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The prognostic role of remnant cholesterol in Asian menopausal women received percutaneous coronary intervention with acute coronary syndrome

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Abstract

Background Remnant cholesterol (RC) exert a significant influence on atherosclerotic cardiovascular disease development. However, the prognostic implications of RC in menopausal women received percutaneous coronary intervention (PCI) who experiencing acute coronary syndrome (ACS) remain uncertain.

Methods RC was derived by subtracting the sum of high-density lipoprotein cholesterol and low-density lipoprotein cholesterol from the total cholesterol. Kaplan-Meier survival and Cox regression analysis were employed for assessing the correlation between continuous RC levels and composite and individual adverse events in Q1-Q4 quartiles. Receiver operator characteristic (ROC) curves, derived from Cox regression, were employed for analyzing the relationship between RC and both composite and individual adverse events.

Results 1505 consecutive menopausal women who underwent PCI and diagnosed with ACS were included. Kaplan-Meier survival analysis demonstrated a progressive reduction in composite adverse event survival rates across the four groups, observed in both the general population and among diabetic individuals, as RC values increased (Log-rank $P < 0.001$). The analysis of multivariate Cox regression indicated RC remained independently associated with both composite and individual adverse events. ROC analysis showed that RC enhanced the area under the curve both in total and diabetic populations for composite adverse events.

Conclusion Among menopausal women diagnosed with ACS who underwent PCI, heightened levels of RC were found to be independently correlated with an increased occurrence of adverse events.

Keywords Remnant cholesterol, Menopause, Diabetes, Percutaneous coronary intervention, Acute coronary syndrome

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Introduction

Arteriosclerotic cardiovascular disease (ASCVD) continued to be a primary contributor to global mortality and morbidity, with abnormal lipid levels serving as significant independent risk factors as for the onset and progression [1]. Besides low-density lipoprotein cholesterol (LDL-C), accumulating evidence indicated that cholesterol transported by intermediate-density lipoproteins, chylomicron remnants, and very low-density lipoprotein, known collectively as remnant cholesterol (RC) [2], were also linked to ASCVD [3]. Even when reaching the LDL-C target advised by guidelines and enhancing other cardiovascular risk factors, the risk of significant adverse cardiovascular events continued, known as residual risk, with its exact mechanism still unclear [4–5]. Genetic and epidemiological evidence indicated that triglyceride-rich lipoproteins (TRL) were significant causal risk factors for ASCVD. [6], while RC referred to cholesterol content rich in TRL, formed when TRL is partially depleted of triglycerides (TG) by lipoprotein lipase [7]. RC can infiltrate and linger in the arterial intima, enhancing the release of various adhesion molecules and cytokines [8], thereby promoting endothelial inflammation and impairment, potentially playing a causal role in the development of atherosclerosis and eventual ASCVD [9]. When abnormal lipid metabolism led to elevated circulating RC levels, an increasing amount of RC entered the arterial wall, promoting foam cell formation and triggering systemic inflammation, ultimately culminating in cardiovascular events [10]. Research findings have pointed to a relationship between the extent of coronary artery atherosclerosis in menopausal women and perturbed TG metabolism [11]. Furthermore, prior research has identified a notable correlation between heightened RC levels and amplified risk of cardiovascular diseases (CVD) in middle-aged and elderly Chinese populations [12]. In a longitudinal cohort study conducted in a Chinese population to identify different trajectories of RC, it was discovered that these trajectories were significantly associated with endothelial function and atherosclerosis [13]. In addition, RC has been increasingly recognized as a significant risk factor for type 2 diabetes mellitus (T2DM) [14–15]. Understanding the interplay between RC and diabetes was crucial, especially for specific populations like menopausal women, who may have distinct lipid metabolism profiles and cardiovascular risk factors. Building upon prior research 4 years ago, which found a significant correlation between coronary artery disease (CAD) and RC among menopausal women with T2DM [16], this study additionally sought to explore the correlation between RC and its prognostic effect in menopausal women received percutaneous coronary intervention (PCI) with acute coronary syndrome (ACS) in total and diabetic population.

Materials and methods

Participants and study design

In this retrospective cohort study carried out at Beijing Anzhen Hospital, we enrolled 1505 consecutive menopausal women diagnosed with ACS who received coronary angiography and primary or elective PCI between January and December 2018. The inclusion criteria comprised: (1) a history of cardiogenic shock or heart failure (N=12); (2) severe renal impairment [estimated glomerular filtration rate (eGFR) below 30 mL/(min*1.73m^2)] (N=17); (3) incomplete clinical, laboratory, or angiographic data (N=330); (4) severe hepatic conditions (N=35); (5) in-hospital mortality or complications (N=2); (6) PCI procedural failure (N=13); and (7) presence of other significant comorbidities, including malignancies (N=17). Then, the total and the diabetic population were divided into Q1 to Q4 groups (Fig. 1).

Data collection, measurement and definition

Clinical characteristics; diagnosis of ACS on admission; medical history including previous myocardial infarction (MI), previous PCI, family CVD, hypertension, hyperlipemia, T2DM, current smoking; coronary angiographic findings; and medications at baseline PCI, were retrieved from the electronic medical records. Laboratory parameters were assessed at the central hospital laboratory employing fasting venous blood samples collected initially. Established protocols determined glycated hemoglobin A1c (HbA1c), fasting blood glucose (FBG), and creatinine (Cr) levels. LDL-C was measured directly through a homogeneous method, while high-density lipoprotein cholesterol (HDL-C), TG, and total cholesterol (TC) levels were determined using conventional enzymatic assays. The left ventricular ejection fraction (LVEF) was assessed by the two-dimensional Simpson's method and based on the Modification of Diet in Renal Disease equation, eGFR was computed [17]. RC was computed as RC=TC - HDL-C - LDL-C [16], and menopausal status was clinically defined after 12 months of amenorrhea [18]. By dividing weight in kilograms by the square of height in meters, body mass index (BMI) was calculated.

Outcome and follow-up

The adverse events, which included all-cause death, cardiac death, nonfatal MI, and target vessel revascularization, were documented either as a combined adverse event or separately, to facilitate the current analysis. All-cause death was defined as death from any cause, including both cardiac and non-cardiac causes. Cardiac death was specified as death resulting from any heart disease [19], including but not limited to MI, heart failure, arrhythmias, cardiomyopathy, or complications arising from valvular heart disease et al., which encompassed

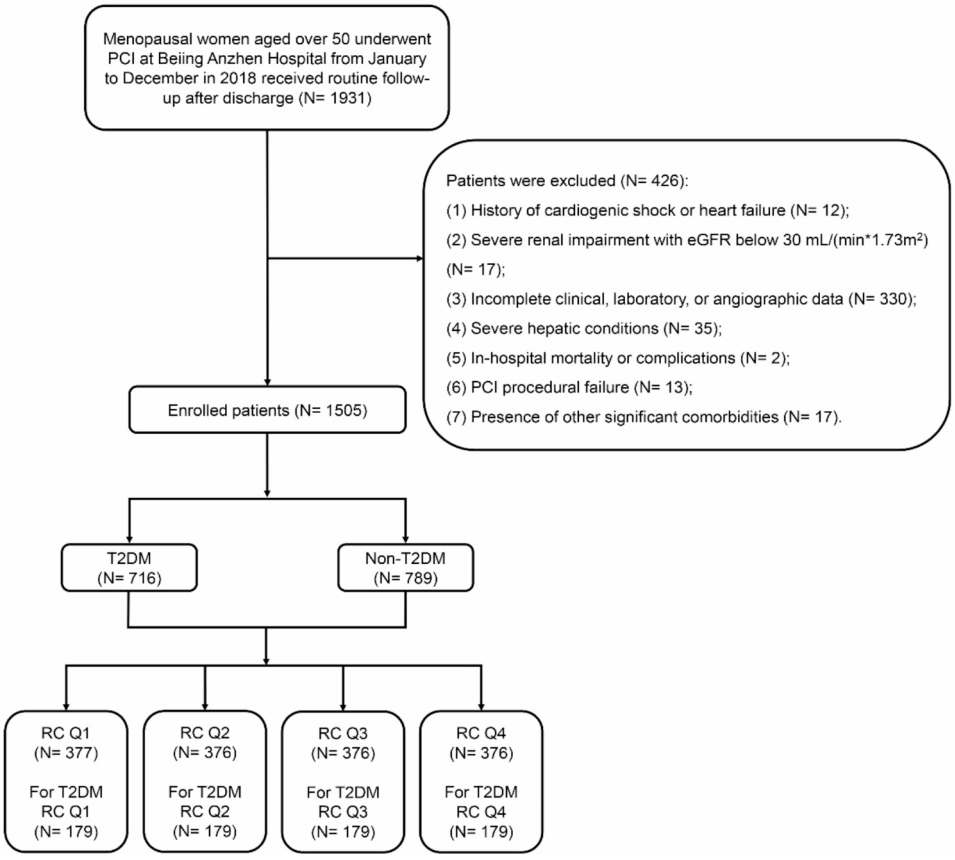

Fig. 1 Flowchart of the study. eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; RC, remnant cholesterol; T2DM, type 2 diabetes mellitus

both sudden and non-sudden events [20]. MI was diagnosed using a combination of clinical assessments and laboratory tests, in accordance with the criteria outlined in the third universal definition of MI [21]. Target vessel revascularization was defined as ischemia-driven or clinically driven revascularization of the target vessel. After undergoing coronary procedures, all participants underwent regular follow-up appointments at intervals of 3, 6, and 12 months, followed by yearly check-ups until the 60th month. In cases where participants experienced multiple adverse events within the 60-month follow-up period, the timing of the composite event is defined by the occurrence of the first event.

Statistical analyses

Categorical data were shown as numbers (percentage). With normal distribution, mean±standard deviation (SD) was used to present continuous variables, while median (interquartile range) was used to present non-normally distributed. Besides Chi-square test for categorical variables, the differences between groups were analyzed through the Kruskal-Wallis test for continuous variables. Participants were divided into quartiles (Q1-Q4) based on RC levels. The occurrence of composite adverse events and their components among these quartiles was assessed through Kaplan-Meier analysis, with differences evaluated via the log-rank test. The relationships between RC and the occurrence of composite adverse events, besides their components were examined using both unadjusted and adjusted Cox proportional hazard models. Adjustments in the multivariable Cox regression model included potential confounders such as age, hypertension, T2DM, smoking status, BMI, and hyperlipidemia for the total population. In the diabetic cohort, however, all participants already have T2DM, so including T2DM as a variable would be redundant, so the multivariable Cox regression model included age, hypertension, smoking status, BMI, and hyperlipidemia for the diabetic population. By excluding T2DM from the diabetic cohort, the analysis remains appropriately tailored to the unique risk profile of diabetic patients. The impact of RC changes, standardized to one SD, on the dependent variables including composite and individual adverse events was assessed using the per SD increase method. Hazard ratios (HR) along with their respective 95% confidence intervals (CI) were computed to accurately quantify these associations. ROC curves based on the Cox model were used to determine the predictive capacity

of RC for both composite and individual adverse events. With significance defined as a two-sided P value < 0.05, statistical analyses were conducted with SPSS 22.0, MedCalc 22.021, and R 4.3.1.

Results

1505 menopausal women with ACS (65.00±7.23 years) were brought into the present study ultimately when meeting the enrollment criteria and completing the follow-up. The overall population was divided into quartiles (Q1, Q2, Q3, and Q4) according to the median RC value, with sample sizes of 377, 376, 376, and 376, respectively. Among these, there were 716 individuals with diabetes. This study also stratified the diabetic population into quartiles (Q1-Q4), each comprising 179 individuals. During the 60-month follow-up, 48 (3.2%) all-cause death, 97 (6.4%) cardiac death/non-fatal MI, and 105 (7.0%) target vessel revascularization were recorded, which included 48 (3.2%) all-cause death, 97 (6.4%) cardiac death/nonfatal MI, and 105 (7.0%) target vessel revascularization in diabetic population. Therefore, there were a cumulative 166 adverse events, constituting 11.0% of the total occurrences.

Baseline characteristics dividing by quartiles of RC

In the general population, noticeable disparities were observed in RLP-C, age, diastolic blood pressure (DBP), HDL-C, eGFR, Cr, TC, LDL-C, and TG, with age, DBP, Cr, LDL-C, TC, HDL-C, TG, gradually increasing, and eGFR decreasing as RC grouping increased (Table 1), where the lipid distribution was visible in Fig. 2A. In the diabetic population, significant differences were observed in RLP-C, LDL-C, eGFR, Cr, TG, HDL-C, and TC, among which Cr, HDL-C, TC, LDL-C, TG, showed a gradual increase, and eGFR showed a gradual decrease as RC grouping increased (supplementary material Table S1), with the lipid distribution depicted in Fig. 2B.

Associations between RC level and adverse events

In composite adverse events, survival analysis indicated significant differences among the four groups in both the general population and the diabetic population, with a gradual decrease in composite adverse event survival rates from Q1 to Q4 groups as the RC value increases (Log-rank P < 0.001) in Fig. 3A & B. In components of composite adverse events, all-cause death, cardiac death/nonfatal MI, and target vessel revascularization showed significant differences in the overall population (Log-rank P < 0.05) (Fig. 4A, C and E). However, in the diabetic population, survival analysis suggested that target vessel revascularization did not exhibit significance (Log-rank P = 0.271) (Fig. 4F), while all-cause death and cardiac death/nonfatal MI demonstrated significant differences (Log-rank P < 0.05) (Fig. 4B and D).

In the Cox regression model, per 1-SD change in RC was associated with risk of composite and individual adverse events higher in diabetic group, including 45.4% vs. 52.5% in composite adverse events, 47.2% vs. 51.7% in all-cause death, 41.5% vs. 45.7% in cardiac death/ nonfatal MI, and 46.4% vs. 49.9% in target vessel revascularization (Table 2). By employing the Q1 group as the reference, in the total population, the Q3 - Q4 groups exhibited a 2.026-fold (95% CI 1.183–3.471) and 2.936-fold (95% CI 1.762–4.892) higher risk for composite adverse events, while in the diabetic group, the Q4 group showed a 2.723-fold (95% CI 1.362–5.448) higher risk. The Q4 group was related with a 2.981-fold (95% CI 1.081–4.219) and 4.836-fold (95% CI 1.043–5.428) risk of all-cause death in the total and diabetic populations, respectively. Regarding cardiac death/nonfatal MI, the Q3 and Q4 groups had a 2.121-fold (95% CI 1.032–3.360) and 2.908-fold (95% CI 1.463–4.777) higher risk in the total population, while the Q4 group had a 2.756-fold (95% CI 1.160–3.546) higher risk. For target vessel revascularization, the Q3 and Q4 groups had a 2.045-fold (95% CI 1.049–2.986) and 2.917-fold (95% CI 1.548–4.495) higher risk in the total population (Table 2).

Prediction values of RC for the adverse events

ROC analysis based on Cox regression model suggested that the addition of RC enhanced the AUC for composite adverse events both in total and diabetic populations (with AUC = 0.599 for baseline model vs. 0.673 for plus RC, P < 0.001; AUC = 0.618 for baseline model vs. 0.688 for plus RC, P = 0.0148) (Fig. 5A and B). As for composite and individual adverse events, the addition of RC enhanced the AUC for target vessel revascularization in total population (0.594 for baseline model vs. 0.658 for plus RC, P = 0.0094), while in other component of adverse events showed enhancement when added RC but with no significant difference (supplementary material Fig. S1).

Discussion

This study marked the initial exploration of the influence of RC on the prognosis of menopausal women with ACS following PCI and examined the relationship between RC and composite and individual adverse events including all-cause death, cardiac death, nonfatal MI, and target vessel revascularization through utilizing the Cox regression model. The main findings revealed that: (1) an independent association between RC and composite adverse events, as well as each individual component; (2) a progressive decline in composite adverse event survival rates across the Q1-Q4 groups in both the general population and the diabetic population, corresponding to an increase in RC values; (3) for every 1-SD increase in RC, compared to the total population, the risk of composite and individual adverse events was higher in the

Table 1 Baseline characteristics of study patients based on RC quartiles

Variables	Total ($n=1505$)	Q1 ($n=377$)	Q2 ($n=376$)	Q3 ($n=376$)	Q4 ($n=376$)	*P* value
Clinical characteristics						
Age, years	65.00 ± 7.23	64.15 ± 7.20	64.76 ± 7.18	65.41 ± 7.19	65.68 ± 7.18	0.017
BMI, kg/m^2	25.29 ± 3.15	25.31 ± 3.18	25.30 ± 3.20	25.06 ± 3.03	25.51 ± 3.16	0.506
SBP, mmHg	130.50 [120.00, 143.00]	130.00 [120.00, 141.00]	130.00 [121.00, 141.00]	130.00 [120.50, 142.00]	133.00 [121.00, 146.00]	0.177
DBP, mmHg	75.00 [68.00, 81.00]	74.00 [67.00, 80.00]	74.50 [68.00, 80.00]	75.00 [68.00, 81.00]	76.00 [70.00, 83.00]	0.020
Diagnosis on admission						
UAP	1324 (88.0)	335 (88.9)	333 (88.6)	330 (87.8)	326 (86.7)	0.803
NSTEMI	92 (6.1)	22 (5.8)	22 (5.9)	25 (6.6)	23 (6.1)	0.963
STEMI	89 (5.9)	20 (5.3)	21 (5.6)	21 (5.6)	27 (7.2)	0.686
Medical history						
Previous MI	121 (8.0)	29 (7.7)	30 (8.0)	31 (8.2)	31 (8.2)	0.991
Previous PCI	330 (22.0)	86 (22.8)	87 (23.2)	81 (21.6)	76 (20.3)	0.765
Family CVD	109 (7.2)	32 (8.5)	25 (6.6)	23 (6.1)	29 (7.7)	0.593
Hypertension	1058 (70.3)	253 (67.1)	260 (69.1)	270 (71.8)	275 (73.1)	0.268
Hyperlipemia	1054 (70.0)	256 (67.9)	259 (68.9)	259 (68.9)	280 (74.5)	0.186
T2DM	716 (47.6)	181 (48.0)	181 (48.1)	167 (44.4)	187 (49.7)	0.515
Current smoking	50 (3.3)	16 (4.2)	9 (2.4)	12 (3.2)	13 (3.5)	0.562
Diseased vessels						
LM disease	84 (5.6)	16 (4.2)	22 (5.9)	26 (6.9)	20 (5.3)	0.444
Three-vessel disease	465 (30.9)	115 (30.5)	110 (29.3)	128 (34.0)	112 (29.8)	0.482
CTO disease	257 (17.1)	59 (15.6)	67 (17.9)	60 (16.0)	71 (18.9)	0.589
ISR disease	110 (7.3)	31 (8.2)	23 (6.1)	26 (6.9)	30 (8.0)	0.666
SYNTAX score	11.00 [7.00, 16.00]	11.00 [8.00, 16.00]	11.00 [7.25, 16.25]	11.00 [7.00, 16.00]	11.00 [7.00, 16.00]	0.617
Number of stents	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	0.448
Diameter of stents, mm	2.75 [2.50, 3.00]	2.75 [2.50, 3.00]	2.75 [2.50, 3.00]	2.75 [2.50, 3.00]	2.75 [2.50, 3.00]	0.382
Length of stents, mm	23.00 [16.00, 30.00]	23.00 [16.00, 30.00]	23.00 [15.00, 30.00]	23.00 [15.25, 30.00]	23.00 [15.75, 30.00]	0.851
Laboratory findings						
LVEF, %	65.00 [60.00, 68.00]	65.00 [60.00, 68.00]	65.00 [61.00, 68.00]	65.00 [60.00, 68.00]	65.00 [60.00, 67.00]	0.355
eGFR, mL/min/1.73 m^2	92.17 [83.83, 98.32]	94.31 [86.69, 100.70]	92.84 [85.25, 98.84]	91.77 [82.16, 97.84]	89.43 [80.06, 96.49]	< 0.001
Cr, μmol/L	57.40 [50.90, 65.40]	55.70 [50.27, 62.82]	55.80 [50.20, 63.10]	58.80 [51.70, 67.00]	59.70 [52.15, 68.20]	< 0.001
TG, mmol/L	1.41 [1.05, 1.90]	0.97 [0.77, 1.17]	1.20 [1.04, 1.46]	1.58 [1.31, 1.85]	2.30 [1.89, 2.80]	< 0.001
TC, mmol/L	4.21 [3.62, 4.92]	3.81 [3.31, 4.42]	4.06 [3.54, 4.64]	4.34 [3.74, 5.01]	4.69 [4.05, 5.44]	< 0.001
HDL-C, mmol/L	1.16 [1.01, 1.35]	1.23 [1.08, 1.43]	1.19 [1.03, 1.36]	1.16 [1.01, 1.33]	1.08 [0.95, 1.27]	< 0.001
LDL-C, mmol/L	2.43 [1.92, 3.08]	2.23 [1.76, 2.79]	2.38 [1.89, 2.94]	2.52 [2.01, 3.19]	2.69 [2.06, 3.32]	< 0.001
RC, mmol/L	0.54 [0.42, 0.69]	0.35 [0.29, 0.39]	0.48 [0.45, 0.51]	0.61 [0.57, 0.65]	0.84 [0.75, 0.98]	< 0.001
HbA1c, %	6.30 [5.80, 7.40]	6.20 [5.70, 7.20]	6.20 [5.80, 7.30]	6.30 [5.80, 7.30]	6.40 [5.90, 7.60]	0.078
FBG, mmol/L	5.91 [5.19, 7.68]	5.85 [5.16, 7.50]	5.88 [5.18, 7.46]	5.88 [5.20, 7.62]	6.05 [5.28, 8.26]	0.137
Medications, n (%)						
DAPT	1504 (99.9)	377 (100.0)	375 (99.7)	376 (100.0)	376 (100.0)	0.391
Statin	1491 (99.1)	375 (99.5)	371 (98.7)	372 (98.9)	373 (99.2)	0.694
β-Blocker	971 (64.5)	228 (60.5)	245 (65.2)	244 (64.9)	254 (67.6)	0.232
ACEI/ARB	712 (47.3)	169 (44.8)	166 (44.1)	189 (50.3)	188 (50.0)	0.183
CCB	573 (38.1)	138 (36.6)	132 (35.1)	155 (41.2)	148 (39.4)	0.309
Antidiabetic drugs						
Insulin	174 (11.6)	35 (9.3)	38 (10.1)	49 (13.0)	52 (13.8)	0.146
OAD	409 (27.2)	95 (25.2)	106 (28.2)	101 (26.9)	107 (28.5)	0.736

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CCB, calcium channel blockers; Cr, creatinine; CTO, chronic total occlusion; CVD, cardiovascular diseases; DAPT, dual antiplatelet therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; ISR, in-stent restenosis; LDL-C, low-density lipoprotein cholesterol; LM, left main; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; OAD, oral antidiabetic drugs; PCI, percutaneous coronary intervention; RC, remnant cholesterol; SBP, systolic blood pressure; STEMI, ST elevation myocardial infarction; SYNTAX, SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; UAP, unstable angina pectoris

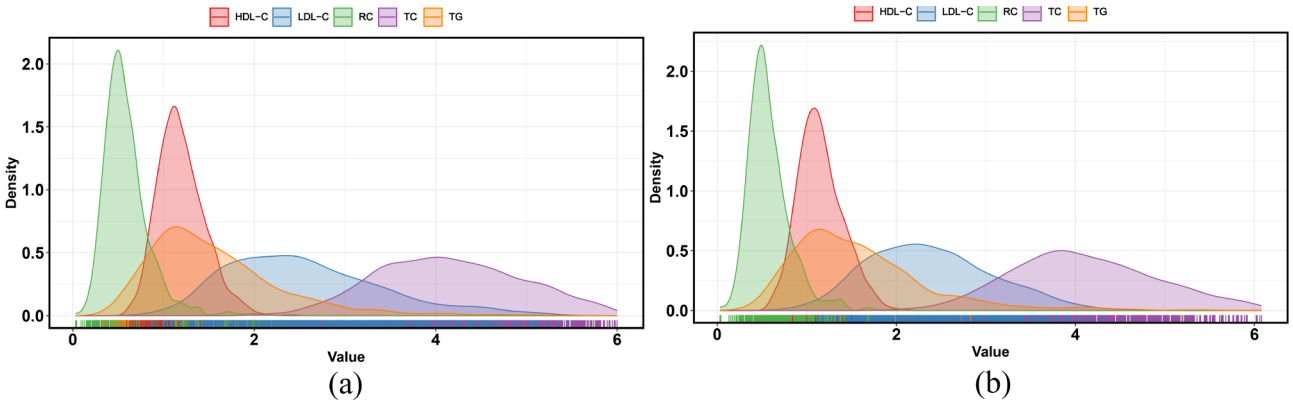

Fig. 2 Density plot of lipid values in total and diabetic populations. (**A**) Density plot of lipid values in total population, (**B**) Density plot of lipid values in diabetic population. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RC, remnant cholesterol; TC, total cholesterol; TG, triglyceride

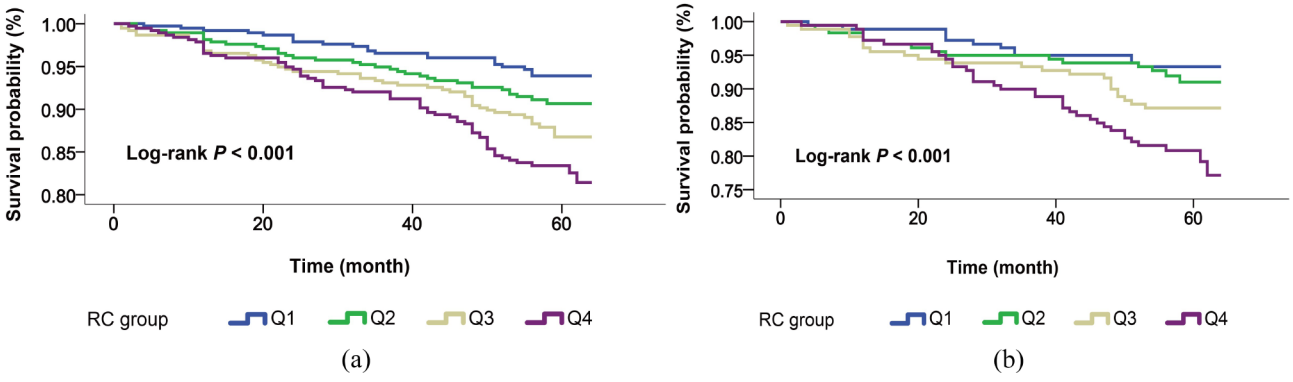

Fig. 3 Kaplan-Meier analysis in composite adverse events according to the RC quartiles in total and diabetic populations. Kaplan-Meier curves for (**A**) composite adverse events in total population, and (**B**) composite adverse events in diabetic population. RC, remnant cholesterol

diabetic population; (4) for composite adverse events, RC improved the AUC based on the Cox regression model in these two populations.

Atherosclerosis was an immune-inflammatory process that may begin early in life. It occurred when atherogenic lipids accumulate in the arterial intima, triggering low-grade inflammation that led to the formation and progression of atherosclerotic plaques [22]. Elevated RC levels and low-grade inflammation jointly promoted atherosclerosis, increasing the number and vulnerability of arterial plaques, which raised the risk of plaque rupture [23]. In addition, high RC levels contributed to multiple pro-atherosclerotic effects, including monocyte activation, increased production of pro-thrombotic factors, and upregulation of pro-inflammatory cytokines [24]. Additionally, serum RC levels were associated with an increased likelihood of entering the arterial wall with elevated level, where macrophages captured and absorbed them, resulting in quicker foam cell formation than with LDL. Through TRL hydrolysis, RC stimulated the production of cytokines and interleukins and releases pro-atherogenic adhesion molecules, triggering inflammation and the coagulation cascade [25]. Moreover, RC could accelerate the aging of endothelial progenitor cells by increasing oxidative stress and induces endothelial dysfunction by inhibiting nitric oxide production [26].

Lipid metabolism in individuals with T2DM differed from that of the general population, characterized by abnormal TRL particle composition, higher levels of LDL-C, and lower levels of HDL-C [27]. Beyond traditional lipid parameters, RC provided additional information in predicting the progression of T2DM [28]. Elevated RC levels in diabetic patients were related with the increased risk of ASCVD. RC and low-grade inflammation can explain the significant excess risk of ASCVD caused by diabetes [29]. RC levels, independent of LDL-C, were linked to major adverse cardiovascular events in T2DM patients, and variability in RC during follow-up helped identify those at higher cardiovascular risk [30]. Similarly, it was worth noting that in T2DM, higher RC levels were correlated with increased risks of all-cause and cardiovascular mortality [31]. Moreover, it was suggested TG and RC with increased levels were significantly correlated with the increasing cardiac metabolic

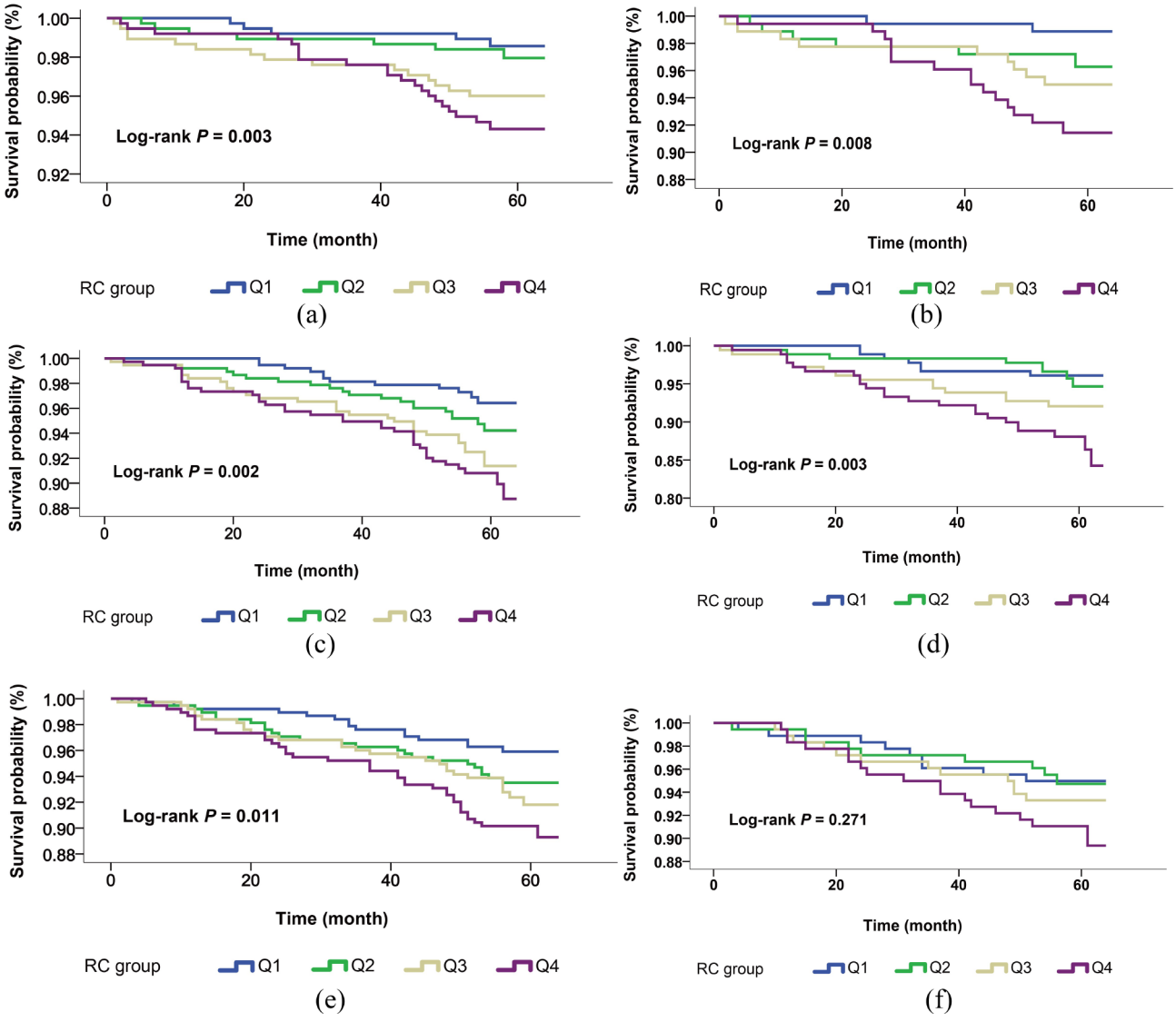

Fig. 4 Kaplan-Meier analysis in each component of adverse events according to the RC quartiles in total and diabetic populations. Kaplan-Meier curves for (**A**) all-cause death, (**C**) cardiac death/ nonfatal MI, and (**E**) target vessel revascularization in total population; (**B**) all-cause death, (**D**) cardiac death/ nonfatal MI, and (**F**) target vessel revascularization in diabetic population. MI, myocardial infarction; RC, remnant cholesterol

comorbidities risk, especially the progression from ischemic heart disease to both ischemic heart disease and T2DM [32]. However, the mechanisms behind the gender differences in the risk of RC and T2DM remained unclear, though sex hormones and body composition might partly explain these differences [14]. Besides the association between LDL-C and T2DM, RC may mediate this link through insulin resistance and inflammation. Additionally, women were more susceptible to T2DM related to RC exposure [33]. What's more, compared to other populations, South Asians have a higher prevalence of coronary artery disease and early-onset myocardial infarction [34], and the level of RC would be higher in this population [35]. In this study, among Asian menopausal women with concomitant diabetes, the risk associated with every 1-SD increase in RC was greater in the diabetic subgroup than in the overall population. Additionally, based on the Cox regression ROC results, the AUC for composite events in the diabetic subgroup was higher than the overall population, with values of 0.688 compared to 0.673, suggesting a potential correlation with the combined state of diabetes and menopausal status.

Female ACS patients were more likely than males to experience non-obstructive CAD, possibly due to differing pathophysiology. Among women with MI, the prevalence of MI with non-obstructive coronary arteries was 10.5%, compared to 3.4% in men [36]. It was also found that female ACS patients had a 20% higher adjusted short-term mortality risk after successful

Table 2 RC levels in relation to composite and each component of adverse events in total and diabetic populations

	Total population				Diabetic population			
	Crude model HR (95% CI)	*P*for crude model	Adjusted model HR (95% CI)	*P* for adjusted model	Crude model HR (95% CI)	*P*for crude model	Adjusted model HR (95% CI)	*P* for adjusted model
Composite adverse events								
RC per-SD increase	1.420 (1.279–1.577)	< 0.001	1.454 (1.293–1.635)	< 0.001	1.466 (1.274–1.686)	< 0.001	1.525 (1.288–1.805)	< 0.001
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2	1.577 (0.922–2.696)	0.096	1.579 (0.899–2.772)	0.899	1.259 (0.589–2.689)	0.552	1.125 (0.495–2.555)	0.779
Q3	2.178 (1.310–3.619)	0.003	2.026 (1.183–3.471)	0.010	1.986 (0.988–3.991)	0.054	1.826 (0.873–3.819)	0.110
Q4	3.082 (1.899–5.003)	< 0.001	2.936 (1.762–4.892)	< 0.001	3.182 (1.655–6.116)	0.001	2.723 (1.362–5.448)	0.005
All-cause death								
RC per-SD increase	1.422 (1.173–1.725)	< 0.001	1.472 (1.134–1.910)	0.004	1.467 (1.169–1.841)	0.001	1.517 (1.099–2.095)	0.011
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2	1.410 (0.447–1.441)	0.558	0.736 (0.197–1.745)	0.736	1.052 (0.616–1.123)	0.172	1.443 (0.240–2.673)	0.689
Q3	3.064 (1.113–3.430)	0.030	2.186 (0.766–2.243)	0.144	2.603 (0.995–3.304)	0.051	3.628 (0.767–4.168)	0.104
Q4	4.285 (1.616–5.365)	0.003	2.981 (1.081–4.219)	0.035	3.758 (1.774–4.926)	0.006	4.836 (1.043–5.428)	0.044
Cardiac death/ Non-fatal MI								
RC per-SD increase	1.389 (1.207–1.599)	< 0.001	1.415 (1.209–1.658)	< 0.001	1.421 (1.179–1.713)	< 0.001	1.457 (1.161–1.828)	0.001
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2	1.681 (0.822–2.440)	0.155	1.759 (0.836–2.698)	0.137	1.126 (0.408–2.105)	0.819	1.038 (0.363–1.967)	0.945
Q3	2.486 (1.269–3.871)	0.008	2.121 (1.032–3.360)	0.041	2.057 (0.830–3.096)	0.119	1.614 (0.623–2.182)	0.324
Q4	3.115 (1.621–4.986)	0.001	2.908 (1.463–4.777)	0.002	3.427 (1.470–4.986)	0.004	2.756 (1.160–3.546)	0.022
Target vessel revascularization								
RC per-SD increase	1.426 (1.251–1.626)	< 0.001	1.464 (1.277–1.679)	< 0.001	1.440 (1.186–1.748)	< 0.001	1.499 (1.210–1.857)	< 0.001
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Q2	1.619 (0.849–2.087)	0.143	1.920 (0.977–2.775)	0.058	0.990 (0.393–1.494)	0.983	1.218 (0.469–2.165)	0.686
Q3	1.901 (1.105–2.559)	0.045	2.045 (1.049–2.986)	0.036	1.344 (0.566–2.191)	0.502	1.414 (0.568–2.520)	0.457
Q4	2.616 (1.439–3.755)	0.002	2.917 (1.548–4.495)	0.001	1.922 (0.857–3.313)	0.113	1.971 (0.847–2.587)	0.115

CI, confidence interval; HR, hazard ratio; RC, remnant cholesterol; SD, standard deviation

PCI compared to males [37]. The impact of T2DM on CVD risk appeared to be greater in females than males, particularly in menopausal women, possibly due to decreased estrogen levels [38]. While advancements in treatment over recent decades have brought benefits to ACS patients, the long-term prognosis after PCI in ACS patients remained suboptimal, primarily due to in-stent restenosis or thrombosis [39]. In menopausal ACS patients with concurrent T2DM, diffuse small vessel disease was characteristic, posing a higher risk of in-stent restenosis or thrombosis following PCI [40]. Meanwhile, RC may be a more accurate predictor of all-cause mortality risk after PCI than LDL-C. Consistently high RC levels can potentially predict both all-cause and cardiovascular mortality risk [41]. In this study, compared to the lowest quartile group, in the overall population, there was a 2.936-fold higher risk for composite adverse events and a 2.723-fold higher risk in the diabetic population. Furthermore, ROC analysis results indicated a significant improvement in the predictive ability for composite events in both populations following RC added. Overall, the findings suggested that RC may serve as a prognostic factor for adverse events in this specific population. Therefore, identifying adverse lipid-related risk factors in menopausal ACS patients undergoing PCI who also had diabetes, stratifying patients based on lipid levels, and initiating early intensive lipid-lowering therapy might be crucial for enhancing the clinical efficacy of PCI in these patients.

Strengths and limitations

This study's strength lied in its exploration of the role of RC in the prognosis of menopausal women with ACS undergoing PCI, which was a relatively novel and cutting-edge research topic, providing a fresh perspective for both research and clinical practice in this field. Focused on menopausal women, the targeted and specific nature of the results can offer more precise guidance for the clinical management of this demographic. Building on previous research exploring the link between RC and CAD,

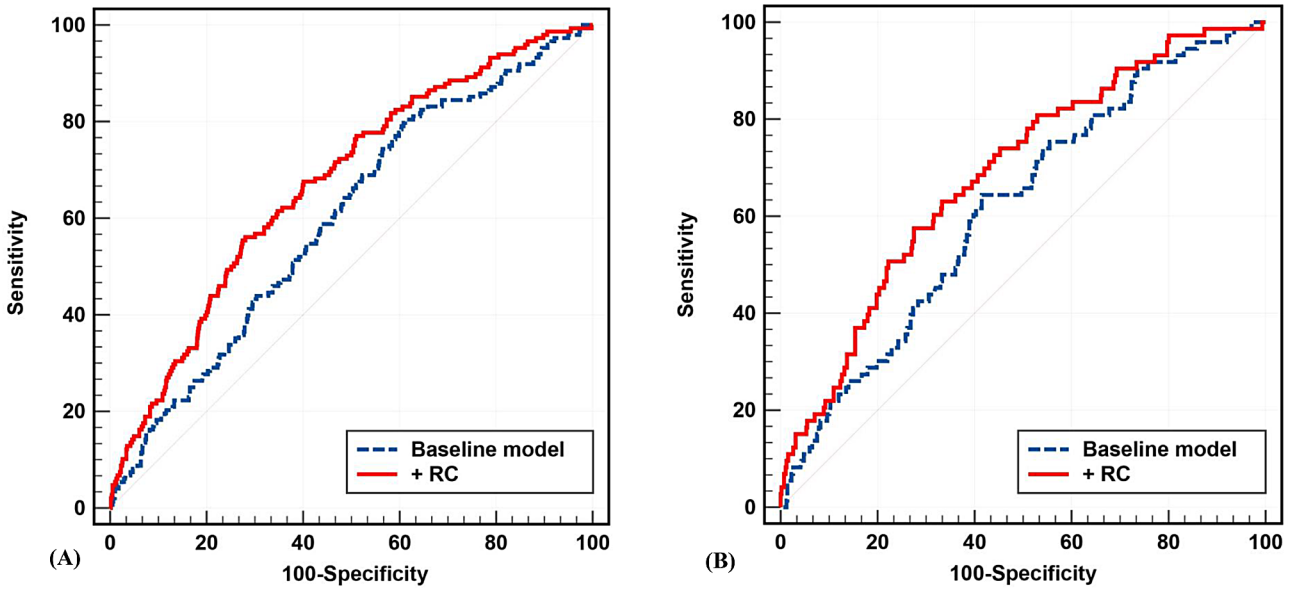

Fig. 5 ROC curves evaluating the predictive value of the model for composite adverse events in total and diabetic populations. ROC curves for (**A**) composite adverse events in total population, and (**B**) composite adverse events in diabetic population. RC, remnant cholesterol

this study examined the role of RC in the prognosis of ACS in menopausal women after PCI. This investigation addressed an understudied area within this subgroup, helped fill a knowledge gap, and encouraged further research and understanding in this field. Nonetheless, limitations of this study included its observational nature, making it susceptible to confounding factors and precluding causal conclusions. However, multiple studies demonstrated the causal genetic relationship between elevated RC and increased ASCVD risk. Despite adjusting for the most significant known risk factors post-PCI, residual confounding factors may still exist. Another limitation was the use of calculated RC rather than directly measured residual cholesterol. However, calculated and measured RC were closely correlated [42–44]. An additional benefit of calculating residual cholesterol was its ease of clinical application, requiring no additional cost as it can be computed based on existing lipid profile measurements. Furthermore, being a single-center observational study, more research was needed to confirm the generalizability of the conclusions. In addition, the exclusion of certain subjects due to missing data introduced a potential bias that could compromise the credibility of this study and weaken the validity. Finally, routine assessment of lipid concentrations was not conducted over the course of follow-up.

Conclusion

Among menopausal women diagnosed with ACS and undergoing PCI, elevated levels of RC emerged as an independent predictor significantly correlated with an elevated incidence of adverse events. This underscored the potential of RC levels to serve as a pivotal lipid prognostic marker within this specific population. The recognition of RC as a substantial prognostic indicator highlighted the importance of vigilant monitoring and management of lipid profiles, particularly RC levels, to optimize clinical outcomes and advance patient care within this demographic.

Abbreviations

ASCVD	Arteriosclerotic cardiovascular disease
LDL	C-Low-density lipoprotein cholesterol
RC	Remnant cholesterol
TRL	Triglyceride-rich lipoproteins
TG	Triglycerides
CVD	Cardiovascular diseases
T2DM	Type 2 diabetes mellitus
CAD	Coronary artery disease
ACS	Acute coronary syndrome
PCI	Percutaneous coronary intervention
eGFR	Estimated glomerular filtration rate
MI	Myocardial infarction
BMI	Body mass index
FBG	Fasting blood glucose
Cr	Creatinine
HbA1c	Glycated hemoglobin A1c
TC	Total cholesterol
HDL-C	High-density lipoprotein cholesterol
LVEF	Left ventricular ejection fraction
SD	Standard deviation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02258-y.

Supplementary Material 1

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Author contributions
Conceptualization: XXF, QYG and YJZ; methodology: XXF and YL; software: XXF, YL and JQY; statistical analysis: XXF, YL and JQY; visualization: XXF and YL; data collection: XXF, YL, JQY, ZMZ, SWY, QYG and YJZ; writing and original draft preparation: XXF; writing, review and editing: XXF, ZMZ, SWY, QYG and YJZ. The final manuscript has been read and approved by all the authors and each contributor has reviewed the final version of the paper.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All laboratory tests in this study were reviewed by the Ethics Review Board of the Beijing Anzhen Hospital. All patients signed an informed consent form and following the principles of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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