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Remnant cholesterol predicts risk of recurrent thrombosis beyond LDL-cholesterol in patients with antiphospholipid syndrome

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Abstract

Background Antiphospholipid syndrome (APS) is notably linked to thrombotic events, particularly cardiovascular disease (CVD). The role of remnant cholesterol (RC) in predicting CVD risk is established, yet its relationship with thrombotic risk in APS patients remains to be elucidated. This study aims to assess the association between RC and recurrent thrombotic risk in patients with APS.

Methods A prospective analysis was conducted based on a cohort of APS patients who met the 2006 Sydney revised classification criteria. Thrombotic risks associated with varying levels of RC were evaluated using Kaplan–Meier survival analysis and Cox proportional hazards regression models. Mendelian randomization (MR) was applied to examine the causal link between RC and different types of thrombotic events.

Results A total of 325 patients with APS were enrolled in this study. Over a median follow-up of 35 months, 51 patients experienced thrombotic events, including 24 venous, 19 arterial, and 16 microvascular incidents. Patients with RC levels above 0.60 mmol/L exhibited significantly higher risks, with multivariable-adjusted hazard ratio (and 95% confidence interval) for all-cause, venous, arterial thrombosis, and microvascular disease being 5.05 (2.23–11.41), 6.34 (1.71–23.54), 3.79 (1.00–14.32), and 4.36 (1.08–17.58), respectively. Notably, elevated RC remained a significant thrombotic risk factor even in patients with normal conventional lipid profiles. MR analysis revealed a significant causal association between RC and arterial thrombosis, but not venous thrombosis.

Conclusions Elevated RC is linked to a substantial increase in the risk of thrombotic events in APS patients. These findings suggest that RC could be a valuable marker for thrombotic risk in this population and a potential target for therapeutic intervention.

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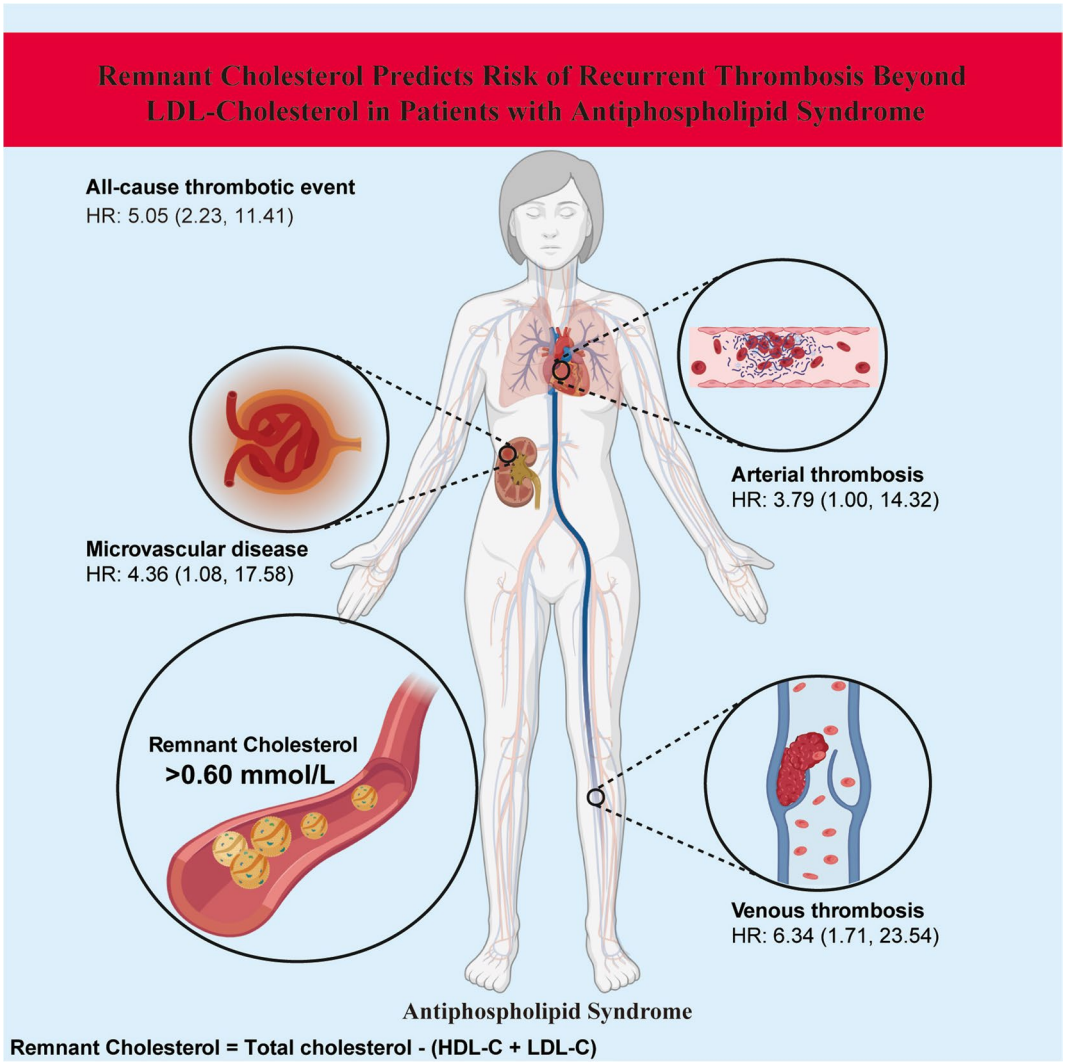
Highlights

1. A more than 5-fold increase in thrombotic risk, including arterial, venous, and microvascular events, is linked to individuals with RC levels>0.60 mmol/L in APS.
2. Elevated RC remains a significant risk factor even in patients with normal conventional lipid indices (LDL-C, TC, TG, and non-HDL-C).
3. Through MR analysis, there was a significant causal relationship between RC and AT in the general population, but not with VT, suggesting the complexity of the pathogenesis of VT in patients with APS.
4. Patients with APS treated with hydroxychloroquine have lower RC levels, and hydroxychloroquine may have the potential to reduce RC.

Keywords Antiphospholipid syndrome, Remnant cholesterol, Thrombotic risk, Low-density lipoprotein cholesterol, Cardiovascular disease

Graphical Abstract



Background

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by thrombotic and/or obstetric events in individuals with persistent antiphospholipid antibodies (aPLs), with an estimated prevalence of 40 to 50 cases per 100,000 people [1, 2]. APS patients are particularly prone to thrombotic events, including venous, arterial, or microvascular thrombosis, leading to an increased risk of cardiovascular events like myocardial infarction (MI) and ischemic stroke (IS). These events significantly amplify the severity and mortality associated with APS, imposing a substantial burden on the patients [3, 4].

The etiology of thrombosis in APS, although incompletely understood, involves a "second-hit" theory. The persistent presence of aPLs, including lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti-beta2 glycoprotein I (aβ2GPI) antibodies, constitutes the "first hit", precipitating a prethrombotic state [2]. This risk is exacerbated by a "second hit" from factors like infection, pregnancy, or traditional cardiovascular risk factors, including dyslipidemia [4]. Despite appropriate anticoagulant or aspirin therapy, recurrent thrombotic events remain a challenge in some APS patients [5]. Identifying potential modifiable factors influencing thrombosis occurrence in APS patients holds great significance for enhancing APS prognosis [6].

Dyslipidemia, a notable thrombotic risk factor, is common in APS patients yet remains underexplored [7]. Previous studies have shown that abnormal lipid metabolism, particularly low-density lipoprotein cholesterol (LDL-C), significantly contributes to thrombotic events like MI and IS [3]. Although LDL-C fails to fully account for thrombotic risk in patients with APS, dyslipidemia has been recognized as an independent predictor of recurrent thrombosis in APS [8]. Recent studies highlighted the significance of high remnant cholesterol (RC), which includes cholesterol carried in chylomicron remnants, very-low-density lipoproteins (VLDLs), and intermediate-density lipoproteins, in increasing the risk of MI and IS in the general population [9–11]. Additionally, both epidemiological and genetic studies confirmed RC as an independent predictor of cardiovascular events [12–14]. However, the correlation between RC and thrombotic risk in APS, particularly concerning different types of thrombosis, remains to be elucidated.

Addressing this gap, our study is the first prospective observational analysis within an APS cohort assessing the association between RC levels and thrombotic events. This study also evaluates RC's predictive efficacy for thrombosis against other lipid markers and employs mendelian randomization (MR) to explore the causal relationship between RC and thrombotic events.

Methods

Study population

This is a study based on a prospective APS cohort at Peking Union Medical College Hospital (PUMCH). We initially screened 526 patients presenting between June 2012 and August 2023 with at least one positive aPL test and meeting one clinical criterion indicative of APS. Of these, 353 met the 2006 Sydney revised classification criteria [15]. After excluding individuals without lipid data ($n = 16$) and lacking follow-up ($n = 12$), 325 APS patients were included in the final analysis (Fig. 1). This study was approved by the Medical Ethics Committee of PUMCH (HS- 3309) and informed consent was obtained from all participants.

Covariates assessment

Lipid tests were collected at the first evaluation after diagnosis of APS. All conventional lipid profiles including total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) were collected after an overnight fast and directly measured using the Automatic Biochemical Analyzer (AU5800, Beckman Coulter, Brea, CA). RC was computed as TC minus the sum of LDL-C and HDL-C according to the previously reported algorithm [10], non-HDL-C was calculated by subtracting HDL-C from TC [16]. The APS patient cohort was characterized based on RC tertiles. LA testing and definition of positivity adhered to the International Society of Thrombosis and Hemostasis (ISTH) guidelines [17], and aCL and aβ2GPI antibodies were detected by enzyme-linked immunosorbent assay (ELISA) (QUANTA Lite® ELISAs, INOVA Diagnostics, San Diego, CA, USA). Moderate titers were defined as values between 40 and 79 units, and high titers were defined as values of ≥ 80 units. Sociodemographic data collected included age, gender, smoking status (current smoker, former smoker, never smoker), and medical history (hypertension, diabetes, hyperlipidemia, chronic kidney disease (CKD), cancer, and systemic lupus erythematosus (SLE), and APS duration). Baseline examination and laboratory data encompassed body mass index (BMI, kg/m^2), platelet count, and C-reactive protein (CRP). SLE was diagnosed according to the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria [18].

Outcome measures

This study's primary outcomes were thrombotic events, categorized into venous, arterial thrombosis, and microvascular disease, while all-cause thrombotic risk was defined as the risk that a patient had experienced at least one of these three events at follow-up. Venous

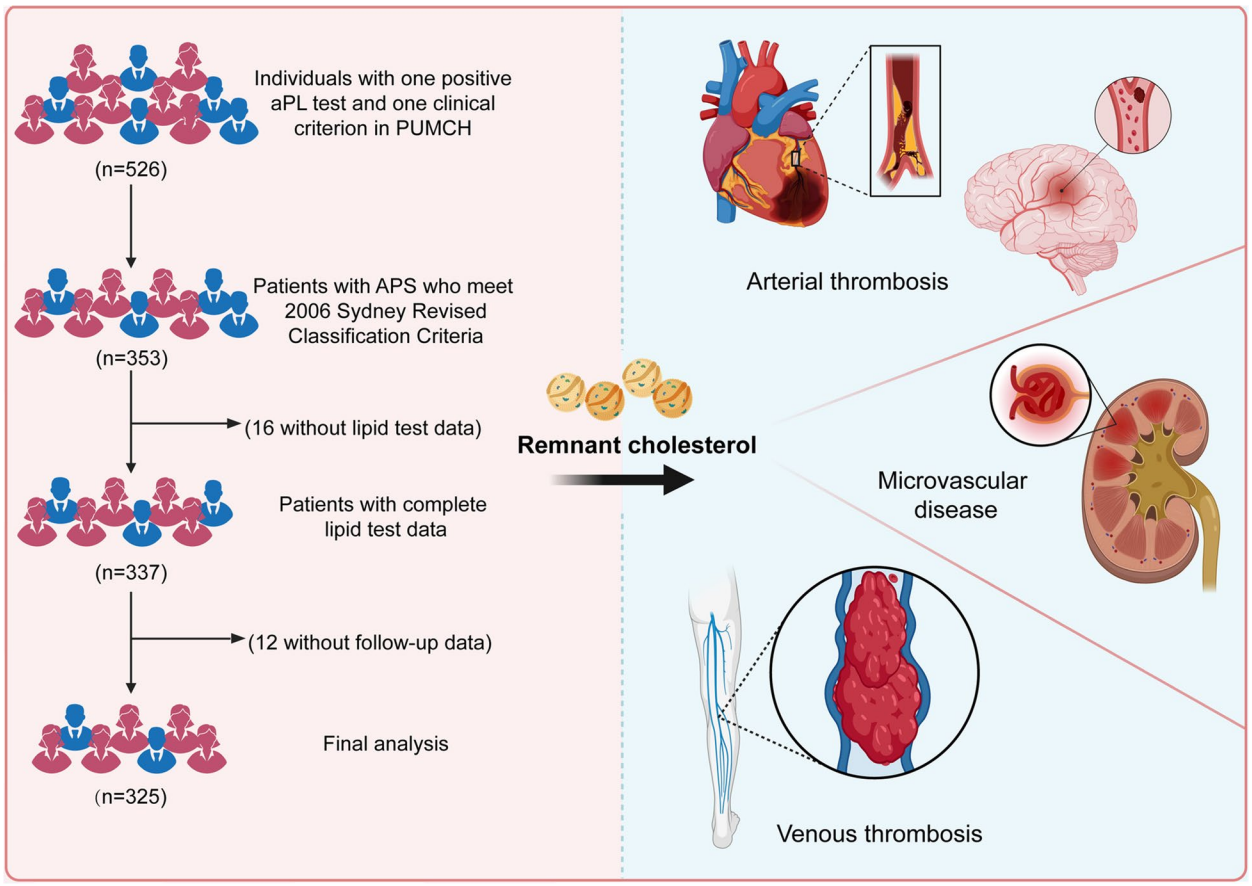


Fig. 1 Study Inclusion Flowchart. The flowchart of this study. A total of 526 individuals with at least one positive aPL test and meeting one clinical criterion indicative of APS were enrolled. Of these, 353 met the 2006 Sydney revised classification criteria. After excluding individuals without lipid data ($n = 16$) and lacking follow-up ($n = 12$), 325 APS patients were included in the final analysis. Created with BioRender.com. APS = antiphospholipid syndrome; aPL = antiphospholipid antibodies; PUMCH = Peking Union Medical College Hospital

thrombosis encompassed extremity venous thrombosis, carotid/subclavian venous thrombosis, chronic thromboembolic pulmonary hypertension (CTEPH), pulmonary embolism, visceral venous thrombosis, cerebral venous sinus thrombosis, and retinal venous thrombosis. Arterial thrombosis was defined as MI, stroke/transient ischemic attack (TIA), extremity artery thrombosis, carotid/subclavian/vertebral artery thrombosis, visceral artery thrombosis, visceral infarction, and retinal artery thrombosis. Microvascular disease was defined as livedoid vasculopathy, aPL nephropathy, pulmonary hemorrhage, myocardial disease, adrenal hemorrhage or microthrombosis [19–23]. Follow-up began from the initiation of lipid testing and continued until thrombotic event occurrence or the final follow-up date.

Statistical analysis

Continuous variables were presented as means ± standard deviations (SD) and analyzed using Analysis of Variance (ANOVA), while categorical variables were described as percentages and evaluated using chi-square tests. The impact of varying RC levels on thrombosis events over time was visualized using Kaplan–Meier survival curves and differences across groups were tested using the log-rank test. To assess the association between RC levels and thrombotic risks (all-cause, venous, arterial, and microvascular), we employed Cox proportional hazards models in three stages of adjustment: Model 1 was unadjusted; Model 2 adjusted for age and sex; and the selection of adjustment variables in Model 3 was informed by Directed acyclic graphs (DAGs) (Supplementary Fig. 1) [24], and adjustment variables included age, sex, BMI, smoking history (yes, no), hyperlipidemia, diabetes, use of statin, hydroxychloroquine, glucocorticoids, immunosuppressant. Stratified analyses of all-cause thrombosis outcome were conducted based on sex (male or female), age (< 40 years or ≥ 40 years), BMI (<

25.00 or ≥25.00), SLE (yes or no), smoking history (yes, no), and APS disease duration (< 3 years or ≥3 years).

Several sensitivity analyses were performed to verify the robustness of our findings. First, we further investigated the association between RC and thrombotic risk in patients with thrombotic APS (Supplementary Table 2). Second, further adjustments were made in multivariable modeling given the potential impact of anticoagulation and antiplatelet therapy on outcomes. Third, further adjusted for triple aPLs positivity because it may lead to a higher risk of thrombosis. Fourth, further adjusted for history of hypertension, SLE (Supplementary Table 3). The *P* values for the product terms between RC levels and stratification variables were used to estimate the significance of interactions. Statistical analyses were performed with R software (version 4.2.0). A two-sided $P < 0.05$ was considered statistically significant.

Mendelian Randomization (MR) analysis

This study followed the STROBE-MR (strengthening the reporting of observational studies in epidemiology using mendelian randomisation) guidelines. This article adheres to the STROBE-MR checklist for reporting (Supplementary Table 4). We employed the TwoSampleMR R package (V.5.1.0) for MR analyses to evaluate causal relationship between RC and thrombosis. Single nucleotide polymorphisms (SNPs) associated with RC were selected based on a *P*-value threshold of less than 5× 10^− 8. Clumping of these SNPs were performed using European sample data from the 1000 Genomes Project, with a clumping window of 10,000 k and an r^2 threshold of less than 0.001. PhenoScanner V2 was used to identify instrumental variable-related phenotypes, and SNPs associated with arterial thrombosis and venous thrombosis were excluded. The MR estimates were calculated using multiple methods (MR Egger, Weighted median, Inverse variance weighted, Inverse variance weighted (multiplicative random effects), Inverse variance weighted (fixed effects), Weighted mode). We also performed horizontal pleiotropy (MR-Egger intercept) to test whether there is horizontal pleiotropy in multiple instrumental variables (IVs), and if the intercept term is far away from 0, it indicates that there is horizontal pleiotropy. In addition, heterogeneity was used to examine the differences between the individual IVs, and if the differences between the different IVs are large, the heterogeneity of these IVs is large and a multiplicative random effects model would be used. In total, we recruited several recent large GWAS cohort datasets for MR analysis, including three RC cohort as exposure and six thrombosis cohorts as outcome, to confirm the accuracy of the analysis. The datasets used in this study were listed in Supplementary Table 5. For MR analysis, we considered *P*-values < 0.05 as statistically significant.

Results

Baseline characteristics

A total of 325 patients with APS (36.85 ± 13.35 years old; 63.08% female) were enrolled in this study. Serum RC levels of the participants ranged from 0.15 to 1.69 mmol/L. Based on RC tertiles, patients were categorized into three groups (T1: ≤0.45; T2: >0.45, ≤0.60; T3: >0.60, mmol/L), setting RC >0.60 mmol/L as the threshold for abnormally high RC. Baseline characteristics revealed that history of hyperlipidemia and hypertension, elevated levels of TC, HDL-C, LDL-C and TG, and immunosuppressant treatment were associated with higher baseline RC level (Table 1). Conversely, hydroxychloroquine treatment correlated with lower RC levels. Besides, higher RC levels seemed to be associated with elevated CRP.

Association of RC with thrombotic risk in patients with APS

Over a median follow-up period of 35 months, 51 patients experienced 59 thrombotic events, comprising 24 venous, 19 arterial, and 16 microvascular events (Table 2). Kaplan–Meier survival analyses revealed that patients with higher RC levels experienced a markedly increased all-cause thrombotic risk than those with lower RC (log-rank $P < 0.001$, Fig. 2A). This elevated risk was consistent across various types of thrombosis: venous (log-rank $P = 0.041$, Fig. 2B), arterial (log-rank $P = 0.082$, Fig. 2C) and microvascular disease (log-rank $P = 0.013$, Fig. 2D).

In Table 2, we further evaluated the roles of RC on the risk of all-cause and cause-specific thrombosis (venous, arterial, and microvascular). Adjusting age and sex (Model 2), individuals with RC >0.60 mmol/L demonstrated a significantly higher risk of all-cause thrombosis (HR: 5.13, 95% CI: 2.32–11.36, $P < 0.01$) compared to those with RC ≤0.45 mmol/L. This trend was consistent across specific type of thrombosis, including venous (HR: 4.93, 95% CI: 1.38–17.60, $P = 0.01$), arterial (HR: 3.96, 95% CI: 1.08–14.48, $P = 0.04$), and microvascular disease (HR: 5.47, 95% CI: 1.47–20.32, $P = 0.01$), with all *P*-trend <0.05. After further adjustment for BMI, smoking history (yes, no), hyperlipidemia, diabetes, use of statin, hydroxychloroquine, glucocorticoids, and immunosuppressant (Model 3), patients with RC >0.60 mmol/L had multivariable-adjusted HRs and 95% CIs of 5.05 (2.23, 11.41) ($P < 0.01$) for all-cause thrombosis, 6.34 (1.71, 23.54) ($P < 0.01$) for venous thrombosis, 3.79 (1.00, 14.32) ($P < 0.05$) for arterial thrombosis, and 4.36 (1.08, 17.58) ($P = 0.04$) for microvascular disease, with all *P*-trend <0.05 except for arterial thrombosis (0.061) (Table 2).

Table 1 Baseline characteristics of patients with APS according to the RC tertiles

	RC Tertiles (mmol/L)				
	Total	**Tertile 1 (≤ 0.45)**	**Tertile 2 (> 0.45, ≤ 0.60)**	**Tertile 3 (> 0.60)**	***P*-value**
N (%)	325	108	113	104	
Female	205 (63.08)	68 (62.96)	70 (61.95)	67 (64.42)	0.931
Age (years)	36.85 ± 13.35	35.69 ± 14.04	36.02 ± 12.29	38.97 ± 13.59	0.143
BMI	25.08 ± 4.94	24.69 ± 4.83	25.54 ± 4.61	24.97 ± 5.37	0.426
Disease duration (years)	5.46 ± 6.45	4.84 ± 6.07	6.09 ± 7.07	5.43 ± 6.13	0.682
Secondary APS	86 (26.46)	27 (25.00)	27 (23.89)	32 (30.77)	0.474
SLE	85 (26.15)	26 (24.07)	27 (23.89)	32 (30.77)	0.430
UCTD	1 (0.31)	1 (0.93)	0 (0.00)	0 (0. 00)	0.365
Laboratory test					
TC (mmol/L)	4.12 ± 1.05	3.59 ± 0.89	4.06 ± 0.88	4.72 ± 1.07	**< 0.001**
TG (mmol/L)	1.36 ± 0.76	0.91 ± 0.33	1.23 ± 0.41	1.96 ± 0.95	**< 0.001**
HDL-C (mmol/L)	1.20 ± 0.38	1.16 ± 0.32	1.15 ± 0.31	1.28 ± 0.48	**0.017**
LDL-C (mmol/L)	2.35 ± 0.84	2.07 ± 0.78	2.38 ± 0.77	2.61 ± 0.90	**< 0.001**
CRP (mg/L)	6.47 ± 24.34	4.44 ± 14.94	5.67 ± 12.06	9.62 ± 38.74	0.08
Venous thrombosis (%)	179 (55.08)	54 (50.00)	62 (54.87)	63 (60.58)	0.301
Limb venous thrombosis	130 (40.00)	42 (38.89)	39 (34.51)	49 (47.12)	0.160
Pulmonary embolism	80 (24.62)	29 (26.85)	27 (23.89)	24 (23.08)	0.796
CTEPH	12 (3.70)	4 (3.70)	3 (2.65)	5 (4.85)	0.694
Visceral venous thrombosis	18 (5.54)	6 (5.56)	6 (5.31)	6 (5.77)	0.989
Carotid/subclavian venous thrombosis	5 (1.54)	2 (1.85)	1 (0.88)	2 (1.92)	0.783
Cerebral venous sinus thrombosis	25 (7.69)	7 (6.48)	11 (9.73)	7 (6.73)	0.600
Retinal venous thrombosis	4 (1.23)	0 (0.00)	2 (1.77)	2 (1.92)	0.363
Arterial thrombosis (%)	121 (37.23)	45 (41.67)	40 (35.40)	36 (34.62)	0.503
Myocardial infarction	19 (5.85)	9 (8.33)	4 (3.54)	6 (5.77)	0.316
Stroke/TIA	64 (19.69)	20 (18.52)	27 (23.89)	17 (16.35)	0.351
Limb artery thrombosis	23 (7.08)	13 (12.04)	4 (3.54)	7 (6.73)	0.052
Carotid/subclavian/vertebral artery thrombosis	11 (3.38)	6 (5.56)	4 (3.54)	1 (0.96)	0.180
Visceral artery thrombosis	8 (2.46)	2 (1.85)	1 (0.88)	5 (4.81)	0.156
Visceral infarction	7 (2.15)	1 (0.93)	5 (4.42)	1 (0.96)	0.120
Retinal artery thrombosis	10 (3.08)	2 (1.85)	5 (4.42)	3 (2.88)	0.537
Microvascular disease (%)	36 (11.77)	10 (9.26)	16 (14.16)	10 (9.62)	0.432
Livedo racemose	16 (4.92)	7 (6.48)	5 (4.42)	4 (3.85)	0.645
Livedoid vasculopathy lesions	2 (0.62)	0 (0.00)	1 (0.88)	1 (0.96)	0.604
Acute/chronic aPL-nephropathy	19 (5.85)	3 (2.78)	10 (8.85)	6 (5.77)	0.157
Pulmonary hemorrhage	1 (0.31)	0 (0.00)	0 (0.00)	1 (0.96)	0.344
Myocardial disease	2 (0.62)	0 (0.00)	1 (0.88)	1 (0.96)	0.604
Adrenal hemorrhage	2 (0.62)	0 (0.00)	2 (1.77)	0 (0.00)	0.151
Meet 2006 pregnancy morbidity criteria (%)	75/156(48.08)	31/53(58.49)	27/50(54.00)	17/53(32.08)	0.099
Cardiac valve (%)	24 (7.38)	8 (7.41)	5 (4.42)	11 (10.58)	0.223
Hematology (%)	153 (47.08)	46 (42.59)	54 (47.79)	53 (50.96)	0.689
Thrombocytopenia	145 (44.62)	44 (40.74)	50 (44.25)	51 (49.04)	0.743
20–130 * 10^9/L	120 (36.92)	40 (37.04)	42 (37.17)	38 (36.54)	0.995
< 20 * 10^9/L	25 (7.69)	4 (3.70)	8 (7.08)	13 (12.50)	0.053
Hemolytic anemia	27 (8.31)	7 (6.48)	14 (12.39)	6 (5.77)	0.148
APLs profiles (%)					
Positive LA (persistent)	298 (91.69)	97 (89.81)	106 (93.81)	95 (91.35)	0.555
aCL IgG/IgM medium/high titer	163 (50.15)	54 (50.00)	62 (54.87)	47 (45.19)	0.363

Table 1 (continued)

	RC Tertiles (mmol/L)				
	Total	**Tertile 1 (≤ 0.45)**	**Tertile 2 (> 0.45, ≤ 0.60)**	**Tertile 3 (> 0.60)**	***P*-value**
aβ2GP IgG/IgM medium/high titer	122 (37.54)	40 (37.04)	46 (40.71)	36 (34.62)	0.646
Multiple positive	152 (46.77)	49 (45.37)	58 (51.33)	45 (43.27)	0.463
Triple positive	108 (33.23)	36 (33.33)	43 (38.05)	29 (27.88)	0.283
Treatments (%)					
Antiplatelet	144 (44.31)	52 (48.15)	50 (44.25)	42 (40.38)	0.524
Anticoagulant	206 (63.38)	65 (60.19)	71 (62.83)	70 (67.31)	0.554
Statins	40 (12.31)	13 (12.04)	15 (13.27)	12 (11.54)	0.922
Hydroxychloroquine	192 (59.08)	69 (63.89)	72 (63.72)	51 (49.04)	**0.041**
Glucocorticoid	118 (36.31)	37 (34.26)	36 (31.86)	45 (43.27)	0.188
Immunosuppressant	83 (25.54)	21 (19.44)	26 (23.01)	36 (34.62)	**0.030**
Smoking status (%)					0.474
current smoker	14 (4.31)	2 (1.85)	5 (4.42)	7 (6.73)	
former smoker	65 (20.00)	20 (18.52)	23 (20.35)	22 (21.15)	
never smoker	246 (75.69)	86 (79.63)	85 (75.22)	75 (72.12)	
Chronic comorbidities (%)					
Hypertension	63 (19.38)	17 (15.74)	17 (15.04)	29 (27.88)	**0.029**
Hyperlipidemia	28 (8.62)	6 (5.56)	7 (6.19)	15 (14.42)	**0.037**
Diabetes	13 (4.00)	3 (2.78)	3 (2.65)	7 (6.73)	0.226
CKD	12 (3.69)	3 (2.78)	2 (1.77)	7 (6.73)	0.127
Cancer	8 (2.46)	3 (2.78)	3 (2.65)	2 (1.92)	0.910

Values are % for categorical variables and mean (SD) for continuous variables

RC Remnant cholesterol, *APS* Antiphospholipid syndrome, *BMI* Body mass index, *SLE* Systemic lupus erythematosus, *TC* Total cholesterol, *TG* Triglyceride, *HDL-C* High-density lipoprotein cholesterol, *LDL-C* Low-density lipoprotein cholesterol, *CRP* C-reactive protein, *CTEPH* Chronic thromboembolic pulmonary hypertension, *TIA* Transient ischemic attack, *aPL* Antiphospholipid antibody, *LA* Lupus anticoagulant, *aCL* Anticardiolipin antibody, *aβ2GPI* Anti-beta2 glycoprotein I, *CKD* Chronic kidney disease, *SD* Standard deviations

Stratified analyses by age, sex, SLE, smoking history, BMI, and APS disease duration demonstrated similar results. No significant interactions were detected between serum RC levels and these stratifying variables (all *P*-interaction > 0.05). (Supplementary Table 1).

In sensitivity analyses, the association between RC and thrombotic risk in patients with APS was essentially unchanged. Similar results were observed when we included only patients with thrombotic APS (Supplementary Table 2); results were consistent when further adjusting for anticoagulation and antiplatelet therapy (Model 1, Supplementary Table 3). Given the significantly higher risk of thrombotic recurrence in triple-positive aPLs patients [25, 26], our findings were consistent after adjusting for triple-positive aPLs (Model 2, Supplementary Table 3). When we further adjusted for and history of hypertension, SLE (Model 3, Supplementary Table 3), the results did not change significantly. These results reinforce the strong association between RC and the risk of thrombotic recurrence in APS patients.

Risk of thrombotic events based on categories of conventional lipid indices and RC levels

According to previous research reports and lipid control guideline recommendations, we defined the threshold for high LDL-C levels as 2.60 mmol/L, and similarly, the cut-offs for defining high levels TC, TG, and non-HDL-C were 3.80 mmol/L, 1.70 mmol/L, and 3.37 mmol/L, respectively [27, 28]. When comparing the thrombotic risk predictive value of RC with these lipid markers, abnormal LDL-C, TC, TG, or non-HDL-C levels did not significantly contribute to thrombotic risk in individuals with RC ≤ 0.60 mmol/L. Interestingly, a RC > 0.60 mmol/L consistently identified patients at higher thrombotic risk, irrespective of the levels of these four lipid markers (Fig. 3).

Causal relationship between RC and arterial and venous thrombosis

Subsequently, we employed MR analyses to investigate the causal relationship between RC and both arterial and venous thrombosis in the general European population.

Table 2 HRs (95% CIs) for all-cause thrombosis and venous, arterial and microvascular events according to RC level among patients with APS

	RC Tertiles (mmol/L)			
	Tertile 1 (≤ 0.45)	**Tertile 2 (> 0.45, ≤ 0.60)**	**Tertile 3 (> 0.60)**	***P*-ternd**
All-cause thrombosis				
Number (%)	8 (7.41)	15 (13.27)	28 (26.92)	
Model 1 HR (95% CI) *P*-value	1.00	1.95 (0.83, 4.60) 0.13	4.58 (2.09, 10.08) < 0.01	< 0.001
Model 2 HR (95% CI) *P*-value	1.00	2.00 (0.85, 4.72) 0.11	5.13 (2.32, 11.36) < 0.01	< 0.001
Model 3 HR (95% CI) *P*-value	1.00	2.10 (0.88, 4.98) 0.09	5.05 (2.23, 11.41) < 0.01	< 0.001
Venous thrombosis				
Number (%)	3 (2.78)	9 (7.96)	12 (11.54)	
Model 1 HR (95% CI) *P*-value	1.00	2.99 (0.81, 11.04) 0.10	4.54 (1.28, 16.10) 0.02	0.018
Model 2 HR (95% CI) *P*-value	1.00	3.03 (0.82, 11.22) 0.10	4.93 (1.38, 17.60) 0.01	0.011
Model 3 HR (95% CI) *P*-value	1.00	3.18 (0.86, 11.85) 0.08	6.34 (1.71, 23.54) < 0.01	0.003
Arterial thrombosis				
Number (%)	3 (2.78)	6 (5.31)	10 (9.62)	
Model 1 HR (95% CI) *P*-value	1.00	2.04 (0.51, 8.15) 0.32	3.79 (1.04, 13.78) 0.04	0.040
Model 2 HR (95% CI) *P*-value	1.00	2.04 (0.51, 8.17) 0.31	3.96 (1.08, 14.48) 0.04	0.035
Model 3 HR (95% CI) *P*-value	1.00	1.97 (0.48, 7.98) 0.34	3.79 (1.00, 14.32) < 0.05	0.061
Microvascular disease				
Number (%)	3 (2.78)	3 (2.65)	10 (9.62)	
Model 1 HR (95% CI) *P*-value	1.00	1.05 (0.21, 5.20) 0.95	4.15 (1.14, 15.11) 0.03	0.029
Model 2 HR (95% CI) *P*-value	1.00	1.17 (0.24, 5.85) 0.85	5.47 (1.47, 20.32) 0.01	0.011
Model 3 HR (95% CI) *P*-value	1.00	1.47 (0.29, 7.45) 0.64	4.36 (1.08, 17.58) 0.04	0.028

Model 1: Non-adjusted

Model 2: Adjusted for age, sex

Model 3: Adjusted for age, sex, BMI, hyperlipidemia, diabetes, smoking history, medicine use of statin, hydroxychloroquine, glucocorticoid, immunosuppressant

RC Remnant cholesterol, *APS* Antiphospholipid syndrome, *HR* Hazard ratio, *CI* Confidence interval, *BMI* Body mass index

The findings indicated a significant causal link between RC with arterial thrombosis, IS and MI, across all datasets from different studies ($P < 0.05$, inverse variance weighted (IVW)) (Fig. 4A, results of other MR methods in Supplementary Table 6). However, no significant causal relationship was observed between RC and venous thrombosis (Fig. 4B, Supplementary Table 7).

Discussion

To our knowledge, this study represents the first comprehensive analysis of the association between RC levels and thrombotic risk in a large APS cohort. Our investigation clearly indicated that patients with high levels of RC (> 0.60 mmol/L) faced a heightened risk of all-cause thrombosis and cause-specific thrombosis (venous, arterial, or microvascular), compared to those with lower RC levels. Intriguingly, even in the presence of normal LDL-C, TC, TG, or non-HDL-C levels, high RC was still associated with an increased thrombotic risk. These findings underscore the importance of recognizing and managing residual risks associated with RC, alongside conventional lipid parameters, to improve thrombosis prevention and clinical outcomes in APS patients.

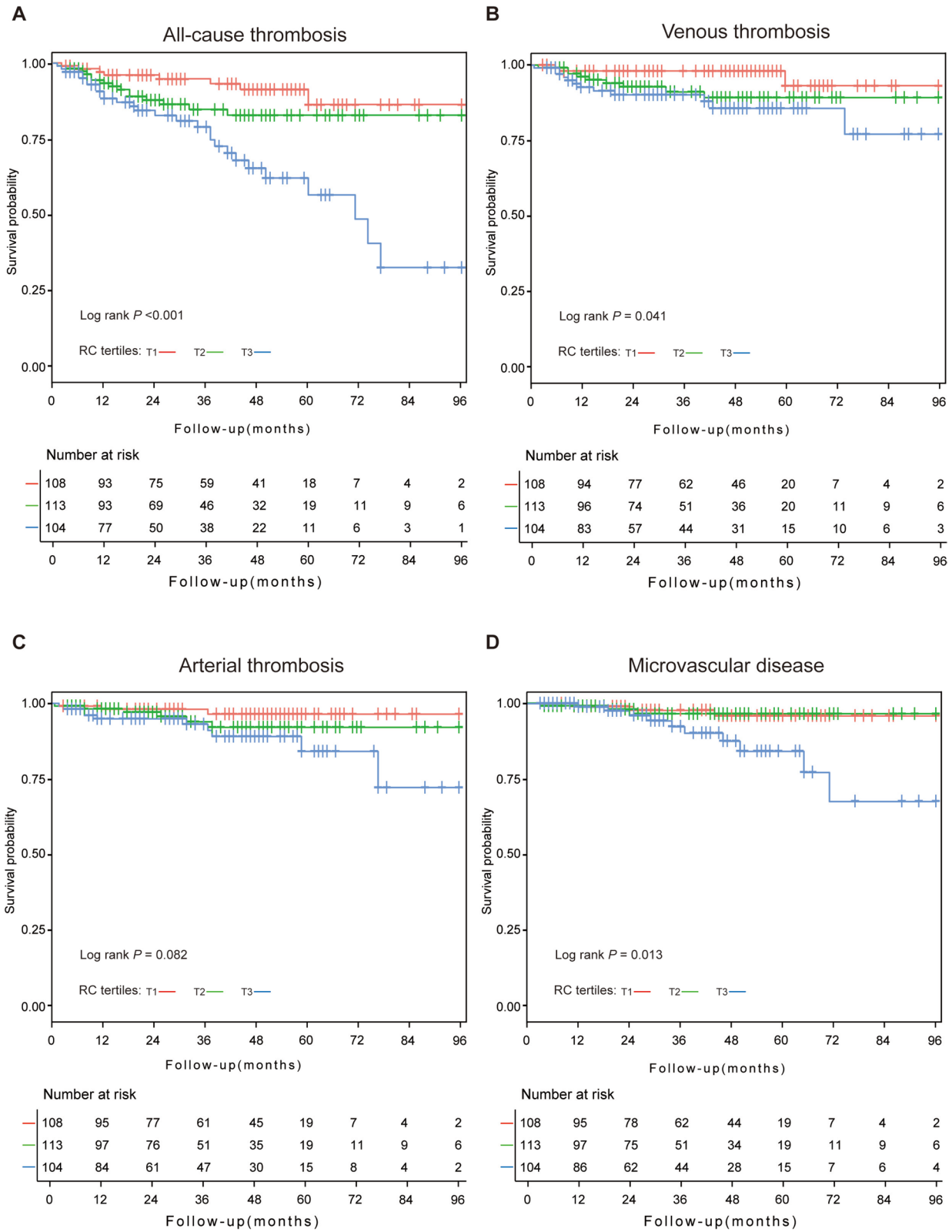


Fig. 2 High RC levels at baseline are associated with thrombotic risk in patients with APS. Kaplan–Meier survival curves were plotted to assess the risk of all-cause thrombosis (**A**) and venous thrombosis (**B**), arterial thrombosis (**C**) and microvascular disease (**D**) according to tertiles of RC levels (T1, T2, and T3). Red lines indicate low RC level of T1, green lines indicate medium RC level of T2, and blue lines indicate high RC level of T3. RC = remnant cholesterol; APS = antiphospholipid syndrome; HR = hazard ratio; CI = confidence interval

Markers that accurately predict the risk of thrombotic recurrence in patients with APS are lacking. Previous studies have shown that LA positivity, triple positivity for aPLs, and persistently elevated medium-to-high aCL levels are associated with an increased risk of thrombosis [29]. However, relying solely on antibody-based risk prediction remains suboptimal, as its predictive accuracy is limited. Based on our previous cohort studies, we have systematically evaluated and confirmed these limitations, further emphasizing the need for additional biomarkers to refine risk assessment [30]. Moreover, aPLs detection methods vary across laboratories, and the lack of standardization in titer measurement presents a challenge in categorizing patients [23]. This variability may lead to inconsistencies in risk stratification and therapeutic decision-making. In contrast, lipid measurements, including RC, are well-standardized and reproducible, making them a reliable marker for risk assessment.

Following adjustment for various confounders, our study robustly demonstrated that elevated levels of RC were significantly linked to an increased risk of diverse thrombotic manifestations in APS. This corroborated with recent large-scale longitudinal studies highlighting the association of elevated RC with arterial thrombotic events such as MI and IS in the general population and specific patient groups [9, 14, 28, 31, 32]. In addition, a notable Finnish multicenter prospective study also linked high RC to the progression of nephropathy and retinopathy in type 1 diabetes [33], suggesting RC's role as a potential risk factor for microvascular complications. Our findings provided novel insights into the role of RC in APS-related thrombotic risk. Mechanistically, the persistence of aPLs induces a prethrombotic state, and the additional triggering of a"second hit"by cardiovascular risk factors such as dyslipidemia may culminate in a clinical event. RC is more likely to penetrate arterial wall and be ingested by macrophage than LDL-C, can accelerate foam cell formation and vascular endothelial damage, this process triggers proinflammatory cytokines and prothrombotic factors, propelling the progression of thrombotic events [34, 35]. Moreover, animal studies have shown that high VLDL-C (a component of RC) enhances the expression of monocyte chemoattractant protein- 1 (MCP1) in mesangial cells and promote monocyte adhesion to the mesangium, potentially leading to microvascular thrombosis [33, 36]. Another potential link between RC and thrombotic events in APS may lie in inflammation; previous studies have demonstrated that high RC contributes to low-grade inflammation and ischemic heart disease [37]. Our study aligned with this, as APS patients with elevated RC exhibited higher CRP levels, indicating that low-grade inflammation due to increased RC could be a critical factor in thrombotic events in APS.

Analysis of MR in the general European population reveals a significant causal relationship between RC and arterial thrombosis, IS and MI. However, this causal link is not observed with venous thrombosis. Previous large-scale MR analyses have consistently shown genetic causality linking RC to cardiovascular outcomes such as IS and MI [38]. Our MR analyses not only corroborated these earlier results but also highlight a strong genetic causality between RC and arterial embolism and thrombosis. Nevertheless, uncertainty surrounds the causal link between RC and venous thrombosis. Consistent with Lee et al.'s report of no significant causal relationship between RC and venous thrombosis [39], our MR study in the general European population supported this, despite observing a significant clinical association in our APS cohort. The disparity between MR analysis and clinical observations may be attributed to different venous thrombosis mechanisms in APS patients compared to general population. The"multiple-hit hypothesis"suggests that thrombosis in the general population results from a combination of genetic and environmental risk factors [40]. In contrast, APS, as a complex thromboinflammatory condition, implies inflammation's critical role in thrombosis [4], where RC may act as a "second hit" exacerbating the inflammatory response and leading to venous thrombosis.

This study revealed RC as a superior indicator of thrombotic risk in APS patients compared to LDL-C, TG, TC, and non-HDL-C. In clinical practice, elevated LDL-C and TG is consistently acknowledged as pivotal risk factors for CVD events and is prioritized as a primary therapeutic target [41, 42]. Nevertheless, patients can still exhibit substantial residual cardiovascular risk despite achieving recommended levels of LDL-C and TG [10, 42]. In line with our results, a comprehensive follow-up cohort study demonstrated that RC more precisely predicted the

(See figure on next page.)

Fig. 3 RC predicts the risk of all-cause thrombosis beyond LDL-C, TC, TG, and non-HDL-C in patients with APS. Risk of thrombosis based on categories of RC and LDL-C (**A**), TC (**B**), TG (**C**), and non-HDL-C (**D**) levels. HRs and 95% CIs were adjusted for age, sex, BMI, smoking history (yes, no), hyperlipidemia, diabetes, use of statin, hydroxychloroquine, glucocorticoids, and immunosuppressant. High RC was associated with higher HRs, irrespective of the levels of these four lipid markers. RC = remnant cholesterol; APS = antiphospholipid syndrome; HR = hazard ratio; CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol

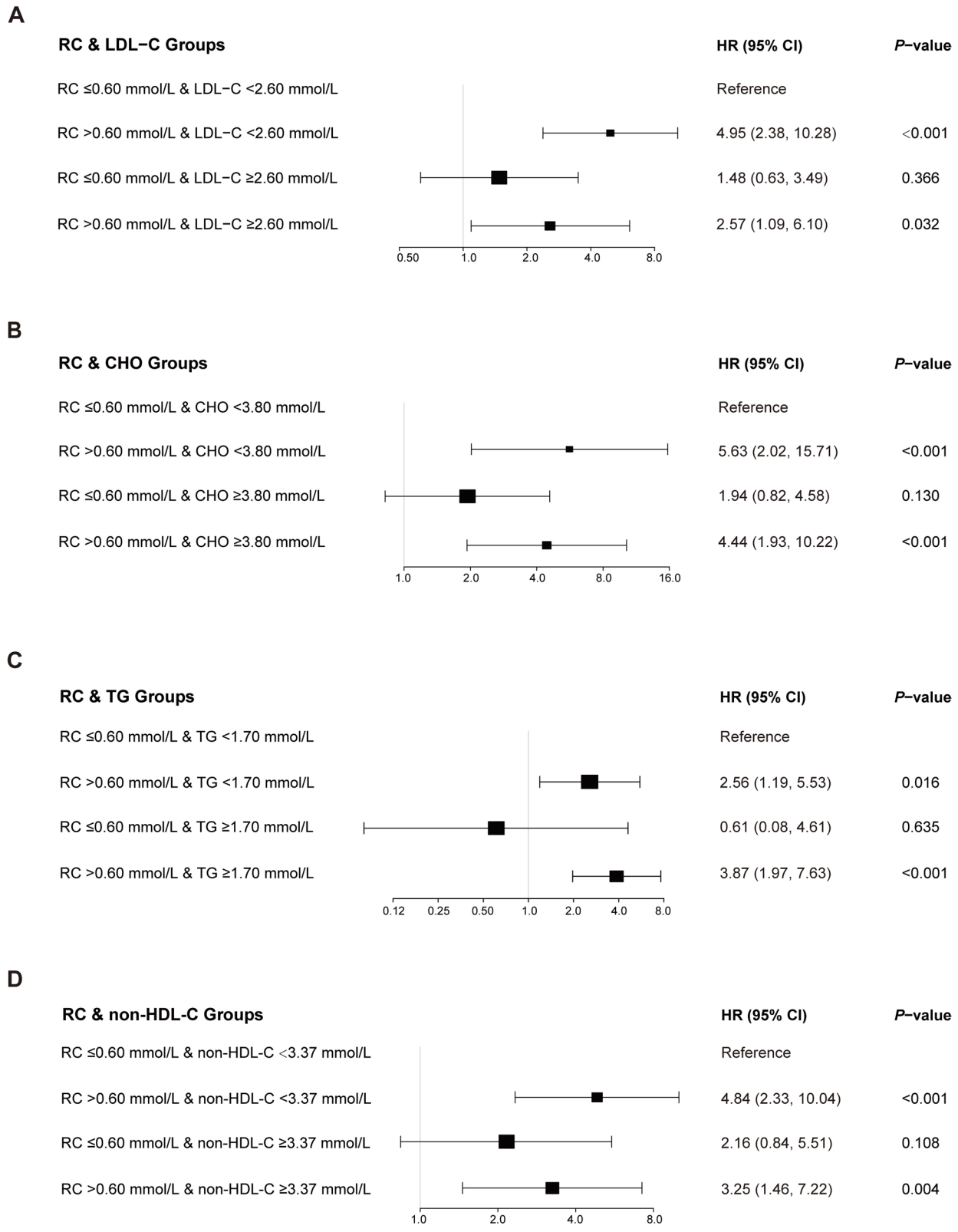
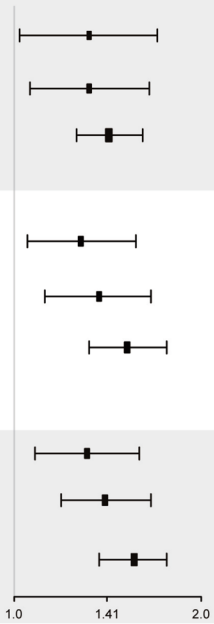


Fig. 3 (See legend on previous page.)

A

Exposure	Outcome	nSNP	OR (95% CI)	*P*–value
RC[1]	AT	40	1.32 (1.02,1.70)	0.036
	IS	39	1.32 (1.06,1.65)	0.012
	MI	40	1.42 (1.26,1.61)	<0.001
RC[2]	AT	47	1.28 (1.05,1.57)	0.016
	IS	47	1.37 (1.12,1.66)	0.002
	MI	47	1.52 (1.32,1.76)	<0.001
RC[3]	AT	40	1.31 (1.08,1.59)	0.008
	IS	39	1.40 (1.19,1.66)	<0.001
	MI	38	1.56 (1.37,1.76)	<0.001



B

Exposure	Outcome	nSNP	OR (95% CI)	*P*–value
RC[1]	VTE[1]	40	1.07 (0.77,1.47)	0.687
	VTE[2]	43	1.00 (0.996,1.01)	0.532
	VTE[3]	44	1.00 (0.996,1.01)	0.503
RC[2]	VTE[1]	47	1.01 (0.8,1.28)	0.940
	VTE[2]	50	1.00 (0.997,1.01)	0.632
	VTE[3]	51	1.00 (0.996,1.01)	0.675
RC[3]	VTE[1]	40	1.01 (0.79,1.30)	0.930
	VTE[2]	43	1.00 (0.996,1.01)	0.720
	VTE[3]	43	1.00 (0.99,1.01)	0.832

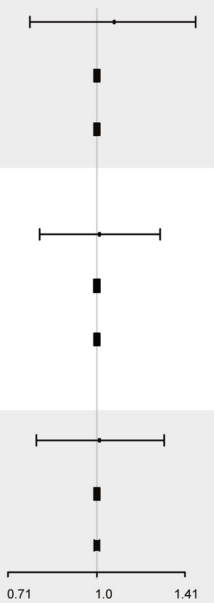


Fig. 4 Causal relationship between RC and arterial and venous thrombosis in general European population. MR analysis between RC with arterial thrombosis (**A**) and venous thrombosis (**B**) were performed by IVW method. Detailed information of each dataset used in MR analysis were listed in Supplemental Table 4. RC = remnant cholesterol; GWAS = genome wide association study; SNP = single nucleotide polymorphism; OR = odds ratio, CI = confidence interval; AT = artery thrombosis; IS = ischemic stroke; MI = myocardial infarction; VTE = venous thromboembolism

risk of major adverse cardiovascular events (MACEs) in individuals with diabetes mellitus, surpassing the predictive accuracy of non-HDL-C and ApoB [34]. Considering the complexity of APS pathogenesis, where chronic inflammation, autoantibodies, and dyslipidemia contribute to recurrent thrombotic events, merely normalizing LDL-C or TG levels may be insufficient. Drawing from this study's outcomes, we recommend a greater focus on RC in the management of patients with APS, even if conventional lipids are at normal levels, to better assess and address their heightened thrombotic risk.

Lipid-lowering therapy has been unfairly neglected, which may partly explain the recurrence episodes of clinical events in APS. In recent decades, prevalent strategies for preventing and treating APS have centered on low-dose aspirin, vitamin K antagonists, and heparin, while statins and hydroxychloroquine have been used only as adjunctive option [43, 44], despite dyslipidemia being a recognized thrombotic risk factor in APS. Considering the robust correlation between RC and thrombotic events in APS, targeting RC reduction appears as a compelling, potentially safer strategy for thrombosis mitigation. Findings from the TNT trial demonstrate that intensive atorvastatin therapy significantly lowers RC levels in patients with CVD with a subsequent decrease in cardiovascular risks, independent of LDL-C reduction [45]. Results from another recent study indicate that the combination of simvastatin and ezetimibe not only significantly reduces RC but also further diminishes cardiovascular events [46]. Beyond intensive lipid-lowering and combined strategies, glucagon-like peptide 1 receptor agonist (GLP- 1RA), high-dose n- 3 fatty acids supplementation, and selective peroxisome proliferator-activated receptor alpha modulator (SPPARMα) emerge as potential candidates for reducing RC [47–49]. Interestingly, our study observed that APS patients on hydroxychloroquine had lower RC levels, suggesting its potential in reducing RC, in line with previous studies on its effects on glucose and lipid metabolism and its anti-inflammatory properties [50, 51].

There are some limitations in our study. Firstly, RC was calculated indirectly, which might deviate from actual measurements. Despite this, previous studies have shown that calculated RC closely correlates with directly measured RC and has been widely used in several large studies, and importantly, indirect calculation of RC is a cost-effective method that not only reduces the burden on patients but also provides valuable data for clinical management [52]. Secondly, the study focused on APS patients with a high thrombotic risk, limiting generalizability to the broader population or other rheumatologic diseases, although we believe that high RC levels may also be involved in adverse cardiovascular events in other rheumatologic diseases. Thirdly, although we have collected data on statins use, we lacked data on other lipid-lowering drugs such fibrates, PCSK9 inhibitors, cholesterol absorption inhibitors, etc., which may affect RC levels. We acknowledge that this is a limitation and will consider including these data in future studies. Finally, although this cohort from PUMCH is a large APS cohort, the inclusion of more APS patients is needed in the future to further validate our conclusions, and in addition, the observational nature of our findings necessitates further experimental studies to establish a causal relationship between RC and thrombosis in APS.

Conclusions

This longitudinal study demonstrated that high RC (> 0.60 mmol/L) was significantly associated with thrombotic risk, either arterial, venous, or microvascular disease risk, and independently of LDL-C, TC, TG, or non-HDL-C levels in a prospective cohort of patients with APS. These findings provide new evidence for the need to monitor RC to avoid thrombotic risk and improve APS prognosis.

Abbreviations

APS	Antiphospholipid syndrome
RC	Remnant cholesterol
SLE	Systemic lupus erythematosus
PUMCH	Peking Union Medical College Hospital
TC	Total cholesterol
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
TG	Triglyceride
VLDLs	Very-low-density lipoproteins
CRP	C-reactive protein
aPL	Antiphospholipid antibody
LA	Lupus anticoagulant
aCL	Anticardiolipin antibody
aβ2GPI	Anti-beta2glycoprotein I
CTEPH	Chronic thromboembolic pulmonary hypertension
BMI	Body mass index
TIA	Transient ischemic attack
MI	Myocardial infarction
IS	Ischemic stroke
CKD	Chronic kidney disease
HR	Hazard ratio
CI	Confidence interval
SD	Standard deviations
DAGs	Directed acyclic graphs
MR	Mendelian randomization
GWAS	Genome-wide association study
SNP	Single nucleotide polymorphisms
FDR	False discovery rate
IV	Instrumental variable
IVW	Inverse variance weighted

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04063-5.

Supplementary Material 1: Table 1. Stratified analyses of the associations between RC and all-cause thrombosis among patients with APS. Table 2. HRs for all-cause thrombosis and venous, arterial and microvascular events according to RC level among thrombotic APS. Table 3. HRs for all-cause thrombosis and venous, arterial and microvascular events according to RC level among APS with further adjustment of treatment of anticoagulant and antiplatelet, triple positivity, history of hypertension, SLE. Table 4. STROBE-MR checklist. Table 5. GWAS datasets used in this study. Table 6. Causal relationship between RC and arterial thrombosis. Table 7. Causal relationship between RC and venous thrombosis. Figure 1. Directed Acyclic Graphof the association between RC and thrombosis events

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Authors' contributions
J.L.Z, X.F.Z and M.T.L conceived the study design and are responsible for the overall content. B.C. and Y.Z.Z. analyzed and interpreted the data and wrote the main manuscript text, X.Z.Y. prepared Figs. 4. Z.Q.W, C.H, H.J, Y.Z, X.P.T and Q.W assisted in the collection and collation of data. Q.Q.X and G.Q.L edited the manuscript. All authors approved the submitted and final versions.

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Data availability
The datasets are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the institutional review board (IRB) of Peking Union Medical College Hospital (Approval number, HS- 3309).

Consent for publication
All authors approved to submit the final manuscript to BMC medicine for publication consideration.

Competing interests
The authors declare no competing interests.

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