 (9.7)	0.403
SBP, mmHg	132.77±21.16	133.00±20.68	131.77±23.15	0.358
HR, bpm	76.79±14.22	76.32±13.90	78.91±15.41	0.004
cTnT, pg/mL	29.16 (10.15, 608.90)	23.61 (10.15, 446.10)	124.50 (19.33, 1821.25)	<0.001
BNP, pg/mL	118.20 (40.40, 333.41)	104.60 (36.50, 333.41)	221.80 (76.75, 592.30)	<0.001
Serum creatinine, mg/dL	0.88 (0.74, 1.05)	0.86 (0.73, 1.03)	0.94 (0.78, 1.18)	<0.001
Uric acids, mg/dL	63.87±18.47	63.31±17.79	66.32±21.09	0.010
Plasma glucose, mg/dL	124.48±56.93	122.99±55.38	131.11±63.03	0.024
Triglyceride, mg/dL	164.75±119.19	160.64±114.00	183.00±138.66	0.003
Total cholesterol, mg/dL	172.40±46.81	171.24±46.51	177.51±47.87	0.034
LDL cholesterol, mg/dL	104.78±34.65	103.94±34.26	108.50±36.15	0.037
HDL cholesterol, mg/dL	44.66±11.66	45.02±11.56	43.05±11.95	0.008
Non-HDL cholesterol, mg/dL	127.74±43.37	126.23±43.25	134.46±43.31	0.003
Lp(a), mg/L	139.10 (65.70, 325.80)	138.30 (65.10, 327.50)	155.30 (70.58, 307.95)	0.639
C-reactive protein, mg/L	2.05 (0.60, 9.08)	1.82 (0.60, 7.82)	3.14 (0.84, 18.97)	<0.001
Diagnosis, n (%)				<0.001
CCS	136 (8.1)	119 (8.7)	17 (5.5)	
UA	739 (44.1)	637 (46.6)	102 (33.1)	
NSTEMI	353 (21.1)	266 (19.5)	87 (28.2)	
STEMI	447 (26.7)	345 (25.2)	102 (33.1)	
Number of stents	1.40±0.86	1.28±0.76	1.93±1.08	<0.001
Length of stents, mm	36.66±26.20	32.83±22.57	53.69±33.46	<0.001
SYNTAX score	14.52±8.68	11.33±5.50	28.66±5.47	<0.001
Remnant cholesterol, mg/dL	22.96±12.43	22.29±11.85	25.96±14.39	<0.001

Notes: Patients were classified into low-risk (SYNTAX score ≤22) and mid/high-risk (SYNTAX score >22) groups. Abbreviations seen as Table 1. Data are presented as mean ± SD, median (IQR) or n (%).

comparing the second, third, and fourth quartiles of RC levels with the first quartile were 1.486 (95% CI,1.005–2.196), 1.710 (95% CI, 1.160–2.520), and 2.112 (95% CI, 1.431–3.117), respectively (Table 3). The sensitivity analysis showed that the significant associations of RC and severity of CAD remained after further adjustment for LDL-C and HDL-C separately (models II, III in Table 3). Multivariable-adjusted spline regression models indicated that RC levels were linearly associated with a mid/high SYNTAX score (P for non-linearity = 0.331; Figure 2).

Discordance Analysis

In the discordance analysis defined by LDL-C clinical cutpoints (70, 100, and 130mg/dL), we demonstrated a significantly higher risk of a mid/high SYNTAX score in the discordant high RC/low LDL-C group than in the concordant low RC/LDL-C group after adjustment for traditional cardiovascular risk factors (Table 4). We found similar results when using medians and optima cutoff values to define discordance (Tables S1 and S2).

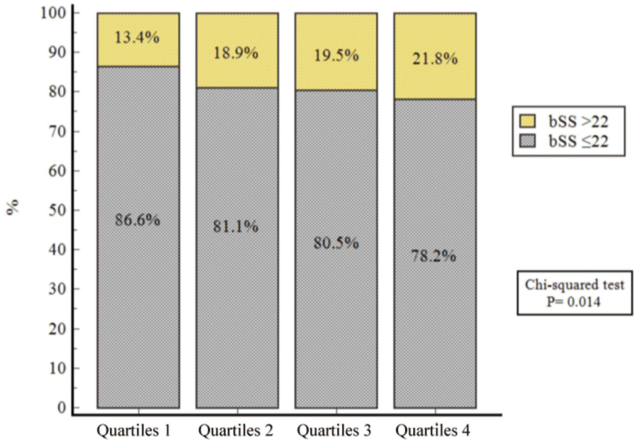

Figure 1 Comparison of the SYNTAX score according to the quartiles of RC. The proportion of patients with a SYNTAX score ≤22 and SYNTAX score >22 stratified according to the quartiles of RC.
Abbreviations: RC, remnant cholesterol; bss, baseline SYNTAX score.

Subgroup Analysis

When participants were stratified by premature CAD, sex, smoking habits, BMI, glucose metabolism status, hypertension, and LDL-C levels, the association between RC levels and severity of CAD was maintained (Figure 3). Higher RC levels were significantly related to increased risks of a mid/high SYNTAX score, which indicates more severe coronary artery lesions.

Incremental Effect of CRP on Risk Stratification for the Complexity of CAD

The synergistic effect of the CRP and the RC on predicting the complexity of CAD is shown in Table 5 and Figure 4. Compared with the baseline model of established risk factors (Model 1), the addition of CRP (Model 2) had a significant increase in the C-statistic from 0.650 (95% CI 0.632–0.678) to 0.671 (95% CI 0.647–0.693) ($P < 0.01$) and a significant improvement in reclassification as assessed by the NRI (0.123, 95% CI 0.014–0.231, P=0.027) and IDI (0.011, 95% CI 0.004–0.017, P=0.002). The addition of RC (Model 3) to the baseline model also resulted in a significant increase in the C-statistic to 0.687 (95% CI 0.664–0.709) ($P < 0.01$) and a significant improvement in reclassification as assessed by the NRI (0.256, 95% CI 0.133–0.378, $P < 0.001$) and IDI (0.020, 95% CI 0.011–0.028, $P < 0.01$). Moreover, the combination of RC and CRP (Model 4) had the strongest incremental effect in terms of the C-statistic from 0.650 (95% CI 0.632–0.678) to 0.698 (95% CI 0.676 to 0.720), NRI (30.6% improvement, $P < 0.001$), and IDI (3.0% improvement, $P < 0.001$).

Table 3 Odds Ratios (95% CIs) of a Mid/High SYNTAX Score According to Quartiles of RC

	Non-Adjusted Model		Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
RC	1.022 (1.013–1.032)	<0.0001	1.030 (1.020–1.041)	<0.0001	1.030 (1.017–1.042)	<0.0001	1.030 (1.020–1.041)	<0.0001
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	1.502 (1.034–2.181)	0.0326	1.486 (1.005–2.196)	0.0469	1.418 (0.953–2.109)	0.0847	1.477 (0.999–2.185)	0.0508
Q3	1.568 (1.083–2.272)	0.0174	1.710 (1.160–2.520)	0.0067	1.540 (1.012–2.342)	0.0437	1.712 (1.161–2.526)	0.0067
Q4	1.799 (1.249–2.591)	0.0016	2.112 (1.431–3.117)	0.0002	1.783 (1.116–2.848)	0.0155	2.143 (1.450–3.166)	0.0001

Notes: The groups were stratified by the quartiles of RC (Q1, RC≤ 13.93 mg/dL; Q2, 13.93< RC≤ 20.51 mg/dL; Q3, 20.51< RC≤ 29.03 mg/dL; Q4, RC >29.03 mg/dL). Model I: adjusted for age, body mass index, diabetes mellitus, heart rates, cardiac troponin T, brain natriuretic peptide, Serum creatinine, uric acids, fasting blood glucose, c-reactive protein; Model II: adjusted for Model I covariates plus low-density lipoprotein cholesterols; Model III: adjusted for Model II covariates plus high-density lipoprotein cholesterols.
Abbreviation: RC, remnant cholesterol.

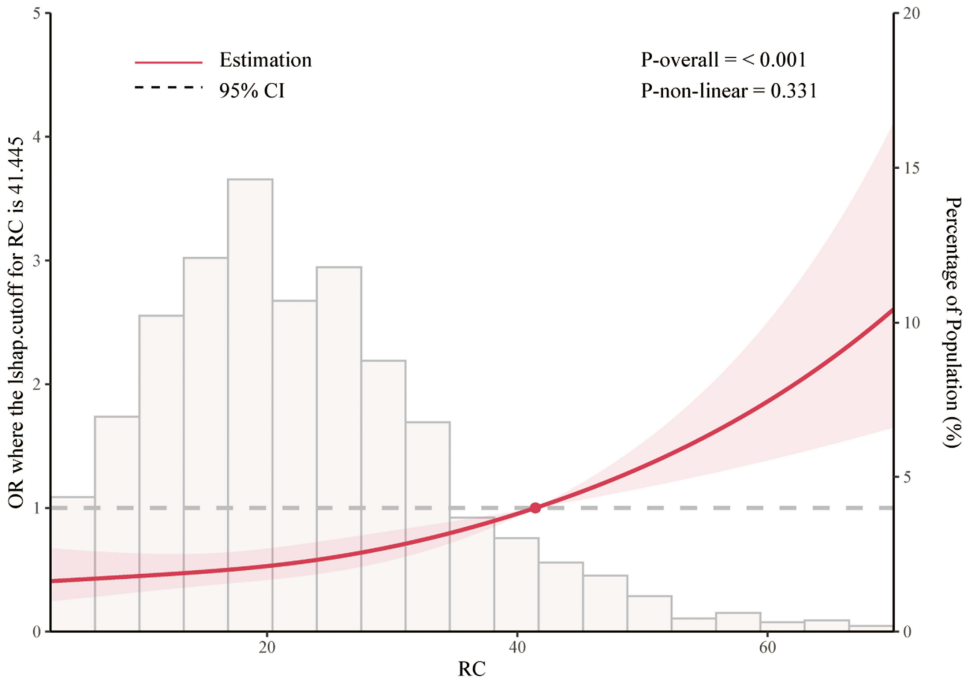

Figure 2 RCS for the odds ratio of a mid/high SYNTAX score. Odds ratios were adjusted for the same variables as Model I in Table 2.
Abbreviations: RCS, restricted cubic spline; OR, odds ratio; SYNTAX score, Synergy Between Percutaneous Coronary Intervention score.

Discussion

In the present study, we investigated the association of RC levels with severity of coronary artery lesions in 1675 patients with confirmed CAD, and found that (1) elevated RC levels were associated with a mid/high SYNTAX score, independent of traditional cardiovascular risk factors, including LDL-C concentrations and glucose metabolism status; (2) The association of RC with severity of CAD was maintained, even in individuals with optimal LDL-C levels; (3) The integration of CRP enhanced the predictive capability of models containing RC in assessing the severity of CAD. Our findings support the potential of targeting RC and inflammation as therapeutic strategies to reduce the risk of CAD.

Although it has been well-documented that LDL-C is a vital risk factor for ASCVD, some patients still suffer from cardiovascular events despite having controlled LDL-C levels with statins. Based on the increasing number of genetic and observational studies, RC is suggested as part of the contributing risk factors for this residual risk.[12,28–30] A nationwide longitudinal cohort study found that RC was associated with the risk of MI and ischemic stroke in Korean patients with type 2 diabetes.[18] Similarly, Shao et al showed that elevated RC was significantly associated with unfavorable prognosis in both diabetic and non-diabetic patients with ACS; however, adding RC to the baseline models only improved the predictive ability for major adverse cardiovascular events in the diabetic subgroup, but not in the non-diabetic subgroup.[31] The present study demonstrates for the first time that increased RC levels are independently associated with a higher risk of severe coronary artery lesions, regardless of traditional cardiovascular risk factors like LDL-C levels and glycemic metabolism status.

Previous studies have demonstrated that RC could serve as a potential marker for subclinical atherosclerosis. For an example, a cross-sectional analysis of the ELSA-Brasil Study (Brazilian Longitudinal Study of Adult Health; n=3845) demonstrated that higher levels of TRLs cholesterol were associated with greater severity of coronary artery calcium, independently of LDL-C, HDL-C, and other conventional risk factors.[32] Lin et al showed that RC levels were associated with coronary atherosclerotic burden as assessed by computed tomography coronary angiography in patients with coronary artery disease. Furthermore, this relationship persisted even in patients with optimal LDL-C levels.[33] It is important to note that a recent analysis of 6544 atherosclerotic cardiovascular disease–free individuals from the CARDIA study (Coronary Artery Risk Development in Young Adults; n=2635) and MESA (Multi-Ethnic Study of Atherosclerosis; n=3909) found that elevated RC levels were associated with an increased risk of coronary artery calcium progression

Table 4 Odds Ratios (95% CIs) of Severe Coronary Lesion Across LDL-C vs RC Concordant/Discordant Groups by LDL-C Clinical Cutpoints (70, 100, and 130 Mg/dL) and Percentile Equivalents for RC

LDL C Groups	RC Groups	bSS>22	Non-Adjusted Model	P value	Model I	P value	Model II	P value	Model III	P value
Cutpoints: LDL C 70mg/dL; RC 13.93mg/dL										
LDL C<cutpoint (n=266)	<cutpoint	24/180	Ref.		Ref.		Ref.		Ref.	
	≧cutpoint	28/86	3.14 (1.68–5.85)	0.0003	2.46 (1.27–4.78)	0.008	2.40 (1.23–4.68)	0.0099	2.15 (1.09–4.23)	0.0268
LDL C≧ cutpoint (n=1409)	<cutpoint	32/238	1.01 (0.57–1.78)	0.9734	0.91 (0.51–1.65)	0.767	1.00 (0.55–1.81)	0.9906	0.89 (0.49–1.61)	0.6927
	≧cutpoint	224/1171	1.54 (0.98–2.42)	0.0632	1.59 (0.99–2.56)	0.054	1.69 (1.05–2.72)	0.0313	1.40 (0.86–2.27)	0.1748
Cut points: LDL C 100mg/dL; RC 29.03mg/dL										
LDL C<cutpoint (n=816)	<cutpoint	110/759	Ref.		Ref.		Ref.		Ref.	
	≧cutpoint	20/57	3.19 (1.79–5.70)	0.0001	3.30 (1.80–6.04)	0.0001	3.05 (1.65–5.60)	0.0003	2.52 (1.32–4.82)	0.0050
LDL C≧ cutpoint (n=859)	<cutpoint	107/498	1.61 (1.20–2.17)	0.0014	1.73 (1.27–2.36)	0.0005	1.92 (1.40–2.64)	0.0001	1.70 (1.25–2.32)	0.0008
	≧cutpoint	71/361	1.44 (1.04–2.01)	0.0284	1.73 (1.22–2.46)	0.0022	1.89 (1.32–2.70)	0.0005	1.49 (1.02–2.16)	0.0368
Cut points: LDL C 130mg/dL; RC 29.03mg/dL										
LDL C<cutpoint (n=1300)	<cutpoint	172/1111	Ref.		Ref.		Ref.		Ref.	
	≧cutpoint	47/189	1.81 (1.25–2.61)	0.0016	2.04 (1.38–3.02)	0.0003	1.96 (1.32–2.90)	0.0008	1.67 (1.10–2.53)	0.0171
LDL C≧ cutpoint (n=375)	<cutpoint	45/146	2.43 (1.65–3.58)	<0.0001	2.96 (1.97–4.45)	<0.0001	3.42 (2.25–5.21)	<0.0001	2.91 (1.93–4.38)	<0.0001
	≧cutpoint	44/229	1.30 (0.90–1.87)	0.1628	1.57 (1.07–2.31)	0.0222	1.75 (1.18–2.59)	0.0053	1.35 (0.90–2.02)	0.1466

Notes: Model I: adjusted for age, body mass index, diabetes mellitus, heart rates, cardiac troponin T, brain natriuretic peptide, Serum creatinine, uric acids, fasting blood glucose, c-reactive protein; Model II: adjusted for Model I covariates plus high-density lipoprotein cholesterols; Model III: adjusted for Model II covariates plus triglyceride.

Abbreviations: RC, remnant cholesterol; bss, baseline SYNTAX score.

Subgroup	No. of Patients	bSS>22	bSS≤22	Forest Plot	OR (95%CI)	P value
All patients	1675	308	1637		1.030 (1.020 - 1.041)	<0.0001
Premature CAD						
Yes	323	38 (11.8%)	285 (88.2%)		1.026 (1.002 - 1.051)	0.037
No	1352	270 (20.0%)	1082 (80.0%)		1.030 (1.018 - 1.042)	<0.0001
Sex						
Male	1193	220 (18.4%)	973 (81.6%)		1.030 (1.017 - 1.042)	<0.0001
Female	482	88 (18.3%)	394 (81.7%)		1.037 (1.016 - 1.058)	0.0004
Smoking						
Yes	859	156 (18.2%)	703 (81.8%)		1.031 (1.016 - 1.046)	<0.0001
No	816	152 (18.6%)	664 (81.4%)		1.032 (1.017 - 1.047)	<0.0001
BMI, kg/m²						
<24	684	143 (20.9%)	541 (79.1%)		1.038 (1.020 - 1.055)	<0.0001
≥24	991	165 (16.6%)	826 (83.4%)		1.026 (1.013 - 1.039)	0.0001
Glucose metabolism status						
NG	604	93 (15.4%)	511 (84.6%)		1.033 (1.014 - 1.053)	0.0006
Pre-DM	429	67 (15.6%)	362 (84.4%)		1.025 (1.001 - 1.049)	0.0381
DM	642	148 (23.1%)	494 (76.9%)		1.032 (1.017 - 1.047)	<0.0001
Hypertension						
Yes	1141	217 (19.0%)	924 (81.0%)		1.026 (1.014 - 1.039)	<0.0001
No	534	91 (17.0%)	443 (83.0%)		1.040 (1.021 - 1.060)	0.0001
LDL-C, mg/dL						
<70	266	52 (19.5%)	214 (80.5%)		1.081 (1.042 - 1.122)	<0.0001
≥70	1409	256 (18.2%)	1153 (81.8%)		1.027 (1.015 - 1.039)	<0.0001

Figure 3 Associations between RC and severity of CAD in different subgroups. Odds ratios were adjusted for the same variables as Model 1 in Table 2.
Abbreviations: CAD, coronary artery disease; BMI, body mass index; DM, diabetes mellitus; NG, normal glucose; bss, baseline SYNTAX score.

independent of traditional cardiovascular risk factors, even in individuals with optimal LDL-C levels.[34] Our findings suggest that RC has the potential to serve as a predictor of the severity of coronary artery lesions, which may provide new information on the importance of monitoring RC to prevent CAD. Moreover, we observed a higher prevalence of specific conditions, including prior PCI and stroke, among individuals in the lower quartiles of RC. This higher prevalence is mainly attributed to these patients receiving statin therapy, a key treatment for atherosclerotic diseases aimed at reducing cholesterol levels. Furthermore, aging, overweight, and hypertension are established risk factors for AF, which may elucidate the increased prevalence of AF in individuals with lower RC levels.

In a recent study, Cao et al demonstrated that increased RC levels were significantly associated with the worse prognosis in DM and pre-DM patients with a history of CAD.[35] Moreover, among obese and overweight patients, elevated RC levels were associated with a 2.6-fold higher risk of ASCVD, even when LDL-C levels were optimal.[17] We found that CAD patients with high RC levels (>13.93 mg/dL) had a greater risk of a mid/high SYNTAX score

Table 5 Incremental Effect of CRP on Risk Stratification for a Mid/High SYNTAX Score

Variables	NRI		IDI		C-Statistic	
	Index (95% CI)	P value	Index (95% CI)	P value	Index (95% CI)	P value
Model 1	Ref	Ref	Ref	Ref	0.655 (0.632–0.678)	< 0.01
Model 2	0.123 (0.014–0.231)	0.027	0.011 (0.004–0.017)	0.002	0.671 (0.647–0.693)	< 0.01
Model 3	0.256 (0.133–0.378)	<0.001	0.020 (0.011–0.028)	<0.001	0.687 (0.664–0.709)	< 0.01
Model 4	0.306 (0.183–0.428)	<0.001	0.030 (0.019–0.041)	<0.001	0.698 (0.676–0.720)	< 0.01
Model 4*	0.268 (0.145–0.391)	<0.001	0.019 (0.011–0.028)	<0.001		
Model 4#	0.156 (0.048–0.265)	0.005	0.010 (0.003–0.017)	0.004		

Notes: Model 1: adjusted for age, BMI, diabetes mellitus, heart rates, cTnT, BNP, Scr, uric acids, FBG; Model 2: adjusted for Model 1 plus CRP; Model 3: adjusted for model 1 plus RC; Model 4: adjusted for model 1 covariates plus CRP and RC; *, compared to model 2; #, compared to model 3.
Abbreviations: CRP, C-reactive protein; RC, remnant cholesterol.

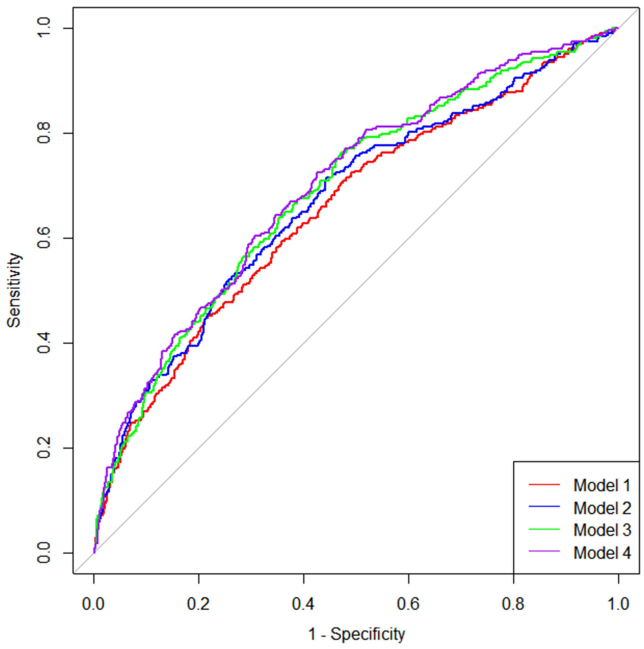

Figure 4 ROC curve analysis of the 4 models to predict the severity of CAD. The areas under the ROC curves of Model 1, Model 2, Model 3, and Model 4 for predicting a mid/high SYNTAX score (SYNTAX score >22) were 0.655 (0.632 to 0.678; P < 0.01), 0.671 (0.647 to 0.693; P < 0.01), 0.687 (0.664 to 0.709; P < 0.01), and 0.698 (0.676 to 0.720; P < 0.01), respectively.
Abbreviations: ROC, receiver operating characteristic; CAD, coronary artery disease.

independent of traditional cardiovascular risk factors, even in individuals with optimal LDL-C levels (<70mg/dL). High RC levels among CAD patients were significantly associated with a 2.15 times higher risk of a mid/high SYNTAX score, although LDL-C levels being in the optimal range. By using subgroup analysis, we found that higher RC levels were consistently associated with an increased risk of severe coronary artery lesions in all clinical subgroups. Our findings indicate that individuals with lower SYNTAX scores tended to be younger, have higher BMIs, and exhibit a greater prevalence of smoking and premature coronary artery disease, while showing lower levels of RC compared to those with higher SYNTAX scores. This aligns with previous research indicating that overweight individuals and smokers are at a heightened risk for premature CAD.[36] According to the current findings, we suggest that elevation in RC levels is associated with complex coronary artery lesions among CAD patients, regardless of LDL-C concentrations. The present study showed that the combination of RC and CRP assisted in identifying individuals with greater odds of severe CAD, implying the combined impact of RC and inflammation in promoting coronary atherosclerosis.

Inflammation plays an important role in the pathogenesis and progression of CAD.[37] The production of acute-phase proteins, such as CRP, is regarded as an accurate measure of systemic inflammation and pro-inflammatory cytokine activity. Increased CRP levels indicate a systemic inflammatory reaction. Epidemiological studies have linked blood inflammatory markers like CRP to the risk of CAD.[38,39] Therapeutic interventions such as Canakinumab, an anti-inflammatory drug, have demonstrated promising outcomes in markedly reducing the likelihood of recurrent cardiovascular events among individuals with elevated hsCRP levels and a previous history of MI.[40] Moreover, Nordestgaard et al, demonstrated that elevated levels of both cholesterol and hsCRP significantly increase the risks of atherosclerotic cardiovascular disease and overall mortality.[1] These findings emphasize the clinical significance of assessing both RC and CRP elevations in predicting CAD risks. In the present study, the observed highest risk of severe coronary lesions aligned with concurrent elevations in cholesterol and CRP, indicating a biological plausibility in their combined impact on CAD risk. Elevated CRP, signifying low-grade inflammation, enhances the predictive value in conjunction with cholesterol for assessing CAD risk. However, further investigations are essential to unveil the underlying mechanisms.

This study has some limitations that should be addressed. First, our research was cross-sectional, making it difficult to establish causality between RC and coronary artery lesions severity. Additionally, since we did not collect data on follow-up RC and SYNTAX score, we were unable to investigate the impact of RC on coronary atherosclerosis progression in a prospective manner. These limitations highlight the need for future prospective cohort studies. Second, the unavailability of data on patients without confirmed CAD may restrict the generalization of our findings. Third, although the use of calculated than directly measured RC could be considered a limitation, both methods are highly correlated, and the former is an affordable method that could provide valuable data for clinical management without additional costs. Fourth, the inflammation level was solely assessed using CRP, without considering other inflammatory markers, and did not examine the specificity and sensitivity of different inflammatory indicators combined with RC for predicting high-risk patients. Finally, our study was conducted exclusively among East Asians, thereby limiting the generalizability of our findings. To the best of our knowledge, no studies have yet suggested any ethnic variations in the capacity of RC to cause atherosclerosis.

Conclusions

Increased levels of RC were associated with the presence of more severe coronary artery lesions, irrespective of conventional risk factors and LDL-C levels. Incorporating CRP into the baseline model containing RC augments its predictive efficacy for evaluating the severity of coronary artery lesions. Consequently, assessing RC and CRP levels in the general population could be beneficial for cardiovascular risk stratification and guiding future interventions.

Abbreviations

CAD, coronary artery disease; SYNTAX score, the Synergy Between Percutaneous Coronary Intervention score; BMI, body mass index; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; SBP, systolic blood pressure; HR, heart rate; BNP, brain natriuretic peptide; Scr, serum creatinine; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein; LDL-C, low density lipoprotein; UA, unstable angina; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; bSS, baseline SYNTAX score; RC, remnant cholesterol; CRP, C-reactive protein.

Data Sharing Statement

The datasets used and/or analyzed in the study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the medical ethics committee of the Third People's Hospital of Chengdu and strictly adhered to the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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