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ORIGINAL RESEARCH

Remnant Cholesterol Predicts Risk of Cardiovascular Events in Patients With Myocardial Infarction With Nonobstructive Coronary Arteries

Side Gao, MD; Haobo Xu, MD; Wenjian Ma, MD; Jiansong Yuan, MD, PhD; Mengyue Yu, MD, PhD

BACKGROUND: Remnant cholesterol (RC) has been reported to promote atherosclerotic cardiovascular disease. Yet little is known regarding the RC-related residual risk in patients with myocardial infarction (MI) with nonobstructive coronary arteries.

METHODS AND RESULTS: A total of 1179 patients with MI with nonobstructive coronary arteries were enrolled and divided according to median level of RC calculated as non–high-density lipoprotein cholesterol minus low-density lipoprotein cholesterol. The primary end point was a composite of major adverse cardiovascular events (MACEs), including all-cause death, nonfatal MI, stroke, revascularization, and hospitalization for unstable angina or heart failure. Kaplan-Meier, Cox regression, and receiver-operating characteristic analyses were used. Patients with higher median level of RC had a significantly higher incidence of MACEs (16.9% versus 11.5%; *P*=0.009) over the median follow-up of 41.7 months. High RC levels were significantly associated with an increased risk of MACEs after adjustment for multiple clinically relevant variables (per 1 SD increase, hazard ratio, 0.61; 95% CI, 1.12–2.31; *P*=0.009). Elevated RC also contributed to residual risk beyond conventional lipid parameters. Moreover, RC had an area under the curve of 0.61 for MACE prediction. When adding RC to the Thrombolysis in Myocardial Infarction risk score, the combined model yielded a significant improvement in discrimination for MACEs.

CONCLUSIONS: Elevated RC was closely associated with poor outcomes after MI with nonobstructive coronary arteries independent of traditional risk factors, indicating the utility of RC for risk stratification and a rationale for targeted RC-lowering trials in patients with MI with nonobstructive coronary arteries.

Key Words: cardiovascular outcomes ■ myocardial infarction with nonobstructive coronary arteries ■ remnant cholesterol

Acute myocardial infarction (AMI) accounts for consistently high rates of morbidity and mortality of atherosclerotic cardiovascular diseases (ASCVD). Recently, a distinct population with myocardial infarction (MI) with nonobstructive coronary arteries (MINOCA) has been increasingly recognized with the widespread use of coronary angiography.[1,2] It is reported that MINOCA occurs in 5% to 10% of AMI. These patients are younger and have fewer comorbidities compared with those with AMI and obstructive coronary artery disease (CAD).[3,4] However, the prognosis of MINOCA is not a trivial thing considering that they are still at considerable risks for long-term adverse events despite the optimal medical therapies.[5–8] Hence, their prognosis deserves more attention and the potential underestimated risk factors should be highlighted.

Dyslipidemia remains a critical contributor to increased cardiovascular risk.[9] Although the definite benefits of low-density lipoprotein cholesterol (LDL-C)-lowering therapies

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CLINICAL PERSPECTIVE

What Is New?

- An independent association of elevated remnant cholesterol (RC) with increased risk of major adverse cardiovascular event was observed in a distinct population with myocardial infarction with nonobstructive coronary arteries.
- RC provided incremental prognostic information in myocardial infarction with nonobstructive coronary arteries and this may expand new insights into the atherogenicity of RC.

What Are the Clinical Implications?

- RC as a residual risk predictor could facilitate risk stratification in patients with myocardial infarction with nonobstructive coronary arteries.
- RC as a preferential antiatherogenic target may influence therapeutic decision making in patients with myocardial infarction with nonobstructive coronary arteries.

Nonstandard Abbreviations and Acronyms

MACE	major adverse cardiovascular event
MINOCA	myocardial infarction with nonobstructive coronary arteries
RC	remnant cholesterol
TIMI	Thrombolysis in Myocardial Infarction
TRL	triglyceride-rich lipoprotein

have been addressed over decades,[10] there are still significant residual risks among statin-treated individuals, even in those with low LDL-C levels.[11,12] Given that the high-density lipoprotein cholesterol (HDL-C)-raising strategies failed to reduce cardiovascular events,[13] recent research focus has shifted to the atherogenic role of triglyceride, triglyceride-rich lipoprotein (TRL), and the remnant cholesterol (RC), which have been reported to promote ASCVD risk.[14,15] RC is the cholesterol content of TRL, composed of chylomicron remnant, very-low-density lipoprotein, and intermediate-density lipoprotein.[16,17] Emerging evidence has identified RC as a residual risk factor of CAD.[18,19] RC can accumulate in the subendothelial space and lead to a variety of vascular injuries including endothelial dysfunction, inflammation, and, ultimately, atherogenesis.[20,21] Mendelian randomization studies also established a causal association between genetically elevated RC and CAD risk.[22,23] Recent data further proved the prognostic power of RC in different clinical settings, either in ASCVD-free individuals in primary prevention[24–27] or in subpopulations with CAD in secondary prevention.[28–30]

Although previous data suggest that RC independently predicts cardiovascular risk, no relevant study has addressed the prognostic implications of elevated RC in patients with MINOCA. Here, we investigated the impact of RC on long-term cardiovascular outcomes after MINOCA and explored whether RC could facilitate risk prediction in this specific population.

METHODS

Study Population

This was a single-center, prospective, and observational cohort study of patients with MINOCA. From January 2015 to December 2019, a total of 23 460 unique hospitalized patients with AMI undergoing coronary angiography were consecutively admitted to Fuwai hospital, including non–ST-segment–elevation MI and ST-segment–elevation MI. MINOCA was diagnosed if patients met the fourth universal definition of AMI,[31] and coronary angiography did not show a stenosis of ≥50% in epicardial coronary arteries[3,4] Exclusion criteria include (1) obstructive CAD (n=21 696); (2) prior revascularization (n=312); (3) thrombolytic therapy for ST-segment–elevation MI since the coronary lesion may be affected by thrombolysis (n=126); (4) alternate explanations for elevated troponin other than coronary-related causes (eg, myocarditis, pulmonary embolism, takotsubo syndrome, n=46); (5) lack of detailed baseline data (n=33); and (6) lost at follow-up (n=68). As a result, 1179 eligible patients with MINOCA were enrolled in the final analysis (Figure 1). Patients were prescribed the evidence-based optimal medical therapies, including dual antiplatelet therapy, statins, β-blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[32,33] This study was approved by the Ethics Committee of Fuwai hospital and complied with the Declaration of Helsinki. All enrolled subjects provided written informed consent.

Data Collection

Patients' baseline characteristics were collected and verified from medical records. Blood samples for biochemical tests were routinely collected from cubital vein in same temporal window under fasting conditions (usually the next morning since admission). Among the lipid parameters, triglyceride, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) were quantified by standard enzymatic methods. LDL-C was determined by the homogeneous direct method. Apolipoprotein A1 and apolipoprotein B were tested with an immunoturbidimetric method. Specifically, RC was calculated as total cholesterol minus LDL-C

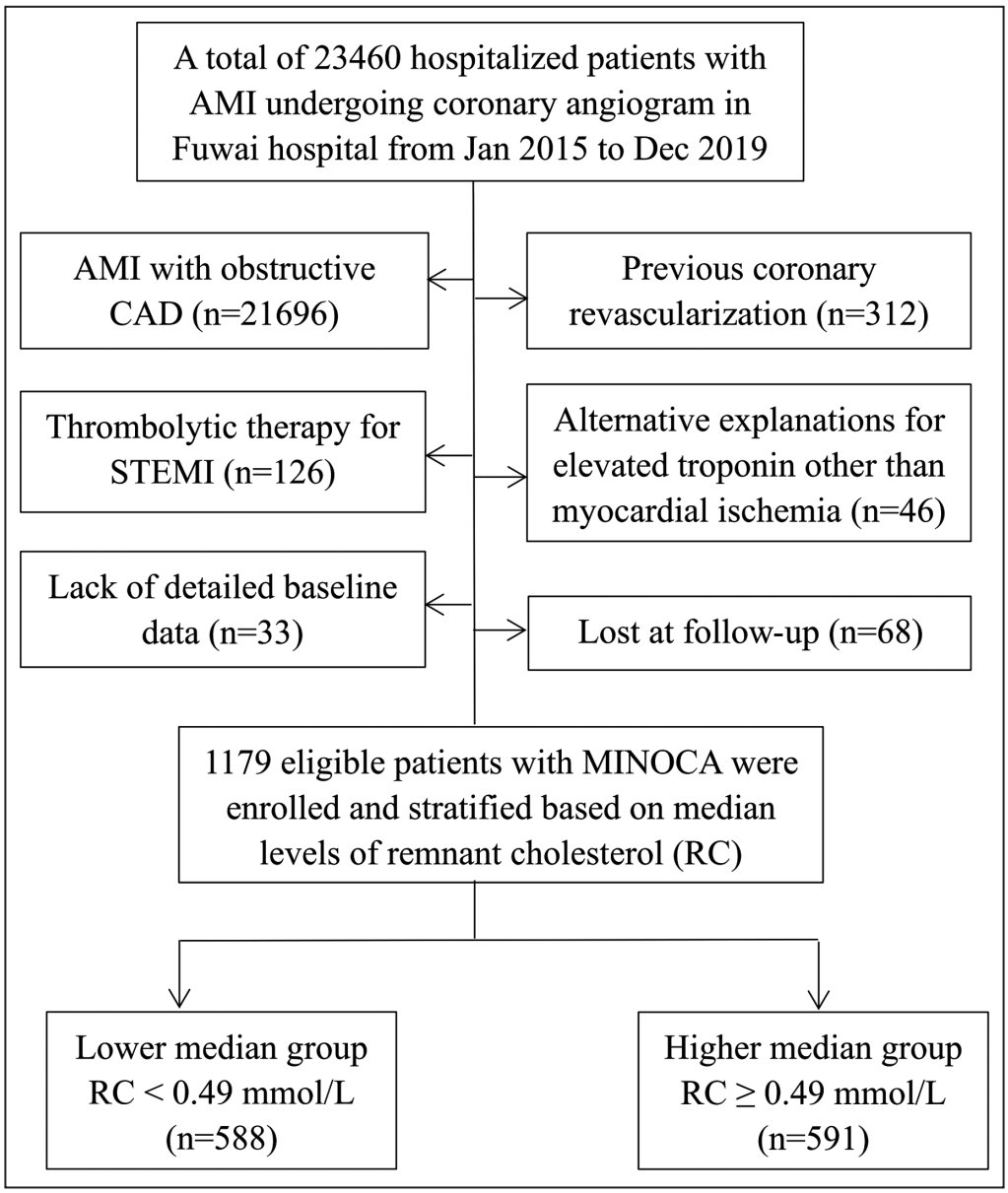

Figure 1. Study flowchart.
AMI indicates acute myocardial infarction; CAD, coronary artery disease; MINOCA, myocardial infarction with nonobstructive coronary arteries; and STEMI, SR-segment–elevation myocardial infarction.

minus HDL-C. Although there is no standard method to estimate RC, this equation has been frequently used in previous studies because it is available from the standard lipid profile at no extra cost.[17–30] Serum concentrations of fasting blood glucose, creatinine, and high-sensitivity C-reactive protein were measured using an automatic biochemistry analyzer. The NT-proBNP (N-terminal pro-B-type natriuretic peptide) at admission and peak cardiac troponin I values were recorded. The biplane Simpson method via echocardiography was applied to evaluate left ventricular ejection fraction. The Thrombolysis in Myocardial Infarction (TIMI) score was calculated since admission as previously described.[32,33] The above data that support the findings of this study are available from the corresponding author upon reasonable request.

Definitions and Outcomes

In this study, diabetes was defined with fasting blood glucose ≥7.0 mmol/L, 2-h plasma glucose ≥11.1 mmol/L, or having a history of diabetes.[34] Hypertension was defined as repeated blood pressure ≥140/90 mm Hg, past history, or taking antihypertensive drugs. Dyslipidemia was diagnosed by medical history or receiving lipid-lowering agents.[35]

The primary study end point was a composite of major adverse cardiovascular events (MACEs), including all-cause death, nonfatal MI, revascularization, nonfatal stroke, and hospitalization for unstable angina or heart failure (HF). The MACE was assessed as time to first event. The secondary end points included each component of MACE and the composite "hard" end point (death, nonfatal MI, nonfatal stroke, and with or without revascularization). The cardiovascular outcomes were analyzed since admission. Reinfarction was diagnosed according to the fourth universal definition of MI.[31] Revascularization was performed at the operator's discretion because of recurrent ischemia and progression of coronary artery lesion. Stroke was defined by the presence of neurological dysfunction and vascular brain injury caused by cerebral ischemia or hemorrhage[36] Hospitalization for unstable angina or HF reflected the clinical status and quality of life after AMI. Patients were regularly followed up by direct interview at clinics or via telephone contact at 6-month intervals by a team of independent and well-trained researchers who were blinded to the purpose of this study and not involved in the management of patients. All the end points were confirmed and adjudicated by at least 2 professional cardiologists who were masked to any of the study data.

Statistical Analysis

Data were expressed as mean± SD or median with interquartile range for continuous variables and numbers with percentages for categorical variables. Differences were assessed using Student's *t* test or Mann-Whitney *U* test for continuous variables and Pearson's χ^2 or Fisher's exact test for categorical variables. Cumulative incidence of MACE among groups were showed by Kaplan-Meier curve and compared using the log-rank test. The univariable and multivariable Cox proportional regression analyses were used to identify longitudinal association between RC and cardiovascular outcomes. The event risk was adjusted by age and sex in model 1 and further adjusted by multiple clinically relevant variables, including age, sex, MI classification (non–ST-segment–elevation MI or ST-segment–elevation MI), hypertension, diabetes, and dyslipidemia. The hazard ratio (HR) with 95% CI were calculated. Accuracy was defined with areas under the curve (AUCs) using a receiver operating characteristic curve analysis. The AUC values were interpreted as small (0.56–0.63), moderate (0.64–0.70), or strong (≥0.71)[37] We further assessed if RC had an incremental predictive value for MACE on the basis of TIMI risk score, and the AUC of 2 models were compared using DeLong's test.[38] All analyses were 2-tailed and *P* value <0.05 was considered statistically significant. Data were analyzed using SPSS version 22.0 (IBM, Armonk, NY) and MedCalc Statistical Software version 19.1(Ostend, Belgium).

RESULTS

Baseline Characteristics

Eligible patients with MINOCA were divided on the basis of the median level of RC (0.49 mmol/L) (Figure 1), which were skewedly distributed in the population (Figure S1). As shown in Table 1, those with higher median of RC were younger and more often men. They had higher percent of ST-segment–elevation MI, higher body mass index, and higher prevalence of diabetes and dyslipidemia. As expected, they also had higher levels of fasting blood glucose, total cholesterol, triglyceride, LDL-C, apolipoprotein B, high-sensitivity C-reactive protein, and peak troponin I; lower levels of HDL-C and apolipoprotein A; and more chance to receive treatment with β-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. There were no significant differences in hypertension, prior MI, left ventricular ejection fraction, Killip class, TIMI score, creatinine, and NT-proBNP. Additionally, we found a strong linear correlation between RC and triglyceride (Figure S2), whereas correlations between RC and the other lipid indexes were weak (Table S1). We also found that RC levels were much higher in patients with diabetes than those without (Figure S3). In this regard, patients with higher RC appeared to have more cardiometabolic risk factors, and RC may approximately mirror the metabolic disorders related to ASCVD.

Association Between RC Level and Outcomes

Over the median follow-up of 41.7 months, 168 patients experienced MACE (18 died, 41 had reinfarction, 46 had revascularization, 12 suffered stroke, and 71 were hospitalized for unstable angina and 48 for HF) (Table 1). The incidence of MACE (16.9% versus 11.5%; *P*=0.009) was significantly higher in patients with a higher median RC level (Table 1, Figure 2A). Characteristics in patients with or without a MACE were also compared and the MACE group had higher RC levels (Table S2). However, we note that the difference of MACE risk was mainly driven by the revascularization and hospitalization for HF. No significant differences were observed in the risk of death, AMI, or stroke, although there was a tendency. The Kaplan-Meier curves revealed an increased cumulative incidence of death, AMI, stroke, or revascularization; yet the risk of the end point of death, AMI, or stroke became nonsignificant after excluding revascularization (Figure 2B and 2C).

Table 1. Baseline Characteristics and Clinical Outcomes in Patients With MINOCA Lower or Higher Median Level of Remnant Cholesterol

Variable	Total (n=1179)	Lower median of RC (n=588)	Higher median of RC (n=591)	*P* value
Male, n (%)	867 (73.5)	413 (70.2)	454 (76.8)	0.010
Age, y	55.7±11.8	57.6±12.0	53.7±11.3	<0.001
BMI, kg/m^2	25.4±3.7	24.8±3.6	26.1±3.7	<0.001
STEMI, n (%)	475 (40.2)	214 (36.3)	261 (44.1)	0.007
History, n (%)				
Hypertension	630 (53.4)	306 (52.0)	324 (54.8)	0.338
Diabetes	187 (15.8)	68 (11.5)	119 (20.1)	<0.001
Dyslipidemia	686 (58.1)	317 (53.9)	369 (62.4)	0.003
Previous MI	58 (4.9)	33 (5.6)	25 (4.2)	0.273
Killip class≥2, n (%)	89 (7.5)	43 (7.3)	46 (7.7)	0.853
LVEF, %	60.5±7.5	60.6±7.1	60.3±7.8	0.474
TIMI risk score	3.4±1.3	3.4±1.1	3.5±1.5	0.312
Blood test				
Fasting glucose, mmol/L	5.69±1.68	5.46±1.32	5.94±1.98	<0.001
Total cholesterol, mmol/L	3.92±0.91	3.62±0.78	4.22±0.93	<0.001
Triglyceride, mmol/L	1.44 (1.05, 2.00)	1.10 (0.88, 1.37)	1.94 (1.53, 2.53)	<0.001
LDL-C, mmol/L	2.29±0.76	2.12±0.68	2.46±0.79	<0.001
HDL-C, mmol/L	1.08±0.29	1.17±0.30	0.99±0.25	<0.001
RC, mmol/L	0.56±0.34	0.32±0.11	0.79±0.33	<0.001
Apolipoprotein A, g/L	1.26±0.25	1.28±0.26	1.24±0.25	0.009
Apolipoprotein B, g/L	0.77±0.23	0.68±0.18	0.86±0.24	<0.001
Creatinine, μmol/L	80.13±17.89	79.16±16.35	81.09±19.26	0.063
hs-CRP, mg/L	2.20 (1.03, 5.75)	1.88 (0.87, 4.79)	2.64 (1.19, 6.48)	0.001
NT-proBNP, pg/mL	372 (112, 683)	365 (109, 674)	379 (118, 691)	0.125
Peak TnI, ng/mL	3.24 (0.72, 6.51)	2.97 (0.55, 5.43)	3.53 (0.96, 7.02)	0.012
In-hospital medication, n (%)				
DAPT	1091 (92.5)	538 (91.4)	553 (93.5)	0.176
Statin	1130 (95.8)	558 (94.8)	572 (96.7)	0.105
β-Blocker	860 (72.9)	402 (68.3)	458 (77.4)	<0.001
ACEI or ARB	759 (64.3)	356 (60.5)	403 (68.1)	0.006
Cardiovascular outcomes, n (%)				
MACE	168 (14.2)	68 (11.5)	100 (16.9)	0.009
Death, nonfatal MI, stroke or revascularization	102 (8.6)	40 (6.8)	62 (10.4)	0.024
All-cause death	18 (1.5)	6 (1.0)	12 (2.0)	0.157
Nonfatal MI	41 (3.4)	19 (3.2)	22 (3.7)	0.645
Revascularization	46 (3.9)	15 (2.5)	31 (5.2)	0.017
Nonfatal stroke	12 (1.0)	5 (0.8)	7 (1.1)	0.568
Hospitalization for UA	71 (6.0)	29 (4.9)	42 (7.1)	0.117
Hospitalization for HF	48 (4.0)	15 (2.5)	33 (5.5)	0.008

Patients were divided on the basis of the median level (0.49 mmol/L) of remnant cholesterol (RC) calculated as non–HDL-C minus LDL-C. Variables including triglyceride, hs-CRP, NT-proBNP and TnI were expressed as median with interquartile range (Q1, Q3). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist; BMI, body mass index; DAPT, dual anti-platelet therapy; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MONICA, myocardial infarction with nonobstructive coronary arteries; NT-proBNP, N-terminal pro-B-type natriuretic peptide; STEMI, ST-segment–elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; TnI, Troponin I; and UA, unstable angina.

At multivariate Cox analysis, higher median RC was significantly associated with an increased risk of MACE (HR, 1.41; 95% CI, 1.03–1.93; *P*=0.029). RC as a continuous variable was also correlated with the MACE risk (per 1 SD increase, HR, 0.61; 95% CI, 1.12–2.31; *P*=0.009) (Table 2). We further identified RC as one of

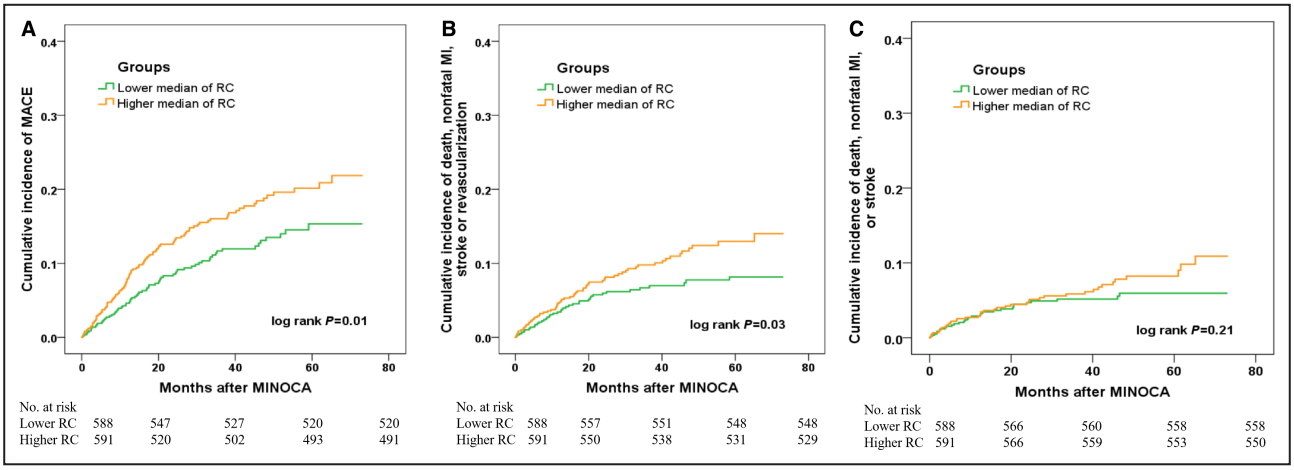

Figure 2. Incidence of composite event in patients with MINOCA with lower or higher median level of RC.
Kaplan-Meier curves showing the cumulative incidence of MACE (**A**), the composite end point of death, nonfatal MI, stroke, or revascularization (**B**), and the composite end point of death, nonfatal MI, or stroke (**C**). MACE indicates major adverse cardiovascular event; MI, myocardial infarction; MINOCA, myocardial infarction with nonobstructive coronary arteries; and RC, remnant cholesterol.

the independent predictors of MACE (Table S3) and found that elevated RC was still associated with MACE risk after adjustment for multiple lipid indexes (Table S4). Moreover, both triglyceride and RC emerged as robust risk factors, whereas the other lipid parameters were not (Table S5). Notably, RC remained a predictor of MACE in various subgroups, especially among patients with LDL-C above or below the target level of 1.8 mmol/L. The effect of RC on MACE risk may differ in subgroups stratified by sex, body mass index, diabetes, and dyslipidemia (*P* for interaction <0.05) (Figure S4). In hard end point analysis, the risk of the composite end point of death, AMI, stroke, or revascularization increased with higher RC levels; however, the relationship between RC and the risk of death, AMI, or stroke did not reach a statistical significance (Table 2, Table S6).

Predictive Value of RC for MACE

The receiver operating characteristic curve analysis confirmed the predictive value of RC for MACE (AUC, 0.61; 95% CI, 0.55–0.66; *P*<0.001). Meanwhile, the TIMI risk score had a moderate discrimination for MACE (AUC, 0.67; 95% CI, 0.62–0.72; *P*<0.001) (Figure 3). When adding RC to the original TIMI score using Cox regression, the combined model enabled a more accurate prediction of MACE (AUC, 0.72; 95%

Table 2. Association Between Remnant Cholesterol Levels and the Composite Event Risk

Group	Unadjusted		Model 1		Model 2	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
MACE						
RC, per 1 SD increase	1.81 (1.29–2.55)	0.001	1.63 (1.14–2.31)	0.006	1.61 (1.12–2.31)	0.009
Lower median of RC	1 (reference)	…	1 (reference)	…	1 (reference)	…
Higher median of RC	1.63 (1.19–2.24)	0.002	1.49 (1.09–2.03)	0.010	1.41 (1.03–1.93)	0.029
Death, MI, stroke or revascularization						
RC, per 1SD increase	2.04 (1.36–3.07)	0.001	1.80 (1.17–2.75)	0.007	1.75 (1.14–2.70)	0.011
Lower median of RC	1 (reference)	…	1 (reference)	…	1 (reference)	…
Higher median of RC	1.77 (1.18–2.65)	0.005	1.64 (1.09–2.48)	0.018	1.54 (1.04–2.30)	0.031
Death, MI, or stroke						
RC, per 1 SD increase	1.75 (0.95–3.21)	0.072	1.66 (0.91–3.02)	0.093	1.56 (0.85–2.84)	0.143
Lower median of RC	1 (reference)	…	1 (reference)	…	1 (reference)	…
Higher median of RC	1.64 (0.98–2.73)	0.057	1.61 (0.98–2.64)	0.060	1.39 (0.87–2.26)	0.137

Model 1 included age and sex. Model 2 included age, sex, body mass index, MI type (non–ST-segment–elevation MI or ST-segment–elevation MI), hypertension, diabetes, and dyslipidemia in the multivariate Cox analysis. HR indicates hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; and RC, remnant cholesterol.

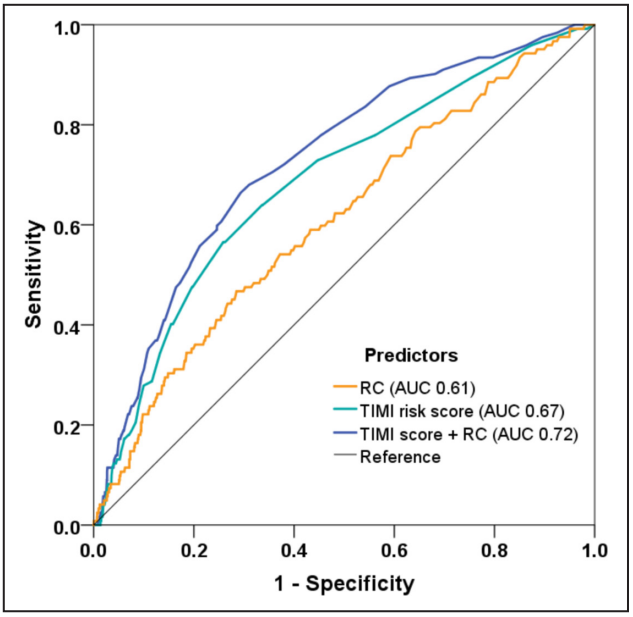

Figure 3. Model improvement in predicting MACE.
Receiver operating characteristic (ROC) curves showing predictive ability of remnant cholesterol (RC), TIMI risk score, and the combined model incorporating RC and TIMI score using Cox regression for MACE. AUC indicates area under the curve; MACE, major adverse cardiovascular event; and TIMI, Thrombolysis in Myocardial Infarction.

CI, 0.68–0.78; $P<0.001$) and accordingly yielded a significant model improvement (ΔAUC, 0.05; $P=0.023$ by DeLong's test).

DISCUSSION

The present study showed a potential contribution of RC to residual risk in patients with MINOCA. Elevated RC was associated with an increased risk of MACE independent of traditional risk factors. RC further improved risk prediction beyond an established risk score. Yet, the prognostic power of RC for hard end point in MINOCA remains doubtful and should be verified by future studies. In sum, these data expand our insights into the atherogenicity of RC, which may support the utility of RC for risk stratification in the contemporary management of MINOCA.

MINOCA is a heterogeneous diagnosis with multiple mechanisms, including plaque rupture, erosion, thromboembolism, coronary spasm, microvascular dysfunction, or supply/demand mismatch.[1] Some nonischemic diseases such as myocarditis may also mimic its presentation.[2] Here, we used the term *MINOCA* to primarily describe those with a definite AMI and nonobstructive coronary arteries, and prospectively established a long-term cohort from the largest cardiovascular center in China (Fuwai hospital). We found that patients with MINOCA did not necessarily have a benign course. Nearly 1.5% of subjects died and 14.2% of them developed MACE during the follow-up. Similarly, previous data reported a considerably high risk of long-term mortality and cardiovascular events after MINOCA.[3–8] Some studies even showed a similar prognosis between MINOCA and AMI and obstructive coronary artery disease despite secondary prevention strategies[5,6] indicating an urgent need to address residual risk factors and improve health care for this specific population.

Beyond the well-known LDL-C, other atherogenic lipid profiles including an excess of serum triglyceride and its TRL also remarkably increase the risk of ASCVD.[9] Since triglyceride can be easily metabolized and degraded in most cells, the cholesterol content of TRL (known as RC) is perceived to be the major harmful component in TRL.[16] RC has the capacity to deposit in the subendothelial space and be taken up by macrophages and smooth muscle cells.[17] The proatherogenic effect of RC has been confirmed,[20,21] which may involve proinflammatory responses, oxidative stress, platelet aggregation, endothelial dysfunction, foam cell formation, and smooth muscle cell proliferation.[39,40] Given its role in atherogenesis, it is not surprising that RC contributes to cardiovascular risk in both genetic and observational studies. The Copenhagen City Heart Study proved that an RC increase of 1 mmol/L was associated with a 2.8-fold causal risk for ischemic heart disease and there was a causal association between genetically elevated RC and risk of MI.[22,23] Moreover, recent data have shown that RC was independently associated with ASCVD risk either in primary prevention cohorts[24–27] or in various subpopulations with CAD.[28–30] Still, data are scarce regarding the prognostic value of RC in patients with MINOCA who remain at high risk even in the statin era.

Our findings were consistent with previous evidence on the critical role of triglyceride and TRL and its RC in CAD, and expanded the implication of RC in MINOCA. In our study, RC was calculated as non–HDL-C minus LDL-C by a standard lipid profile. This method has been widely used before with high availability and low cost. We found that to some extent, high RC levels mirrored cardiometabolic disorders. The incidence and adjusted risk of MACEs increased with higher RC levels. This association remained significant after adjustment for traditional risk factors and lipid indexes, indicating the contribution of RC to residual risk. When added to TIMI risk score, high RC still yielded additional prognostic information. RC can also identify high-risk patients with LDL-C below the target level of 1.8 mmol/L. Here, we should note that no statistically significances were found in the hard end point. The risks of death, MI, or stroke were similar between groups. There might be 2 reasons. First, the sample size and number of each ischemic event are small and

may not be efficient for statistical significance. Second, the impact of RC may be attenuated by the overall improvement in the management of AMI. Based on this result, it remains doubtful to conclude a define deleterious effect of RC in MINOCA, which warrants further investigation. Moreover, we found that the rate of HF increased with rising RC, suggesting a potential role of RC in the HF progression after MINOCA. Taken together, these data confirm the previous evidence on the role of RC in ASCVD and support the incremental value of RC for risk prediction in MINOCA.

Not only as a prognostic marker, RC may also serve as a potential therapeutic target for intensified management and better prognosis. A recent study estimated that lowering RC by 32 mg/dL reduced recurrent MACEs by 20% in secondary prevention.[41] Another study showed that intensive lipid-lowering therapy among patients with higher RC was of additional cardiovascular benefits.[42] Currently, several strategies have been proposed to lower RC levels, including PCSK9 inhibitors, n-3 fatty acids, and antisense-oligonucleotide inhibitors of *ApoC-III* and *ANGPTL3* genes.[18,19] However, their long-term effects on cardiovascular outcomes remain to be verified. Given that RC may modify ASCVD risk beyond the atherogenic burden related to LDL-C, a tailored treatment targeting RC is promising, particularly in subjects with high RC even when LDL-C targets are reached. Future randomized trials are needed to answer whether an RC-targeted strategy in combination with statin is superior to an intensive LDL-C lowering strategy.

Limitations

Some limitations should be acknowledged. First, the sample size and event numbers are limited because of the single-center design of our study and the relatively low incidence of cardiovascular events in MINOCA population. We focused on the combined outcomes instead of hard end points only given that the number of each event may not reach the required number of statistical significance. Future larger-scale studies are needed to validate our findings. Besides, selection bias may exist in our cohort and nationwide registry studies of MINOCA may be more representative. Second, as with all observational studies, we cannot conclude a causal relationship between RC and cardiovascular outcomes after MINOCA. Also, we cannot exclude the possibility of residual confounding despite the multivariate adjustment and subgroup analyses. Although we have considered multiple confounders, we did not assess all the metabolic factors. Third, we did not capture the exact etiologies for each patient. The prognostic value of RC in different phenotypes of MINOCA needs further investigation. Fourth, the RC levels were calculated but not directly measured. Whether calculated versus directly measured RC had a similar discrimination of MACEs should be further verified. In addition, RC levels were assessed only at baseline. The on-treatment RC and its fluctuation pattern may be more clinically significant.

CONCLUSIONS

Elevated RC was associated with an increased risk of MACE in patients with MINOCA. In daily practice, assessment of RC may improve risk stratification and further facilitate decision making in the real-world management of MINOCA. Our data also provide a rationale for taking RC as a preferential antiatherogenic target. Randomized controlled trials with hard end points are warranted to identify the benefit of targeted RC-lowering treatments in this population, particularly when LDL-C targets have been achieved.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S6
Figures S1–S4

REFERENCES

1. Beltrame JF. Assessing patients with myocardial infarction and nonobstructed coronary arteries (MINOCA). *J Intern Med*. 2013;273:182–185. doi: 10.1111/j.1365-2796.2012.02591.x
2. Niccoli G, Scalone G, Crea F. Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management. *Eur Heart J*. 2015;36:475–481. doi: 10.1093/eurheartj/ehu469
3. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation*. 2015;131:861–870. doi: 10.1161/CIRCULATIONAHA.114.011201
4. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, De Caterina R, Zimarino M, Roffi M, Kjeldsen K, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. *Eur Heart J*. 2017;38:143–153. doi: 10.1093/eurheartj/ehw149
5. Planer D, Mehran R, Ohman EM, White HD, Newman JD, Xu K, Stone GW. Prognosis of patients with non–ST-segment–elevation myocardial infarction and nonobstructive coronary artery disease: propensity-matched analysis from the Acute Catheterization and Urgent Intervention Triage Strategy trial. *Circ Cardiovasc Interv*. 2014;7:285–293. doi: 10.1161/CIRCINTERVENTIONS.113.000606
6. Andersson HB, Pedersen F, Engstrøm T, Helqvist S, Jensen MK, Jørgensen E, Kelbæk H, Räder SBEW, Saunamäki K, Bates E, et al.

Long-term survival and causes of death in patients with ST-elevation acute coronary syndrome without obstructive coronary artery disease. *Eur Heart J*. 2018;39:102–110. doi: 10.1093/eurheartj/ehx491
7. Abdu FA, Liu L, Mohammed AQ, Luo Y, Xu S, Auckle R, Xu Y, Che W. Myocardial infarction with non-obstructive coronary arteries (MINOCA) in Chinese patients: clinical features, treatment and 1 year follow-up. *Int J Cardiol*. 2019;287:27–31. doi: 10.1016/j.ijcard.2019.02.036
8. Gao S, Ma W, Huang S, Lin X, Yu M. Sex-specific clinical characteristics and long-term outcomes in patients with myocardial infarction with non-obstructive coronary arteries. *Front Cardiovasc Med*. 2021;8:670401. doi: 10.3389/fcvm.2021.670401
9. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, et al.; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111–188. doi: 10.1093/eurheartj/ehz455
10. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681. doi: 10.1016/S0140-6736(10)61350-5
11. Wong ND, Zhao Y, Quek RGW, Blumenthal RS, Budoff MJ, Cushman M, Garg P, Sandfort V, Tsai M, Lopez JAG. Residual atherosclerotic cardiovascular disease risk in statin-treated adults: the Multi-Ethnic Study of Atherosclerosis. *J Clin Lipidol*. 2017;11:1223–1233. doi: 10.1016/j.jacl.2017.06.015
12. Joshi PH, Martin SS, Blumenthal RS. The remnants of residual risk. *J Am Coll Cardiol*. 2015;65:2276–2278. doi: 10.1016/j.jacc.2015.03.543
13. Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, Wallendszus K, Craig M, Jiang L, Collins R, et al. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014;371:203–212. doi: 10.1056/NEJMoa1300955
14. Lawler PR, Akinkuolie AO, Chu AY, Shah SH, Kraus WE, Craig D, Padmanabhan L, Glynn RJ, Ridker PM, Chasman DI, et al. Atherogenic lipoprotein determinants of cardiovascular disease and residual risk among individuals with low low-density lipoprotein cholesterol. *J Am Heart Assoc*. 2017;6:e005549. doi: 10.1161/JAHA.117.005549
15. Chapman MJ, Ginsberg HN, Amarenco P, Andreotti F, Borén J, Catapano AL, Descamps OS, Fisher E, Kovanen PT, Kuivenhoven JA, et al. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J*. 2011;32:1345–1361. doi: 10.1093/eurheartj/ehr112
16. Twickler TB, Dallinga-Thie GM, Cohn JS, Chapman MJ. Elevated remnant-like particle cholesterol concentration: a characteristic feature of the atherogenic lipoprotein phenotype. *Circulation*. 2004;109:1918–1925. doi: 10.1161/01.CIR.0000125278.58527.F3
17. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet*. 2014;384:626–635. doi: 10.1016/S0140-6736(14)61177-6
18. Varbo A, Benn M, Nordestgaard BG. Remnant cholesterol as a cause of ischemic heart disease: evidence, definition, measurement, atherogenicity, high risk patients, and present and future treatment. *Pharmacol Ther*. 2014;141:358–367. doi: 10.1016/j.pharmthera.2013.11.008
19. Sandesara PB, Virani SS, Fazio S, Shapiro MD. The forgotten lipids: triglycerides, remnant cholesterol, and atherosclerotic cardiovascular disease risk. *Endocr Rev*. 2019;40:537–557. doi: 10.1210/er.2018-00184
20. Tabas I, Williams KJ, Borén J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications. *Circulation*. 2007;116:1832–1844. doi: 10.1161/CIRCULATIONAHA.106.676890
21. Chait A, Ginsberg HN, Vaisar T, Heinecke JW, Goldberg IJ, Bornfeldt KE. Remnants of the triglyceride-rich lipoproteins, diabetes, and cardiovascular disease. *Diabetes*. 2020;69:508–516. doi: 10.2337/dbi19-0007
22. Varbo A, Benn M, Tybjærg-Hansen A, Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. *J Am Coll Cardiol*. 2013;61:427–436. doi: 10.1016/j.jacc.2012.08.1026
23. Jørgensen AB, Frikke-Schmidt R, West AS, Grande P, Nordestgaard BG, Tybjærg-Hansen A. Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. *Eur Heart J*. 2013;34:1826–1833. doi: 10.1093/eurheartj/ehs431
24. Quispe R, Martin SS, Michos ED, Lamba I, Blumenthal RS, Saeed A, Lima J, Puri R, Nomura S, Tsai M, et al. Remnant cholesterol predicts cardiovascular disease beyond LDL and ApoB: a primary prevention study. *Eur Heart J*. 2021;42:4324–4332. doi: 10.1093/eurheartj/ehab432
25. Castañer O, Pintó X, Subirana I, Amor AJ, Ros E, Hernáez Á, Martínez-González MÁ, Corella D, Salas-Salvadó J, Estruch R, et al. Remnant cholesterol, not LDL cholesterol, is associated with incident cardiovascular disease. *J Am Coll Cardiol*. 2020;76:2712–2724. doi: 10.1016/j.jacc.2020.10.008
26. Aday AW, Lawler PR, Cook NR, Ridker PM, Mora S, Pradhan AD. Lipoprotein particle profiles, standard lipids, and peripheral artery disease incidence. *Circulation*. 2018;138:2330–2341. doi: 10.1161/CIRCULATIONAHA.118.035432
27. Joshi PH, Khokhar AA, Massaro JM, Lirette ST, Griswold ME, Martin SS, Blaha MJ, Kulkarni KR, Correa A, D'Agostino RB, et al. Remnant lipoprotein cholesterol and incident coronary heart disease: the Jackson Heart and Framingham offspring cohort studies. *J Am Heart Assoc*. 2016;5:e002765. doi: 10.1161/JAHA.115.002765
28. Elshazly MB, Mani P, Nissen S, Brennan DM, Clark D, Martin S, Jones SR, Quispe R, Donnellan E, Nicholls SJ, et al. Remnant cholesterol, coronary atheroma progression and clinical events in statin-treated patients with coronary artery disease. *Eur J Prev Cardiol*. 2020;27:1091–1100. doi: 10.1177/2047487319887578
29. Zhao Q, Zhang TY, Cheng YJ, Ma Y, Xu YK, Yang JQ, Zhou YJ. Prognostic impact of estimated remnant-like particle cholesterol in patients with differing glycometabolic status: an observational cohort study from China. *Lipids Health Dis*. 2020;19:179. doi: 10.1186/s12944-020-01355-y
30. Cao Y-X, Zhang H-W, Jin J-L, Liu H-H, Zhang Y, Gao Y, Guo Y-L, Wu N-Q, Hua QI, Li Y-F, et al. The longitudinal association of remnant cholesterol with cardiovascular outcomes in patients with diabetes and pre-diabetes. *Cardiovasc Diabetol*. 2020;19:104. doi: 10.1186/s12933-020-01076-7
31. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol*. 2018;72:2231–2264. doi: 10.1016/j.jacc.2018.08.1038
32. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, et al.; ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267–315. doi: 10.1093/eurheartj/ehv320
33. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, et al.; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177. doi: 10.1093/eurheartj/ehx393
34. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2018. *Diabetes Care*. 2018;41:S13–S27. doi: 10.2337/dc18-S002
35. Rabar S, Harker M, O'Flynn N, Wierzbicki AS; Guideline Development Group. Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. *BMJ*. 2014;349:g4356. doi: 10.1136/bmj.g4356
36. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, Solomon SD, Marler JR, Teerlink JR, Farb A, et al.; Standardized Data Collection for Cardiovascular Trials Initiative (SCTI). 2017 cardiovascular and stroke endpoint definitions for clinical trials. *J Am Coll Cardiol*. 2018;71:1021–1034. doi: 10.1016/j.jacc.2017.12.048
37. Ma H, Bandos AI, Rockette HE, Gur D. On use of partial area under the ROC curve for evaluation of diagnostic performance. *Stat Med*. 2013;32:3449–3458. doi:10.1002/sim.5777
38. Delong ER, Delong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–845. doi: 10.2307/2531595
39. Doi H, Kugiyama K, Oka H, Sugiyama S, Ogata N, Koide SI, Nakamura SI, Yasue H. Remnant lipoproteins induce proatherothrombogenic molecules in endothelial cells through a redox-sensitive mechanism. *Circulation*. 2000;102:670–676. doi: 10.1161/01.CIR.102.6.670
40. Bernelot Moens SJ, Verweij SL, Schnitzler JG, Stiekema LCA, Bos M, Langsted A, Kuijk C, Bekkering S, Voermans C, Verberne HJ, et al. Remnant cholesterol elicits arterial wall inflammation and a multilevel

cellular immune response in humans. *Arterioscler Thromb Vasc Biol*. 2017;37:969–975. doi: 10.1161/ATVBAHA.116.308834

41. Langsted A, Madsen CM, Nordestgaard BG. Contribution of remnant cholesterol to cardiovascular risk. *J Intern Med*. 2020;288:116–127. doi: 10.1111/joim.13059

42. Vallejo-Vaz AJ, Fayyad R, Boekholdt SM, Hovingh GK, Kastelein JJ, Melamed S, Barter P, Waters DD, Ray KK. Triglyceride-rich lipoprotein cholesterol and risk of cardiovascular events among patients receiving statin therapy in the TNT trial. *Circulation*. 2018;138:770–781. doi: 10.1161/CIRCULATIONAHA.117.032318

SUPPLEMENTAL MATERIAL

Table S1. Correlation of remnant cholesterol with other lipid parameters

Variable	Coefficient of correlation (Pearson)	Coefficient of correlation (Spearman)
LDL-C	0.188	0.240
HDL-C	-0.350	-0.410
ApoA	-0.078	-0.115
ApoB	0.415	0.458
Triglyceride	0.812	0.773

Coefficient of correlation was interpreted as negligible (<0.3), small (0.3-0.5), moderate (0.5-0.8) or strong (≥0.8). LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, ApoA: apolipoprotein A, ApoB: apolipoprotein B.

Table S2. Baseline characteristics in patients with or without MACE

Variable	All MINOCA (n=1179)	With MACE (n=168)	Without MACE (n=1011)	P value
Female, n(%)	312 (26.5%)	48 (28.5%)	264 (26.1%)	0.504
Age, years	55.7±11.8	57.7±13.2	55.3±11.5	0.014
BMI, kg/m^2	25.4±3.7	25.4±3.8	25.4±3.7	0.924
STEMI, n(%)	475 (40.2%)	88 (52.3%)	387 (38.2%)	0.001
Past history				
Hypertension	630 (53.4%)	93 (55.3%)	537 (53.1%)	0.590
Diabetes	187 (15.9%)	41 (24.4%)	146 (14.4%)	0.001
Dyslipidemia	686 (58.2%)	105 (62.5%)	581 (57.4%)	0.221
Previous MI	58 (4.9%)	9 (5.3%)	49 (4.84%)	0.114
Killip class≥2, n(%)	89 (7.5%)	21 (12.5%)	68 (6.7%)	0.001
LVEF (%)	60.5±7.5	53.0±11.7	61.7±5.6	<0.001
Laboratory tests				
Fasting glucose, mmol/L	5.98±0.98	5.98±1.91	5.66±1.66	0.021
Total cholesterol, mmol/L	3.92±0.91	3.92±0.95	3.92±0.90	0.952
Triglyceride, mmol/L	1.44 (1.05, 2.00)	1.53 (1.13, 2.32)	1.42 (1.04, 1.98)	0.034
LDL-C, mmol/L	2.29±0.76	2.32±0.78	2.28±0.75	0.498
HDL-C, mmol/L	1.08±0.29	1.05±0.28	1.08±0.29	0.148
RC, mmol/L	0.56±0.34	0.62±0.36	0.54±0.33	0.005
ApoA, g/L	1.26±0.25	1.23±0.24	1.27±0.25	0.054
ApoB, g/L	0.77±0.23	0.78±0.23	0.77±0.23	0.755
Creatinine, μmol/L	80.1±17.8	84.3±22.4	79.4±16.9	0.001
hs-CRP, mg/L	2.20 (1.03, 5.75)	2.46 (1.05, 6.38)	2.14 (1.02, 5.66)	0.212
NT-proBNP, pg/mL	372 (112, 683)	578 (214, 858)	369 (107, 664)	<0.001
Peak TnI, ng/mL	3.24 (0.72, 6.51)	4.32 (0.94, 8.13)	3.13 (0.64, 6.27)	<0.001

Patients were divided based on the occurrence of major adverse cardiovascular events (MACE). BMI: body mass index, STEMI: ST-segment elevation myocardial infarction,

LVEF: left ventricular ejection fraction, LDL-C: low density lipoprotein-cholesterol, HDL-C: high-density lipoprotein cholesterol, RC: remnant cholesterol, ApoA: apolipoprotein A, ApoB: apolipoprotein B, hs-CRP: high-sensitive C-reactive protein, NT-proBNP: N-terminal pro-B-type natriuretic peptide, TnI: Troponin I.

Table S3. Potential risk factors of MACE in MINOCA patients

Variable	Univariate Cox analysis		Multivariate Cox analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.06 (1.02-1.11)	0.004	1.02 (1.01-1.04)	0.012
Female	1.16 (0.83-1.62)	0.372	NA	…
BMI	0.99 (0.95-1.03)	0.893	NA	…
STEMI	1.42 (1.05-1.92)	0.022	1.22 (0.87-1.71)	0.237
Hypertension	1.09 (0.80-1.47)	0.575	NA	…
Diabetes	1.86 (1.31-2.65)	0.001	1.50 (1.04-2.16)	0.030
Dyslipidemia	1.18 (0.86-1.61)	0.300	NA	…
Previous MI	1.01 (0.51-1.99)	0.981	NA	…
LVEF	0.92 (0.91-0.93)	<0.001	0.96 (0.93-0.99)	0.012
ln (NT-proBNP)	1.39 (1.22-1.58)	<0.001	1.17 (0.66-2.06)	0.587
Peak TnI	1.02 (1.01-1.03)	0.015	1.01 (0.99-1.02)	0.223
Creatinine	1.04 (1.02-1.06)	<0.001	1.03 (1.02-1.04)	0.035
RC	1.81 (1.29-2.55)	0.001	1.49 (1.03-2.16)	0.032

Statistically significant variables with univariate Cox analysis were further enrolled in the multivariate model. Hazard ratio (HR) for per 1 standard deviation increased in each continuous variable. NT-proBNP was natural logarithmically transformed to ln (NT-proBNP). NA: not assessed, CI: confidence interval, BMI: body mass index, STEMI: ST-segment elevation myocardial infarction, LVEF: left ventricular ejection fraction, NT-proBNP: N-terminal pro-B-type natriuretic peptide, TnI: Troponin I, RC: remnant cholesterol.

Table S4. Effect of RC on MACE risk after adjustment for other lipid indexes

Model	Cox analysis	
	HR (95% CI)	P value
Effect of RC on MACE risk, unadjusted	1.81 (1.29-2.55)	0.001
Effect of RC on MACE risk, adjusted for		
Baseline model +LDL-C	1.62 (1.14-2.31)	0.007
Baseline model +HDL-C	1.59 (1.10-2.32)	0.013
Baseline model +ApoA	1.61 (1.13-2.30)	0.008
Baseline model +ApoB	1.85 (1.30-2.62)	0.001
Baseline model +Triglyceride	5.73 (3.26-10.06)	<0.001
Baseline model +LDL-C + HDL-C +ApoA +ApoB +Triglyceride	8.23 (4.32-13.67)	<0.001

Baseline model included age, sex, BMI, MI type (NSTEMI or STEMI), hypertension, diabetes and dyslipidemia. LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, ApoA: apolipoprotein A, ApoB: apolipoprotein B, RC: remnant cholesterol, HR: hazard ratio, CI: confidence interval.

Table S5. Association of each lipid parameter with MACE risk

Variable	Unadjusted		Adjusted	
	HR (95% CI)	P value	HR (95% CI)	P value
LDL-C	1.04 (0.86-1.26)	0.671	NA	…
HDL-C	0.74 (0.43-1.27)	0.275	NA	…
ApoA	0.59 (0.32-1.09)	0.097	NA	…
ApoB	1.05 (0.93-1.43)	0.385	NA	…
Triglyceride	1.33 (1.04-1.69)	0.020	1.11 (1.02-1.30)	0.043
RC	1.81 (1.29-2.55)	0.001	1.61 (1.12-2.31)	0.009

Statistically significant variables with univariate Cox analysis were further assessed in the multivariate Cox model including age, sex, BMI, MI type (NSTEMI or STEMI), hypertension, diabetes and dyslipidemia. Hazard ratio (HR) for per 1 standard deviation increased in each continuous variable. LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, ApoA: apolipoprotein A, ApoB: apolipoprotein B, RC: remnant cholesterol, CI: confidence interval, NA: not assessed.

Table S6. Hard endpoint analysis showing the relationship between RC levels and event risk

Hard endpoint	Event rate (lower vs. higher RC), p value	Cox regression analysis (RC as categorical variable, lower RC as reference)		Cox regression analysis (RC as continuous variable, for per 1 SD increase in RC)	
		HR (95% CI)	P value	HR (95% CI)	P value
All-cause death	1.0% vs. 2.0%, p=0.157	2.01 (0.74-5.39)	0.165	1.86 (0.67-5.16)	0.233
Nonfatal MI	3.2% vs. 3.7%, p=0.645	1.04 (0.60-1.76)	0.761	1.49 (0.68-3.24)	0.316
Nonfatal stroke	0.8% vs. 1.1%, p=0.568	1.39 (0.44-4.42)	0.569	1.42 (0.30-6.73)	0.657
Revascularization	2.5% vs. 5.2%, p=0.017	2.11 (1.12-3.96)	0.019	2.35 (1.26-4.37)	0.007
Death, MI or stroke	5.1% vs. 6.9%, p=0.105	1.39 (0.87-2.26)	0.137	1.56 (0.85-2.84)	0.143
Death, MI, stroke or revascularization	6.8% vs. 10.4%, p=0.024	1.54 (1.04-2.30)	0.031	1.75 (1.14-2.70)	0.011

Incidence of hard endpoint events were compared among patients with higher or lower median level (0.49 mmol/L) of remnant cholesterol (RC). Multivariate Cox regression analyses were used to evaluate the effect of RC levels on event risk (RC as categorical variable: lower RC group as reference; RC as continuous variable: for per 1 SD increase in RC). Adjusted model included age, sex, BMI, MI type (NSTEMI or STEMI), hypertension, diabetes and dyslipidemia. HR: hazard ratio, CI: confidence interval.

Figure S1. Distribution of the remnant cholesterol

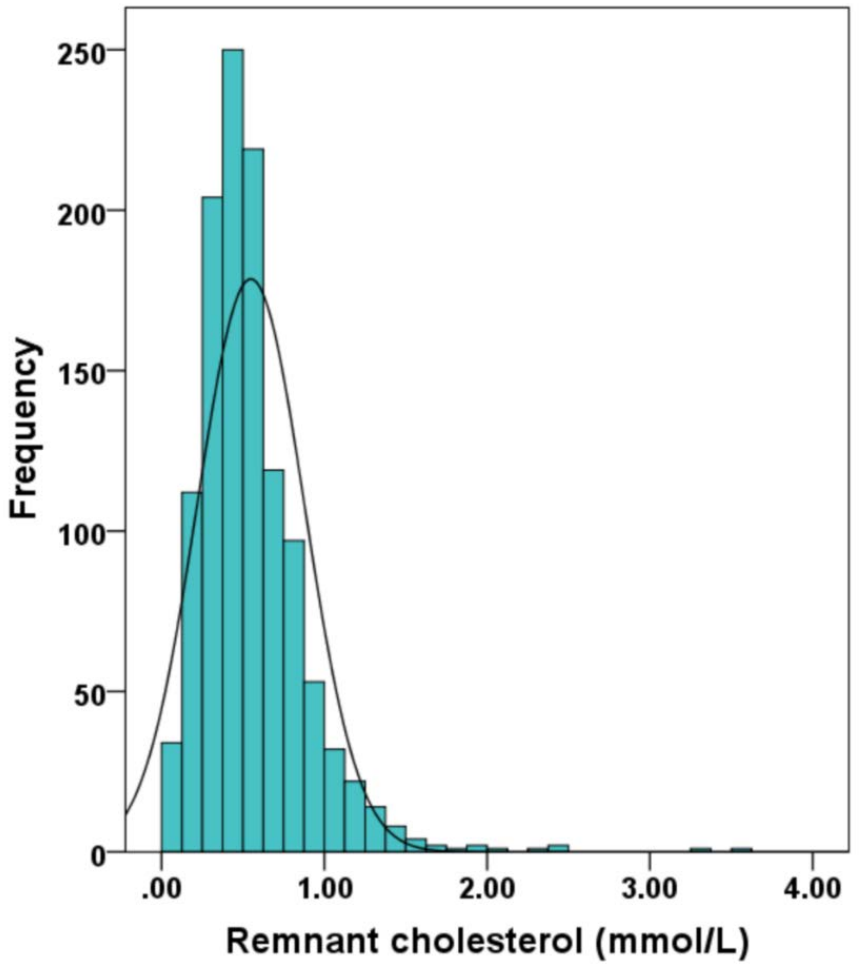


Figure S2. A strong linear correlation between RC and triglyceride

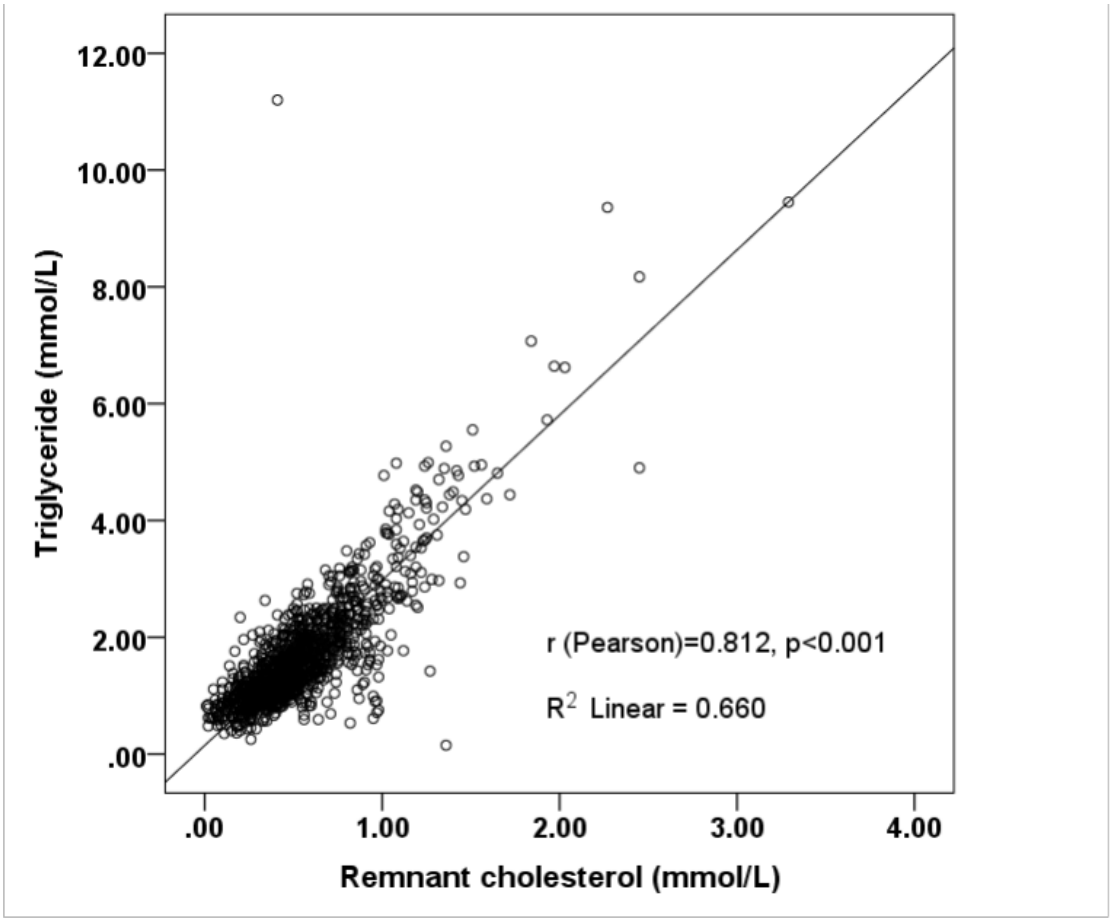


Figure S3. Levels of RC in patients with different glucometabolic status

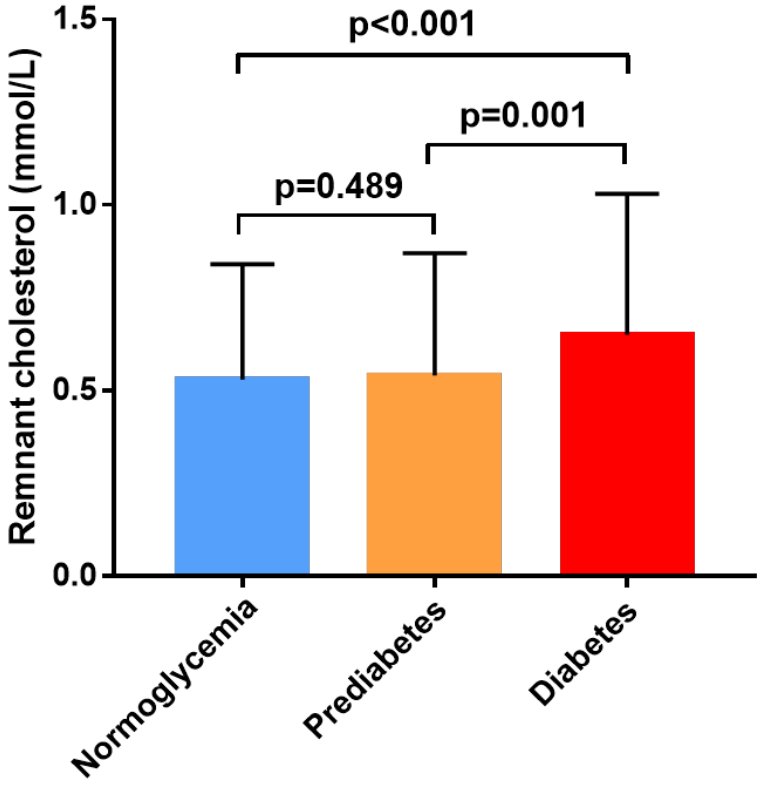
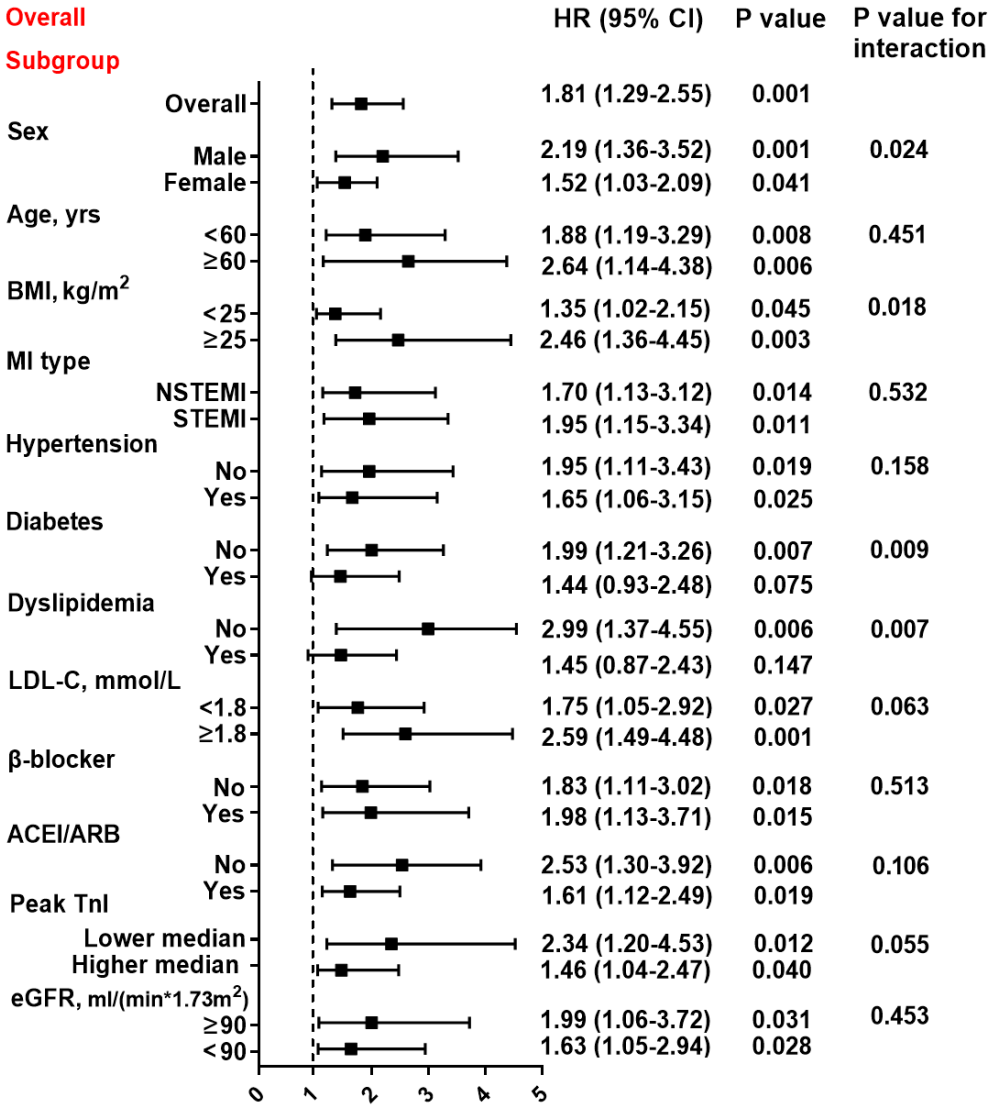


Figure S4. Association between the RC level and risk of MACE in subgroups



Subgroup analysis for association between the remnant cholesterol (RC) level and MACE risk in patients stratified by the age, sex, MI type, BMI, hypertension, diabetes, dyslipidemia, LDL-C level, use of β-blocker, use of ACEI/ARB, peak TnI and eGFR values. Hazard ratio (HR) was calculated by the univariate Cox regression analysis. HR for per 1 standard deviation increased in RC level. P value for interaction was calculated. Vertical dotted line indicated the HR value of 1. BMI: body mass index, STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST-segment elevation myocardial infarction, LDL-C: low-density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate.