Cardiovascular Diabetology

RESEARCH

Open Access

Impact of remnant cholesterol on short-term and long-term prognosis in patients with prediabetes or diabetes undergoing coronary artery bypass grafting: a large-scale cohort study

Zhongchen Li[1,2,3,4†], Chunyu Yu[1,2,3,4†], Heng Zhang[1,2,3,4], Runze Chen[1,2,3,4], Yan Zhao[1,2] and Zhe Zheng[1,2,3,4,5*]

Abstract

Background Remnant cholesterol (remnant-C) contributes to atherosclerotic cardiovascular disease (ASCVD), particularly in individuals with impaired glucose metabolism. Patients with impaired glucose metabolism and ASCVD remain at significant residual risk after coronary artery bypass grafting (CABG). However, the role of remnant-C in this population has not yet been investigated.

Methods Adult patients with prediabetes or diabetes undergoing isolated CABG were consecutively enrolled in a longitudinal cohort between 2013 and 2018. The impact of remnant-C on short-term and long-term outcomes after CABG was evaluated. The short-term outcomes included major perioperative complications. The long-term outcomes were major adverse cardiovascular and cerebrovascular events (MACCEs). Remnant-C was analyzed as both a categorical and continuous variable. Logistic regression, Cox regression, and restricted cubic spline analyses were performed with multivariate adjustments.

Results In terms of perioperative outcomes, patients with elevated remnant-C had a higher incidence of acute kidney injury (AKI) stage 2/3 (high vs. low remnant-C: 3.2% vs. 2.4%; OR: 1.404, 95% CI 1.080–1.824). Each 1-standard deviation (SD) increase in remnant-C was associated with a 16.6% higher risk of AKI stage 2/3 (OR: 1.160, 95% CI 1.067–1.260). Long-term outcomes were assessed after a median follow-up of 3.2 years, during which 1,251 patients (9.3%) experienced MACCEs. Each 1-SD increase in remnant-C was associated with a 6.6% higher risk of MACCEs (HR: 1.066, 95% CI 1.012–1.124), a 7.1% higher risk of all-cause death (HR: 1.071, 95% CI 1.008–1.209), and an 11.2% higher risk of myocardial infarction (HR: 1.112, 95% CI 1.011–1.222). These associations remained consistent when remnant-C was treated as a categorical variable. Importantly, the association between remnant-C and MACCEs was independent of LDL-C levels;

†Zhongchen Li and Chunyu Yu contributed equally to this work.

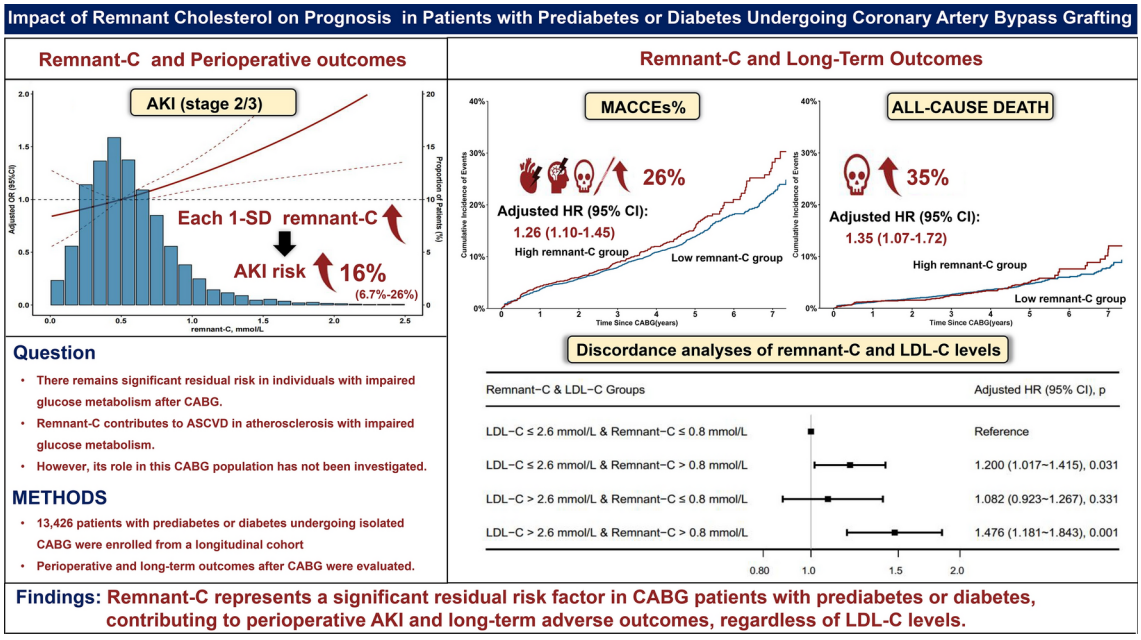
*Correspondence:
Zhe Zheng
zhengzhe@fuwai.com

Full list of author information is available at the end of the article

higher remnant-C levels were associated with increased MACCE risk regardless of whether LDL-C was ≤ 2.6 mmol/L or > 2.6 mmol/L. Subgroup analysis indicated that this risk was more pronounced in insulin-treated patients.

Conclusions Remnant-C is associated with AKI and MACCEs in patients with diabetes or prediabetes undergoing CABG. The MACCE risk associated with remnant-C is independent of LDL-C and is more pronounced in insulin-treated patients.

Graphical Abstract Remnant cholesterol (Remnant-C) may be an important risk factor for patients with impaired glucose metabolism undergoing coronary artery bypass grafting (CABG), however its role remains unknown. In our study, 13,426 CABG patients with prediabetes or diabetes were enrolled from a large longitudinal cohort to assess the impact of remnant-C on both perioperative and long-term outcomes. We found that higher remnant-C levels were significantly associated with an increased risk of acute kidney injury (AKI) perioperatively, as well as long-term adverse outcomes, including major adverse cardiovascular and cerebrovascular events (MACCEs), independent of LDL-C levels. *HR*, hazard ratio; *CI*, confidence interval; *SD*, Standard deviation; *remnant-C*, remnant cholesterol; *MACCEs*, major adverse cardiovascular and cerebrovascular events; *CABG*, coronary artery bypass grafting.



Keywords Remnant cholesterol, Diabetes mellitus, Prediabetes, Coronary artery bypass grafting, Outcomes, Acute kidney injury

Background

The global prevalence of diabetes is steadily increasing, with over 600 million people projected to have type 2 diabetes and a similar number expected to develop prediabetes by 2045 [1]. A significant proportion of these individuals also suffer from atherosclerotic cardiovascular disease (ASCVD), the leading cause of mortality in this population [2]. Compared to ASCVD patients with normal glucose metabolism, those with diabetes or prediabetes typically present with dyslipidemia characterized by elevated plasma triglycerides [contained in very low-density lipoproteins, intermediate-density lipoproteins, and in chylomicron remnants; collectively known as triglyceride-rich lipoproteins (TRLs)], low high-density lipoprotein cholesterol (HDL-C), and increased small, dense low-density lipoproteins (LDL) particles [3, 4]. These lipid abnormalities are strongly associated with poor ASCVD outcomes, even when LDL cholesterol (LDL-C) levels are substantially lowered or optimized according to current guidelines [5–8]. Remnant cholesterol (remnant-C) is the cholesterol content of TRLs [4]. Unlike triglycerides (TGs) in TRLs, which can be metabolized by most cells, remnant-C accumulates in arterial walls, playing a crucial role in the development of atherosclerosis [3, 4, 9]. Previous studies have shown that remnant-C levels are significantly elevated in patients with diabetes or prediabetes [10], and this elevation is associated with an increased risk of major adverse cardiac and cerebrovascular events (MACCEs) in both primary and secondary prevention of ASCVD [5, 6, 11].

Patients with impaired glucose metabolism exhibit a higher prevalence, extent, and severity of obstructive

coronary artery disease (CAD) compared to those with normal glucose metabolism [12]. For these individuals, coronary artery bypass grafting (CABG) remains a crucial treatment option [8]. Despite advancements in surgical techniques, perioperative care, and pharmacotherapy, patients with impaired glucose metabolism continue to experience significant residual cardiovascular risk after CABG. In the SYNTAX trial, the 5-year rate of MACCE in patients with diabetes was 29% [13]. In ODYSSEY OUTCOMES, even with LDL-C levels targeted between 25 and 50 mg/dL, patients randomized to alirocumab with a history of CABG still had a 4-point MACCE rate of 24.5% [14]. Remnant-C, a significant source of residual risk, may contribute to poor outcomes in this patient population [3, 9]. However, no studies have yet explored the prognostic implications of remnant-C in patients with diabetes or prediabetes undergoing CABG. Thus, we aimed to evaluate the association between remnant-C and prognosis in a large prospective cohort of these patients. Novel RNA-silencing therapies have shown promise in effectively lowering remnant-C levels [15]. Our findings may offer valuable insights into the potential clinical applications of these therapies.

Methods

Study population

The data used in the study were from a large prospective registry-based cohort at Fuwai Hospital, National Center for Cardiovascular Diseases in Beijing (ClinicalTrials.gov number, NCT02400125), as described in previous studies [16, 17]. All consecutive adult patients with diabetes or prediabetes who underwent isolated primary CABG between January 1, 2013, and December 31, 2018 were considered for the analysis. Patients with missing data on remnant-C or those lost to follow-up were excluded. According to the American Diabetes Association guidelines, prediabetes was defined as the 5.7% ≤ HbA1c < 6.5%, or 5.6 mmol/L ≤ fasting plasma glucose (FPG) < 7.0 mmol/L. Diabetes was defined as any one of the following: FPG ≥ 7.0 mmol/L, HbA1c ≥ 6.5%, with self-reported physician diagnosed diabetes, and use of anti-diabetic medications [18]. Data on demographic characteristics, laboratory tests, surgical procedures and medications were extracted from the registry further supplemented with electronic medical records. All data were collected according to definitions of the Society of Thoracic Surgeons National Adult Cardiac Database (http://www.sts.org/) [16, 17]. Patients were followed up through scheduled outpatient visits or telephone calls by trained cardiovascular research nurses as part of standard institutional protocols. If adverse events were reported during the follow-up period, patients were asked to provide medical records for further verification. The accuracy and completeness of these data were confirmed and ensured through multiple procedures described previously [16, 17]. This study was approved by the institutional review board at Fuwai Hospital, and the requirement for written informed consent was waived.

Laboratory measurement

Blood laboratory analyses were performed on patients in an overnight fasting state within 24 h of admission. Glucose concentrations were measured using the enzymatic hexokinase method, and glycated hemoglobin A1c (HbA1c) levels were detected with a Tosoh Automated Glycohemoglobin Analyzer HLC-723G8. The concentrations of total cholesterol (TC), TG, LDL-C, and HDL-C were directly assessed via the Hitachi 7150 automatic biochemistry analyzer. Of them, LDL-C and HDL-C were determined by homogeneous method. Remnant-C levels were calculated as follows: Remnant-C (mmol/L) = TC − HDL-C − LDL-C(18). High remnant-C levels were defined as ≥ 0.8 mmol/L, following clinical practice guidelines and consensus statements on cholesterol management [19, 20]. Moreover, multiple observational studies have corroborated that remnant-C levels exceeding approximately 0.8 mmol/L markedly increase the risk of MACCEs [5, 6].

Clinical management

Patients were managed in accordance with clinical practice guidelines, and all CABG procedures adhering to standardized techniques (Supplemental Method S1). The internal thoracic artery was preferred for the revascularization of the left anterior descending artery whenever feasible. The choice of cardiopulmonary bypass was made by the principal surgeon based on the patient's condition. Postoperative secondary prevention medications were recommended for all eligible patients, in accordance with the most current guidelines available at the time of recruitment (the 2013 European Society of Cardiology guidelines or the 2015 American Heart Association scientific statement) [21, 22].

Outcomes

The primary outcome was the first occurrence of MACCEs, defined as a composite of all-cause death, myocardial infarction (MI), cerebrovascular accident and repeat revascularization. Secondary outcomes included the individual components of this composite, as well as perioperative outcomes. Perioperative outcomes consisted of in-hospital death, cardiac death, perioperative myocardial infarction, cerebrovascular accident, acute kidney injury (AKI) stage 2/3, as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [23], and reoperation. Detailed definitions of the outcome components are provided in Supplemental Method S2. All

outcome measures were pre-specified, rigorously verified, and adjudicated by independent clinicians.

Statistical analysis

Normally distributed continuous data are expressed as mean±standard deviation (SD), while non-normally distributed continuous data are expressed as median (interquartile range). Categorical data are expressed as numbers (percentages). Continuous variables were compared using Welch's t test or Wilcoxon rank-sum test, while categorical variables were analyzed using the chi-square test.

The impact of remnant-C on outcomes was assessed both as a categorical and a continuous variable. For the categorical analysis, patients were stratified into two groups based on remnant-C levels: low and high, using a threshold value of 0.8 mmol/L as mentioned above. When analyzed as a continuous variable, the effect of remnant-C was evaluated per SD, and a *p*-value for trend was calculated. Multivariate logistic regression models were employed to compare perioperative outcomes. The Kaplan–Meier curves, log-rank tests and adjusted Cox proportional hazards regression model were utilized to compare long-term prognosis. Both categorical and continuous analyses of remnant-C were performed to assess its differential effects. Variables deemed clinically significant or those with p-values below 0.1 in the univariate regression model were included in the multivariate Cox or logistic regression models, with the exception of those excluded due to collinearity.

A restricted cubic spline transformation of remnant-C was used to evaluate nonlinear associations between remnant-C and outcomes by segmenting the variable and fitting cubic polynomials within each segment, with the significance of nonlinearity assessed using a likelihood ratio test. Additionally, pre-specified subgroup analyses for primary outcomes were performed using multivariable survival models, stratified by key clinical variables. Interaction effects were evaluated by including interaction terms in the multivariable models to assess the heterogeneity of treatment effects across subgroups. Confounders that were included in spline plots and subgroup analyses are the same as those in the main analysis.

A discordance analysis was conducted to identify whether the risk associated with remnant-C was independent of LDL-C levels. An LDL-C threshold of 2.6 mmol/L was used, as it aligned with the secondary prevention guidelines for post-CABG patients available at the time of patient recruitment [22]. Discordant groups were classified as low remnant-C/high LDL-C and high remnant-C/low LDL-C, while concordant groups included low remnant-C/low LDL-C and high remnant-C/high LDL-C. Multivariable Cox regression models were employed to assess the associations between these four groups and the occurrence of MACCEs, adjusting for the same confounders as in the primary analysis.

Statistical analysis was performed via R 4.2.1 (R Development Core Team) software.

Results

Remnant-C distribution and baseline characteristics of the study population

A total of 13,426 patients were included (Supplemental Fig. S1). The median remnant-C level was 0.5 mmol/L (interquartile range, 0.34–0.71 mmol/L), and 2516 (18.7%) were identified as high remnant-C level (>0.8 mmol/L) (Fig. 1). The baseline characteristics of these patients (mean age, 61.4±8.4 years; men, 76.2%; diabetes, 61.6%; prediabetes, 38.4%; on-pump, 46.6%; mean number of grafts, 3.2±1.0; and the use of left

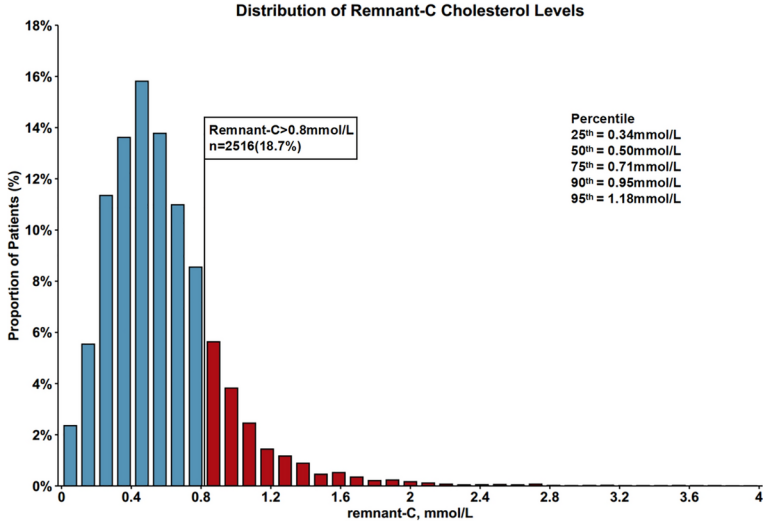


Fig. 1 The distribution of remnant cholesterol in the cohort. *Remnant-C*, remnant cholesterol

Table 1 Baseline characteristics of the cohort by remnant cholesterol level

Variables	All patients (n = 13,426)	Remnant Cholesterol, mmol/L		*P*
		≤ 0.8 (n = 10,910)	> 0.8 (n = 2516)	
Demographics				
Age, years	61.4 ± 8.4	61.8 ± 8.3	59.7 ± 8.6	< 0.001
Male	10,215 (76.1)	8398 (77.0)	1817 (72.2)	< 0.001
BMI, kg/m^2	26.0 ± 3.1	25.9 ± 3.1	26.4 ± 3.1	< 0.001
Comorbidity status				
Smoking	7569 (56.4)	6140 (56.3)	1429 (56.8)	0.637
Type 2 diabetes	8247 (61.4)	6637 (60.8)	1610 (64)	0.003
Prediabetes	5179 (38.6)	4273 (39.2)	906 (36)	
Insulin-treated diabetes	1530 (11.4)	1243 (11.4)	287 (11.4)	0.984
Hypertension	8863 (66.0)	7140 (65.4)	1723 (68.5)	0.004
Hyperlipidemia	9651 (71.9)	7780 (71.3)	1871 (74.4)	0.002
PAD	1565 (11.7)	1296 (11.9)	269 (10.7)	0.094
COPD	171 (1.3)	140 (1.3)	31 (1.2)	0.837
CKD	144 (1.1)	107 (1)	37 (1.5)	0.032
CVE	1976 (14.7)	1645 (15.1)	331 (13.2)	0.014
NYHA class III/IV	4225 (31.5)	3506 (32.1)	719 (28.6)	< 0.001
Previous PCI	759 (5.7)	600 (5.5)	159 (6.3)	0.180
Clinical parameters				
HbA1C, %	6.4 (5.9, 7.5)	6.4 (5.9, 7.4)	6.6 (6.0, 7.7)	< 0.001
FBG, mmol/L	6.4 (5.4, 8.2)	6.3 (5.4, 8.2)	6.6 (5.6, 8.6)	< 0.001
Total cholesterol, mmol/L	3.7 ± 1.2	3.5 ± 1.1	4.4 ± 1.4	< 0.001
Remant-C, mmol/L	0.5 (0.3, 0.7)	0.4 (0.3, 0.6)	1.0 (0.9, 1.2)	< 0.001
LDL-C, mmol/L	2.2 ± 1.0	2.1 ± 1.0	2.4 ± 1.2	< 0.001
HDL-C, mmol/L	0.9 ± 0.3	1.0 ± 0.3	0.8 ± 0.3	< 0.001
Non HDL, mmol/L	2.7 ± 1.1	2.5 ± 1.0	3.6 ± 1.3	< 0.001
Triglycerides, mmol/L	1.4 (1.0, 2.0)	1.3 (1.0, 1.7)	2.6 (2.0, 3.3)	< 0.001
Hs-CRP, mg/L	1.6 (0.8, 3.3)	1.5 (0.8, 3.1)	2.0 (1.1, 4.0)	< 0.001
Serum creatinine, μmol/L	80.3 ± 18.6	80.0 ± 18.0	81.7 ± 20.7	0.014
eGFR, mL/min/1.73 m^2 *	89.3 ± 15.4	89.4 ± 15.2	88.9 ± 16.1	0.057
AST, IU/L	20.0 (16.0, 26.0)	20.0 (16.0, 26.0)	20.0 (16.0, 27.0)	0.195
NT-proBNP, ng/L	146.4 (63.2, 404.7)	149.3 (64.0, 404.6)	134.2 (58.2, 404.2)	0.145
LVEF, %	60.4 ± 8.4	60.4 ± 8.3	60.0 ± 8.8	0.027
Procedure characteristics				
EuroSCORE	1.7 ± 1.7	1.7 ± 1.8	1.6 ± 1.7	< 0.001
On pump	6253 (46.6)	5089(46.6)	1164 (46.3)	0.746
IABP use	117 (0.9)	100 (0.9)	17 (0.7)	0.241
No. of grafts	3.2 ± 1.0	3.2 ± 1.0	3.1 ± 1.0	0.003
No. of arterial grafts	1.0 ± 0.4	1.0 ± 0.4	1.0 ± 0.4	0.174
No. of vein grafts	2.2 ± 1.0	2.3 ± 1.0	2.2 ± 1.0	< 0.001
LIMA graft	12,625 (94.0)	10,266(94.1)	2359 (93.7)	0.550
LM	2631 (19.6)	2145 (19.7)	486 (19.3)	0.695
TVD	11,006 (82.0)	8965 (82.2)	2041 (81.1)	0.216
Discharge medication				
Statin	10,965 (81.7)	8961 (82.1)	2004 (79.7)	0.004
Non-statin	110 (0.8)	94 (0.9)	16 (0.6)	0.258
Aspirin	13,108 (97.6)	10,646 (97.6)	2462 (97.9)	0.416

Table 1 (continued)

Variables	All patients (n = 13,426)	Remnant Cholesterol, mmol/L		*P*
		≤ 0.8 (n = 10,910)	> 0.8 (n = 2516)	
β-Blocker	12,521 (93.3)	10,175 (93.3)	2346 (93.2)	0.971
ACEI/ARB	1530(11.4)	1215 (11.1)	315(12.5)	0.053

Data are presented as mean ± SD or as n (%). P value were obtained by using the chi—square test or Welch's t test. *BMI*, body mass index; *PAD*, peripheral artery disease; *COPD*, chronic obstructive pulmonary disease; *AF*, atrial fibrillation; *CKD*, chronic kidney disease; *CVE*, cerebrovascular event; *PCI*, percutaneous coronary intervention; *FBG*, fasting blood glucose; *LDL-C*, low-density lipoprotein cholesterol; *HDL-C*, high-density lipoprotein cholesterol; *Remnant-C*, remnant cholesterol; *AST*, aspartate aminotransferase; *eGFR*, estimated glomerular filtration rate; *NT-proBNP*, N-terminal pro-B-type natriuretic peptide; *hs-CRP*, high-sensitivity C-reactive protein; *NYHA*, New York Heart Association; *LVEF*, left ventricular ejection fraction; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation; *IABP*, intra—aortic balloon pump; *LIMA*, left internal mammary artery; *LM*, left main disease; *TVD*, three-vessel disease; CCB, calcium- channel blocker; *ACEI*, angiotensin-converting enzyme inhibitor; and *ARB*, angiotensin receptor blocker

*Calculated with the Chronic Kidney Disease–Epidemiology Collaboration creatinine equation

Table 2 Perioperative outcome

Outcomes	All patients (n = 13,426)	Remnan-C, mmol/L		Crude OR (95% CI) *P* valve	Adjusted OR (95% CI) *P* valve	Adjusted OR (95% CI) Per SD increase *P* for trend
		≤ 0.8 (n = 10,910)	> 0.8 (n = 2516)			
In-hospital death	39 (0.2%)	33 (0.3%)	6 (0.2%)	0.788 (0.330–1.882) 0.592	0.983 (0.366–2.638) 0.973	0.877 (0.527–1.459) 0.613
Cardiac Death	24 (0.1%)	20 (0.1%)	4 (0.1%)	0.830 (0.318–2.162) 0.702	1.352 (0.398–4.586) 0.629	0.835 (0.138–5.069) 0.845
Perioperative MI	284 (2.1%)	230 (2.1%)	54 (2.1%)	1.018 (0.755–1.374) 0.905	0.934 (0.741–1.363) 0.975	1.024 (0.913–1.149) 0.687
CVA	44 (0.3%)	31 (0.2%)	13 (0.5%)	1.823 (0.952–3.488) 0.070	1.891 (0.975–3.666) 0.071	1.081 (0.835–1.400) 0.553
AKI stage 2/3	352 (2.7%)	271 (2.4%)	81 (3.2%)	1.306 (1.015–1.680) 0.038	1.404 (1.080–1.824) 0.011	1.160 (1.067–1.260) 0.001
Reoperation	182 (1.3%)	153 (1.3%)	29 (1.1%)	0.820 (0.550–1.222) 0.330	0.879 (0.586–1.321) 0.536	0.837 (0.526–1.332) 0.452

Values are n (%). Adjusted covariates including age, sex, BMI, smoking, hypertension, hyperlipidemia, diabetes, insulin-treated diabetes, PAD, AF, COPD, CVE, CKD, NYHA class III/IV, LVEF, HbA1C, FPG, LDL-C, Hs-CRP, Serum creatinine, EuroSCORE, On pump, LM, TVD (Abbreviations as in Table 1)

MI, myocardial infarction; *AKI*, acute kidney injury; *CVA*, cerebrovascular accident; *OR*, odds ratio; *CI*, confidence interval

internal mammary artery graft, 93.9%) are summarized in Table 1. Compared with the low remnant-C group, the high remnant-C group was younger, had a higher proportion of women and had higher BMI. Diabetes, hypertension, hyperlipidemia, and chronic kidney disease (CKD) were more prevalent in the high remnant-C group. New York Heart Association class III/IV and cerebrovascular events were more common in the low remnant-C group. Patients in the high remnant-C group demonstrated a higher level of HbA1C, fasting blood glucose, TG, TC, and LDL-C.

Baseline remnant-C levels and perioperative outcomes

The overall in-hospital mortality rate was 0.2%. High remnant-C was associated with an increased risk of AKI stage 2/3 (high remnant-C group vs. low remnant-C group: 3.2% versus 2.4%, adjusted odds ratio [aOR]: 1.404, 95% CI 1.080–1.824, $P=0.011$; remnant-C per SD increase: aOR: 1.160, 95% CI 1.067–1.260, P for trend = 0.001) (Table 2). In multivariate adjusted restricted cubic spline plots, the risks of AKI stage 2/3 were positively associated with remnant-C level (P for nonlinearity = 0.922) (Fig. 2). Subgroup analyses in pre-diabetic and diabetic patients separately showed that remnant-C was significantly associated with AKI stage 2/3 in both groups (Supplemental Table S1 and Supplemental Fig. S2). No significant differences were observed in other perioperative outcomes before or after multivariate adjustment (Table 2).

Baseline remnant-C levels and long-term outcomes

During a median follow-up of 3.2 years, 1251 patients (9.3%) developed MACCEs. As shown in Table 3 and Fig. 3, high remnant-C was associated with an increased risk of MACCEs. Similarly, the risk of all-cause death, MI and repeat revascularization also increased with increasing remnant-C. Compared to patients with remnant-C levels <0.8 mmol/L, those with remnant-C levels >0.8 mmol/L exhibited a significantly higher risk of MACCEs (adjusted hazard ratio [aHR]: 1.259, 95% CI 1.098–1.445, $P=0.001$), all-cause death (aHR: 1.353, 95% CI 1.066–1.718, $P=0.013$), MI (aHR: 1.431, 95% CI 1.089–1.881, $P=0.010$), and repeat revascularization (aHR: 1.426, 95% CI 1.053–1.93, $P=0.022$) after adjusting for multiple variables (Table 3 and Fig. 3). When remnant-C was analyzed as a continuous variable, a 1-SD increase in remnant-C was associated with a 6.6% higher

Table 3 Long-term outcomes

Outcomes	All patients (n = 13,426)	Remnant-C, mmol/L		Crude HR (95% CI) *P* valve	Adjusted HR (95% CI) *P* valve	Adjusted HR (95% CI) Per SD increase *P* for trend
		≤ 0.8 (n = 10,910)	> 0.8 (n = 2516)			
MACCEs	1251 (9.3%)	987 (9.0%)	264 (10.5%)	1.168 (1.019–1.338) 0.025	1.259 (1.098–1.445) 0.001	1.066 (1.012–1.124) 0.017
All-cause death	427 (3.2%)	338 (3.1%)	89 (3.5%)	1.140 (0.972–1.439) 0.273	1.353 (1.066–1.718) 0.013	1.071 (1.008–1.209) 0.041
MI	286 (2.1%)	216 (2.0%)	70 (2.8%)	1.411 (1.078–1.848) 0.012	1.431 (1.089–1.881) 0.010	1.112 (1.011–1.222) 0.029
CVA	613 (4.6%)	491 (4.5%)	122 (4.8%)	1.074 (0.881–1.311) 0.480	1.124 (0.919–1.374) 0.254	1.045 (0.968–1.129) 0.259
Repeat revascularisation	232 (1.7%)	175 (1.6%)	57 (2.3%)	1.415 (1.050–1.909) 0.023	1.426 (1.053–1.930) 0.022	1.097 (0.985–1.222) 0.091

Values are n (%). Adjusted covariates including age, sex, BMI, smoking, hypertension, hyperlipidemia, diabetes, insulin-treated diabetes, PAD, AF, COPD, CVE, CKD, NYHA class III/IV, LVEF, HbA1C, FPG, LDL-C, Hs-CRP, Serum creatinine, EuroSCORE, On pump, LM, TVD, and prescription of β-Blocker, aspirin, statin and ACEI/ARB at discharge (Abbreviations as in Table 1).

MACCEs, major adverse cardiac and cerebrovascular events; *MI*, myocardial infarction; *CVA*, cerebrovascular accident; *HR*, hazard ratio; *CI*, confidence interval.

risk of MACCEs (aHR: 1.066, 95% CI 1.008–1.209, *P* for trend = 0.017), a 7.1% higher risk of all-cause death (aHR: 1.071, 95% CI 1.008–1.209, *P* for trend = 0.041), and an 11.2% higher risk of MI (aHR: 1.112, 95% CI 1.008–1.209, *P* for trend = 0.029) after multivariable adjustments (Table 3). In multivariate adjusted restricted cubic spline plots, the risks of MACCEs were positively associated with remnant-C level (*P* for nonlinearity = 0.2) (Fig. 4).

Subgroup analysis

The association between remnant-C and MACCEs remained consistent across most predefined subgroups. Subgroup analyses of prediabetic and diabetic patients separately showed no significant interaction between remnant-C and glucose metabolic status (P for interaction = 0.304) (Fig. 5), with RCS analysis in both groups revealing a positive, nonlinear association between remnant-C and MACCEs (Supplemental Fig. S3). However, a significant interaction between remnant-C and insulin treatment status was observed. Remnant-C was associated with a higher risk of MACCEs in insulin-treated patients (aHR: 1.764, 95% CI 1.256–4.478), while this effect was less evident in those not on insulin (aHR: 1.178, 95% CI 1.013–1.369, P for interaction = 0.041) (Fig. 5).

Contribution of remnant-C to residual lipid risk by LDL-C level

We performed a discordance analysis to examine the relative risk of MACCEs in discordant and concordant

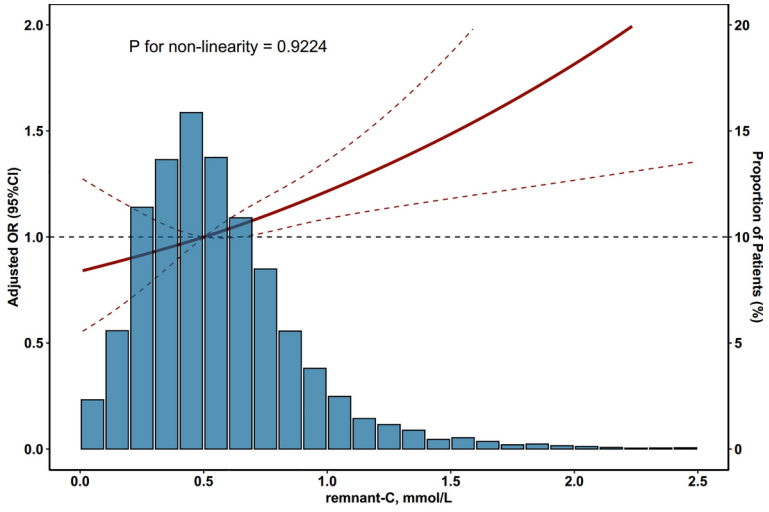


Fig. 2 Restricted cubic spline plot for AKI stage 2/3 by remnant-C levels. The background histogram (blue) represents the proportion of the density distribution of remnant cholesterol in the study population. The solid red line indicates the estimated adjusted odds ratio, while the red dashed lines represent the 95% confidence interval. The horizontal gray dashed line indicates a odds ratio of 1.0. Adjusted covariates including age, sex, BMI, smoking, hypertension, hyperlipidemia, diabetes, insulin-treated diabetes, PAD, AF, COPD, CVE, CKD, NYHA class III/IV, LVEF, HbA1C, FPG, LDL-C, Hs-CRP, Serum creatinine, EuroSCORE, On pump, LM, TVD (Abbreviations as in Table 1). *OR*, odds ratio; *CI*, confidence interval; *remnant-C*, remnant cholesterol

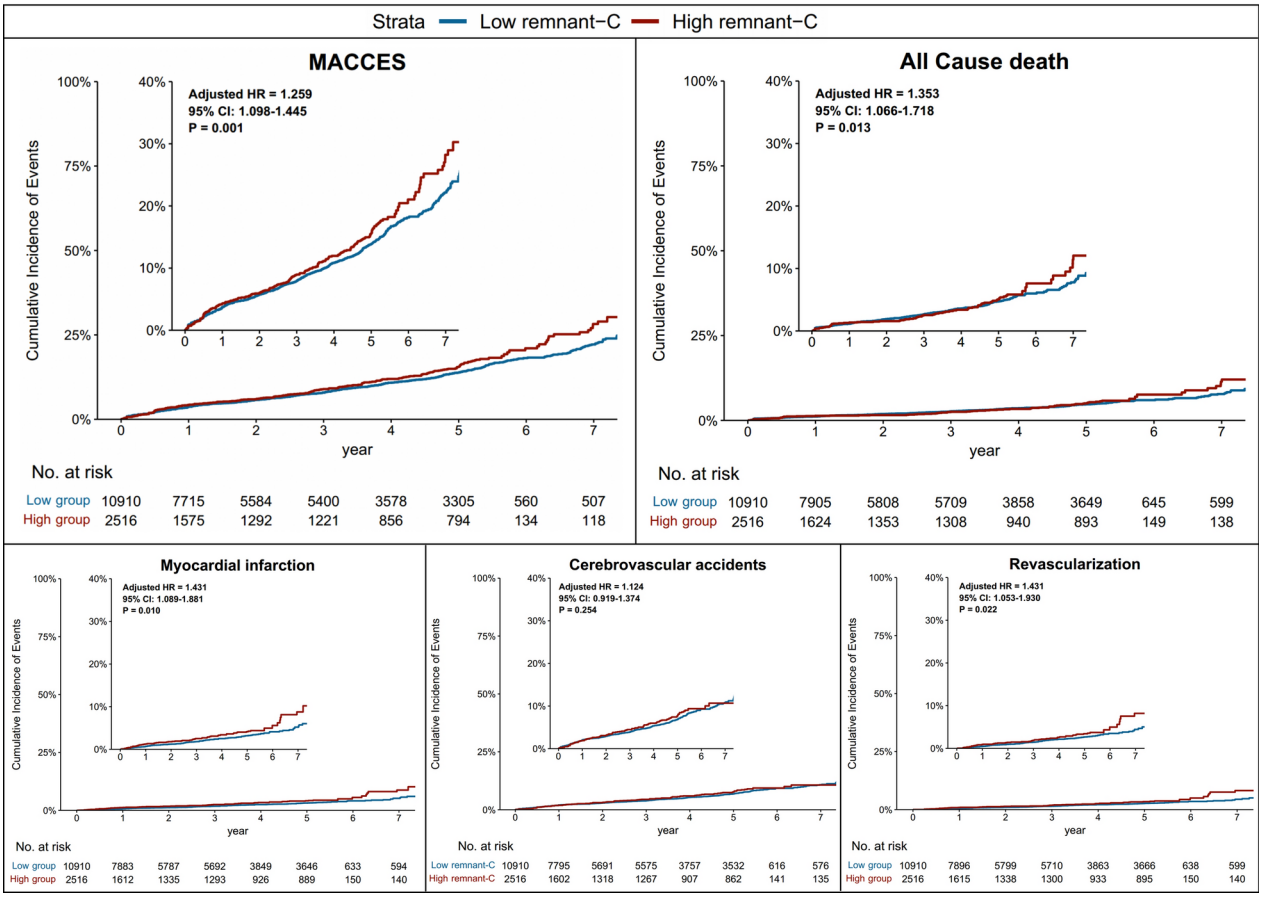


Fig. 3 Cumulative incidence of long-term outcomes. The Kaplan–Meier method was used to plot cumulative incidence curves. The red line indicates the high remnant-C group, and the blue line indicates the low remnant-C group. Adjusted covariates including age, sex, BMI, smoking, hypertension, hyperlipidemia, diabetes, insulin-treated diabetes, PAD, AF, COPD, CVE, CKD, NYHA class III/IV, LVEF, HbA1C, FPG, LDL-C, Hs-CRP, Serum creatinine, EuroSCORE, On pump, LM, TVD, and prescription of β-Blocker, aspirin, statin and ACEI/ARB at discharge (Abbreviations as in Table 1). *HR*, hazard ratio; *CI*, confidence interval; *remnant-C*, remnant cholesterol; *MACCEs*, major adverse cardiovascular and cerebrovascular events

groups of remnant-C and LDL-C. Consistent with the secondary prevention guidelines for post-CABG patients available at the time of patient recruitment [22], high LDL-C was defined as >2.6 mmol/L. The results indicated that individuals with remnant-C levels ≥0.8 mmol/L were at a higher risk for MACCEs, regardless of whether their LDL-C levels were concordantly high (aHR: 1.476, 95% CI 1.181–1.843, P=0.001) or discordantly low (aHR: 1.200, 95% CI 1.017–1.415, P=0.031). Conversely, when LDL-C levels were high but remnant-C levels were <0.8 mmol/L, the risk of MACCEs was not significant (aHR: 1.082, 95% CI 0.923–1.267, P=0.331). These findings suggest that remnant-C is an independent predictor of MACCEs in patients with diabetes or prediabetes undergoing CABG, regardless of LDL-C levels (Fig. 6).

Sensitivity analysis

We performed a sensitivity analysis by dividing remnant-C into four quartiles to assess its association with the outcomes. The results confirmed that the highest RC quartile was significantly associated with an increased risk of AKI stage 2/3 and MACCE compared to the lowest quartile (Supplemental Tables S2 and S3). These findings support the robustness of our results.

Discussion

This large-scale cohort study is the first to demonstrate an association between elevated remnant-C and poor outcomes in patients with diabetes or prediabetes undergoing CABG. In the short term, elevated remnant-C was associated with an increased risk of perioperative AKI stage 2/3. Over the long term, elevated remnant-C was associated with a higher risk of MACCEs, all-cause mortality, MI, and repeat revascularization, and this association was more pronounced in insulin-treated patients compared to those not on insulin therapy. Furthermore, remnant-C is independently associated with MACCEs, regardless of LDL-C levels.

LDL-C is a well-established risk factor for ASCVD and a key target for both primary and secondary prevention.

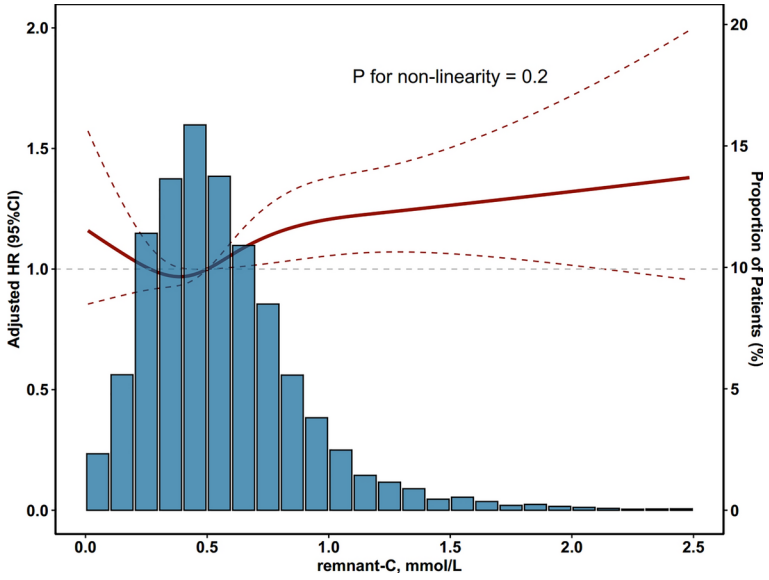


Fig. 4 Restricted cubic spline plot for MACCEs by remnant-C levels. The background histogram (blue) represents the proportion of the density distribution of remnant cholesterol in the study population. The solid red line indicates the estimated adjusted hazard ratio, while the red dashed lines represent the 95% confidence interval. The horizontal gray dashed line indicates a hazard ratio of 1.0. Adjusted covariates including age, sex, BMI, smoking, hypertension, hyperlipidemia, diabetes, insulin-treated diabetes, PAD, AF, COPD, CVE, CKD, NYHA class III/IV, LVEF, HbA1C, FPG, LDL-C, Hs-CRP, Serum creatinine, EuroSCORE, On pump, LM, TVD, and prescription of β-Blocker, aspirin, statin and ACEI/ARB at discharge (Abbreviations as in Table 1). *HR*, hazard ratio; *CI*, confidence interval; *remnant-C*, remnant cholesterol; *MACCEs*, major adverse cardiovascular and cerebrovascular events

However, despite significant reductions in LDL-C, recurrent ASCVD events still occur in patients [8, 14]. Remnant-C has been shown to have a strong pro-atherogenic effect and may be an important contributor to this residual risk [4]. In individuals with impaired glucose metabolism, elevated remnant-C levels are observed, while LDL-C levels remain relatively normal [10]. A study found that elevated levels of remnant cholesterol are associated with poor glycemic control in individuals with diabetes, as assessed by continuous glucose monitoring devices [24]. Therefore, The residual risk associated with remnant-C in this population deserves special attention. Studies indicate that insulin resistance and pro-inflammatory states, prevalent in individuals with prediabetes or diabetes, not only promote remnant-C production but also amplify its cardiovascular impact [25, 26]. For CAD patients with impaired glucose metabolism, CABG is a key treatment, especially for those with multi-vessel disease [8, 13]. However, patients with diabetes or prediabetes undergoing CABG are at high ASCVD risk due to postoperative residual risk and underappreciated risk factors, which contribute to higher rates of both short- and long-term adverse events [27]. Notably, no studies have yet investigated the association between remnant-C and adverse outcomes in patients with impaired glucose metabolism undergoing CABG. This study is the first to explore this issue.

In the perioperative outcomes of this large longitudinal cohort of 13,426 patients undergoing CABG, we found that baseline remnant-C levels were significantly associated with AKI stages 2/3. Each 1-SD (0.4 mmol/L) increase in remnant-C was associated with a 16.6% increased risk of AKI after multivariate adjustment. This novel finding, for the first time, establishes a link between remnant-C and AKI after CABG. Prior studies have mainly focused on the impact of dyslipidemia on CKD. The Atherosclerosis Risk in Communities study showed that low HDL, high LDL-C, and elevated TG are linked to an increased risk of CKD [28], consistent with findings from large Mendelian randomization studies [29]. Additionally, in patients with diabetes, multiple epidemiological studies have confirmed that typical dyslipidemia strongly correlates with the incidence and progression of CKD [30]. However, few studies have investigated the relationship between blood lipids and perioperative AKI, with only limited observational evidence suggesting a modest association between HDL-C and AKI following both cardiac and non-cardiac surgeries [31, 32]. AKI is the most common major complication of cardiac surgery, occurring more frequently in patients with impaired glucose metabolism compared to those with normal glucose levels [33, 34]. Moreover, given the strong association between AKI, especially stages 2/3, and adverse outcomes, the management of AKI in cardiac surgery is a critical concern [34]. Our study demonstrates that remnant-C is associated with the occurrence of AKI Stage 2/3 in patients with diabetes or prediabetes undergoing CABG. This finding highlights

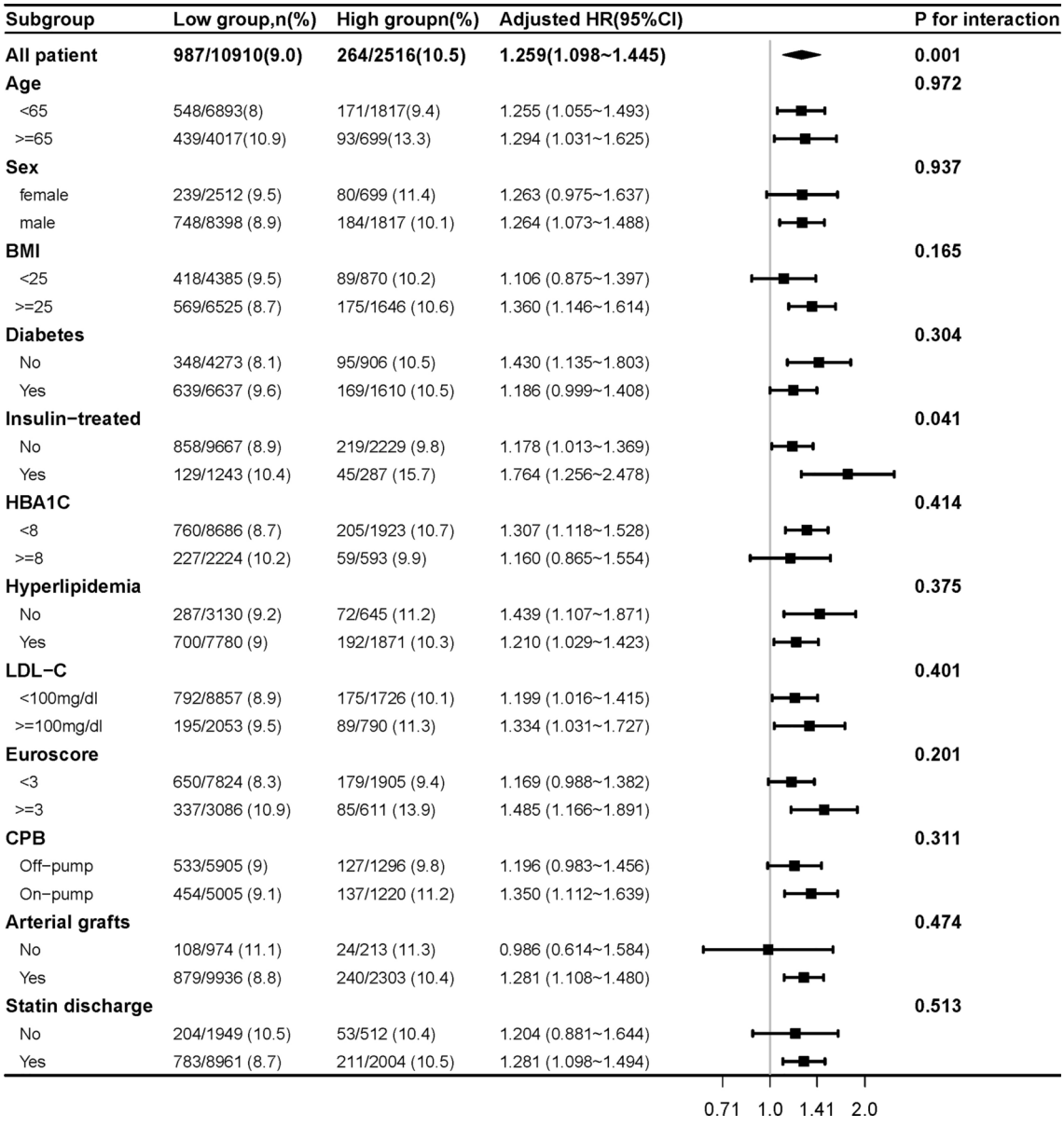


Fig. 5 Subgroup analysis of MACCEs. Values are n (%). Adjusted covariates including age, sex, BMI, smoking, hypertension, hyperlipidemia, diabetes, insulin-treated diabetes, PAD, AF, COPD, CVE, CKD, NYHA class III/IV, LVEF, HbA1C, FPG, LDL-C, Hs-CRP, Serum creatinine, EuroSCORE, On pump, LM, TVD, and prescription of β-Blocker, aspirin, statin and ACEI/ARB at discharge (Abbreviations as in Table 1). *LDL-C*, low-density lipoprotein cholesterol; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation; *CPB*, cardiopulmonary bypass; *HR*, hazard ratio; *CI*, confidence interval

the potential for remnant-C as a novel biomarker for early identification, risk stratification, and targeted clinical intervention. However, the mechanisms underlying the association between remnant-C and AKI remain unclear. Several hypotheses offer insights into potential pathways. First, the lipid nephrotoxicity hypothesis, which links dyslipidemia to CKD, suggests that persistent hyperlipidemia leads not only to atherosclerosis but also to glomerular arteriosclerosis [35]. Furthermore, the gradual accumulation of various circulating lipoproteins in the basement membrane and mesangial cells damages podocytes, mesangial cells, and renal tubular structures, promoting CKD progression [35]. Notably, in the context of impaired glucose metabolism, the renal microvasculature shows a unique susceptibility to dyslipidemia, which may be a key mechanism of renal injury [36]. Impaired glucose metabolism is often associated with insulin resistance and a pro-inflammatory state [25], both of which contribute to endothelial dysfunction. This dysfunction increases the permeability of renal microvasculature, promotes inflammation and oxidative stress, and alters renal microcirculatory hemodynamics [36, 37]. Moreover, in patients with impaired glucose metabolism, the elevated levels of various lipoproteins and lipids [38],

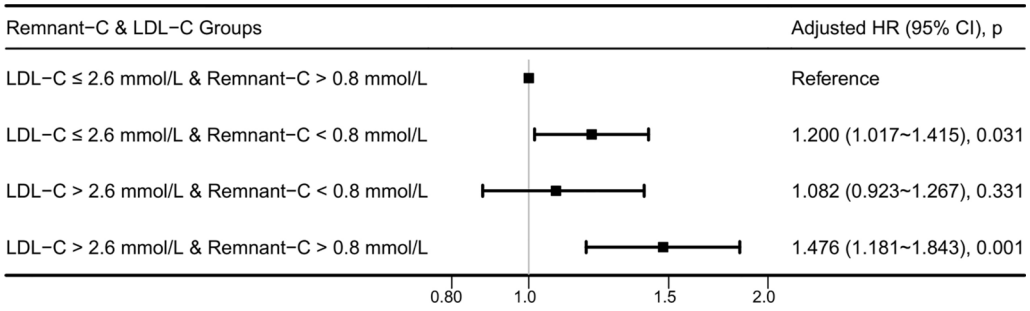


Fig. 6 Discordance analyses of remnant-C and LDL-C levels. The four groups, from top to bottom, are: Low LDL-C and Low Remnant-C group (serving as the baseline for comparison); Low LDL-C and High Remnant-C group (focusing on the effect of elevated remnant cholesterol in the context of low LDL-C levels); High LDL-C and Low Remnant-C group (focusing on the effect of elevated LDL-C in the context of low remnant cholesterol levels); High LDL-C and High Remnant-C group (focusing on the combined effect of both elevated LDL-C and remnant cholesterol levels on cardiovascular risk. Adjusted covariates including age, sex, BMI, smoking, hypertension, hyperlipidemia, diabetes, insulin-treated diabetes, PAD, AF, COPD, CVE, CKD, NYHA class III/IV, LVEF, HbA1C, FPG, Hs-CRP, Serum creatinine, EuroSCORE, On pump, LM, TVD, and prescription of β-Blocker, aspirin, statin and ACEI/ARB at discharge (Abbreviations as in Table 1). HR, hazard ratio; CI, confidence interval. LDL-C, low-density lipoprotein cholesterol

particularly TRLs, further exacerbates inflammation and damage to the renal microvasculature, thus worsening glomerular injury and tubular-interstitial fibrosis, which ultimately accelerates the progression of kidney injury [36–38]. Meanwhile, the mechanisms related to remnant-C and cardiovascular events include the elevation of inflammatory cytokine levels, increased systemic oxidative stress, induction of endothelial dysfunction, and disruption of immune regulation [3, 4, 9, 25]. These mechanisms may also be involved in the development of AKI. In clinical practice, perioperative remnant-C/TG are often overlooked by physicians. Given our results, it is essential to further investigate the role of remnant-C in AKI after CABG, as well as to explore the underlying mechanisms.

Our study also revealed that elevated remnant-C has an impact on long-term clinical outcomes in patients with diabetes or prediabetes undergoing CABG. For each SD increase (0.4 mmol/L) in remnant-C, the risk of MACCEs increased by 6.6%, with corresponding increases of 7.1% in all-cause death and 11.2% in MI risk. Importantly, in this high-risk ASCVD group of patients with impaired glucose metabolism, remnant-C was identified as the primary cholesterol component driving MACCEs following CABG. Regardless of whether LDL-C levels were ≤2.6 mmol/L, patients with remnant-C levels ≥0.8 mmol/L had a higher risk of MACCEs, suggesting that remnant-C can predict cardiovascular outcomes independently of LDL-C levels. These findings support the consideration of remnant-C as both a clinical predictor and therapeutic target in patients with prediabetes and diabetes undergoing CABG. Current guidelines recommend long-term statin therapy for patients after CABG without contraindications [8]. However, the effect of statins on remnant-C is limited. A national longitudinal cohort study, involving approximately 2 million patients with diabetes, found that the association between remnant-C and cardiovascular disease was even stronger in those on statin therapy than in those not using statins [39]. A recent study suggest that lowering remnant-C by 0.8 mmol/L in secondary prevention can reduce the risk of recurrent MACCEs by 20% [11]. Based on these data, we reasonably postulate that treatment of residual risk, measured as remnant-C, was likely more beneficial than further reduction of LDL-C levels in patients with impaired glucose metabolism after CABG who are already receiving appropriate doses of statins. In fact, the effects of LDL-lowering drugs such as statins, ezetimibe and PCSK9 inhibitors on remnant-C levels are usually modest, while fibrates, commonly used in clinical practice to lower TG/TRL/remnant-C, have more profound effects [25]. In the PROMINENT trial [40], pemafibrate significantly reduced TG levels by 26.2% and remnant-C levels by 25.6% in patients with diabetes, but these changes did not translate into a reduction in MACCEs. Further analysis revealed that pemafibrate did not truly reduce remnant-C, but instead promoted its conversion to LDL-C rather than hepatic clearance. Consequently, pemafibrate-mediated reductions in remnant-C were accompanied by a 12.3% increase in LDL-C levels in this study [40]. Ongoing trials involving novel agents, such as RNA-based therapies targeting apolipoprotein C-III, angiopoietin-like protein 3 (ANGPTL3) inhibitors, protein-level interventions targeting ANGPTL3, and gene-editing therapies like CRISPR-Cas-mediated ANGPTL3 modification, are expected to improve the clearance of remnant-C rather than converting it to LDL particles, thereby reducing the atherogenic effects of remnant-C [15, 41, 42]. Moreover, selecting the appropriate patient population for remnant-C-lowering therapies is essential. Theoretically, patients with higher residual risk driven by remnant-C are more likely to benefit from these therapies. In our study, we specifically focused on patients with diabetes or prediabetes undergoing CABG,

who represent a group with particularly high residual cardiovascular risk [13, 14, 27]. Therefore, our findings provide valuable insights into the selection of patient groups for remnant-C-lowering therapies.

In addition to the primary findings, our subgroup analysis revealed an interesting observation: the association between remnant-C and MACCEs was more pronounced in patients receiving insulin therapy compared to those not on insulin. Insulin-treated patients often have a longer duration of diabetes and more severe insulin resistance [43, 44]. Additionally, exogenous insulin acts as a pro-inflammatory agent, potentially exacerbating inflammatory responses through multiple mechanisms [44, 45]. This heightened insulin resistance and inflammatory state may amplify the effects of remnant-C on cardiovascular risk [25, 44]. In particular, exogenous insulin may enhance immune responses associated with inflammation and overstimulate hormonal signaling pathways, which could increase the uptake of remnant-C by macrophages in arterial walls, thereby accelerating the progression of atherosclerosis [45, 46]. This finding emphasizes the importance of paying more attention to the subgroup of insulin-treated patients with diabetes undergoing CABG, as these patients may be more vulnerable to the adverse effects of remnant-C.

The strengths of this study are as follows: it is based on a large-scale, well-validated longitudinal cohort with complete follow-up, and adequate adjustment for confounding factors, which together contribute to the robustness of the findings. Moreover, LDL-C was directly measured via the homogeneous method rather than estimated via the Friedewald equation. Both HDL-C and TC were also directly measured. Consequently, the remnant-C level, calculated as TC−HDL-C−LDL-C, provided a more accurate estimation. However, this study has several limitations. First, epidemiological and genomic studies have confirmed ethnic and regional variations in lipid profiles and associated cardiovascular risks [47, 48]. Given that this study is based on a Chinese population, the generalizability of its findings to other regions and ethnicities may be limited. Second, during long-term follow-up, remnant-C levels may fluctuate over time, but these fluctuations are difficult to track. Third, although we adjusted for known major covariates, the potential of residual or unmeasured confounding factors remained. Data on unmeasured confounders, such as patient lifestyle behaviors (e.g., diet, physical activity, alcohol consumption) and adherence to prescribed treatments, were not available during the follow-up period. These factors may contribute to cumulative exposure and variability in remnant-C levels, potentially influencing the observed associations between remnant-C and outcomes [49]. It is well established that socioeconomic status is closely related to the management, complications, and prognosis of diabetes, and it may also influence the observed associations in our study. Additionally, the lack of data on the duration of diabetes and its related complications further limits the comprehensiveness of our multivariate model, which may affect the interpretation of the results, particularly in the subgroup analysis involving insulin treatment. Finally, due to the inherent limitations of the observational study design, although we employed various statistical methods (e.g., restricted cubic splines, logistic regression, and Cox models) to ensure the reliability of the results, we acknowledge that confounding factors cannot be fully eliminated. Therefore, a causal relationship between remnant-C and MACCEs cannot be definitively established due to the potential influence of confounding and reverse causation.

Abbreviations

ASCVD	Atherosclerotic cardiovascular disease
TRLs	Triglyceride-rich lipoproteins
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
TC	Total cholesterol
Remnant-C	Remnant cholesterol
TG	Triglycerides
MACCEs	Major adverse cardiac and cerebrovascular events
MI	Myocardial infarction
CAD	Coronary artery disease
CABG	Coronary artery bypass grafting
AKI	Acute kidney injury
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02537-z.

Supplementary Material 1.

Acknowledgements

We thank staffs at the Information Center, Fuwai Hospital, National Center for Cardiovascular Diseases for help with data acquisition and Li He for her coordination of the patient follow-up.

Author contributions

Z.L. and C.Y. researched data, contributed to discussion, and wrote the first draft of the manuscript. H.Z. and Z.Z reviewed and edited the manuscript. R.C contributed to discussion and reviewed and edited the manuscript. Y.Z. help prepared the database. All authors approved the final version of the manuscript. Z.Z. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding

This work was supported by grants from the high-level hospital clinical research of Fuwai Hospital, Chinese Academy of Medical Sciences (2022-GSP-GG-28), the National Natural Science Foundation of China (Key Program; 81830072), the Ministry of Science and Technology of People's Republic of China (2016YFC1302000), the National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences (NCRC2020004) and the State Sponsored Postdoctoral Researcher Programme (GZC20230304).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the institutional review board at Fuwai Hospital and the requirement for written informed consent was waived.

Consent for publication
Written informed consent for publication was obtained from all participants.

Competing interests
The authors declare no competing interests.

Author details
[1]State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 167 Beilishi Rd, Xicheng District, Beijing 100037, People's Republic of China
[2]National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences, Beijing, People's Republic of China
[3]Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China
[4]Department of Cardiovascular Surgery, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China
[5]Key Laboratory of Coronary Heart Disease Risk Prediction and Precision Therapy, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China

Received: 22 October 2024 / Accepted: 5 December 2024
Published online: 08 January 2025

References

1. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018;138:271–81.
2. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol. 2018;17(1):83.
3. Ginsberg HN, Packard CJ, Chapman MJ, Borén J, Aguilar-Salinas CA, Averna M, et al. Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies-a consensus statement from the European Atherosclerosis Society. Eur Heart J. 2021;42(47):4791–806.
4. Borén J, Taskinen MR, Björnson E, Packard CJ. Metabolism of triglyceride-rich lipoproteins in health and dyslipidaemia. Nat Rev Cardiol. 2022;19(9):577–92.
5. Fu L, Tai S, Sun J, Zhang N, Zhou Y, Xing Z, et al. Remnant cholesterol and its visit-to-visit variability predict cardiovascular outcomes in patients with type 2 diabetes: findings from the ACCORD cohort. Diabetes Care. 2022;45(9):2136–43.
6. Castañer O, Pintó X, Subirana I, Amor AJ, Ros E, Hernáez Á, et al. Remnant cholesterol, not LDL cholesterol, is associated with incident cardiovascular disease. J Am Coll Cardiol. 2020;76(23):2712–24.
7. Vallejo-Vaz AJ, Fayyad R, Boekholdt SM, Hovingh GK, Kastelein JJ, Melamed S, et al. Triglyceride-rich lipoprotein cholesterol and risk of cardiovascular events among patients receiving statin therapy in the TNT trial. Circulation. 2018;138(8):770–81.
8. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255–323.
9. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet. 2014;384(9943):626–35.
10. Watanabe N, Taniguchi T, Taketoh H, Kitagawa Y, Namura H, Yoneda N, et al. Elevated remnant-like lipoprotein particles in impaired glucose tolerance and type 2 diabetic patients. Diabetes Care. 1999;22(1):152–6.
11. Langsted A, Madsen CM, Nordestgaard BG. Contribution of remnant cholesterol to cardiovascular risk. J Intern Med. 2020;288(1):116–27.
12. Rana JS, Dunning A, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, et al. Differences in prevalence, extent, severity, and prognosis of coronary artery disease among patients with and without diabetes undergoing coronary computed tomography angiography: results from 10,110 individuals from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes): an InteRnational Multicenter Registry. Diabetes Care. 2012;35(8):1787–94.
13. Kappetein AP, Head SJ, Morice MC, Banning AP, Serruys PW, Mohr FW, et al. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. Eur J Cardiothorac Surg. 2013;43(5):1006–13.
14. Goodman SG, Aylward PE, Szarek M, Chumburidze V, Bhatt DL, Bittner VA, et al. Effects of alirocumab on cardiovascular events after coronary bypass surgery. J Am Coll Cardiol. 2019;74(9):1177–86.
15. Ballantyne CM, Vasas S, Azizad M, Clifton P, Rosenson RS, Chang T, et al. Plozasiran, an RNA interference agent targeting APOC3, for mixed hyperlipidemia. N Engl J Med. 2024;391(10):899–912.
16. Rao C, Zhang H, Gao H, Zhao Y, Yuan X, Hua K, et al. The chinese cardiac surgery registry: design and data audit. Ann Thorac Surg. 2016;101(4):1514–20.
17. Zhang H, Yuan X, Zhang H, Chen S, Zhao Y, Hua K, et al. Efficacy of long-term β-blocker therapy for secondary prevention of long-term outcomes after coronary artery bypass grafting surgery. Circulation. 2015;131(25):2194–201.
18. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022; 45(Suppl 1):S17–S38.
19. Nordestgaard BG, Langsted A, Mora S, Kolovou G, Baum H, Bruckert E, et al. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. Eur Heart J. 2016;37(25):1944–58.
20. Hu DY. New guidelines and evidence for the prevention and treatment of dyslipidemia and atherosclerotic cardiovascular disease in China. Zhonghua Xin Xue Guan Bing Za Zhi. 2016;44(10):826–7.
21. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34(38):2949–3003.
22. Kulik A, Ruel M, Jneid H, Ferguson TB, Hiratzka LF, Ikonomidis JS, et al. Secondary prevention after coronary artery bypass graft surgery: a scientific statement from the American Heart Association. Circulation. 2015;131(10):927–64.
23. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013;17(1):204.
24. Raposo-López JJ, Tapia-Sanchiz MS, Navas-Moreno V, Arranz Martín JA, Marazuela M, Sebastian-Valles F. Association of remnant cholesterol with glycemic control and presence of microvascular complications in individuals with type 1 diabetes mellitus. Rev Clin Esp (Barc). 2024;224(1):43–7.
25. Laufs U, Parhofer KG, Ginsberg HN, Hegele RA. Clinical review on triglycerides. Eur Heart J. 2020;41(1):99–109c.
26. Cao YX, Zhang HW, Jin JL, Liu HH, Zhang Y, Gao Y, et al. The longitudinal association of remnant cholesterol with cardiovascular outcomes in patients with diabetes and pre-diabetes. Cardiovasc Diabetol. 2020;19(1):104.
27. Verma S, Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, et al. Icosapent ethyl reduces ischemic events in patients with a history of previous coronary artery bypass grafting: REDUCE-IT CABG. Circulation. 2021;144(23):1845–55.
28. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. Kidney Int. 2000;58(1):293–301.
29. Lanktree MB, Thériault S, Walsh M, Paré G. HDL cholesterol, LDL cholesterol, and triglycerides as risk factors for CKD: a Mendelian randomization study. Am J Kidney Dis. 2018;71(2):166–72.
30. Rutledge JC, Ng KF, Aung HH, Wilson DW. Role of triglyceride-rich lipoproteins in diabetic nephropathy. Nat Rev Nephrol. 2010;6(6):361–70.
31. Zhou Y, Yang HY, Zhang HL, Zhu XJ. High-density lipoprotein cholesterol concentration and acute kidney injury after noncardiac surgery. BMC Nephrol. 2020;21(1):149.
32. Smith LE, Smith DK, Blume JD, Linton MF, Billings FTT. High-density lipoprotein cholesterol concentration and acute kidney injury after cardiac surgery. J Am Heart Assoc. 2017;6(12):e006975.
33. Mina GS, Gill P, Soliman D, Reddy P, Dominic P. Diabetes mellitus is associated with increased acute kidney injury and 1-year mortality after transcatheter aortic valve replacement: a meta-analysis. Clin Cardiol. 2017;40(9):726–31.
34. Wang Y, Bellomo R. Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. Nat Rev Nephrol. 2017;13(11):697–711.
35. Ruan XZ, Varghese Z, Moorhead JF. An update on the lipid nephrotoxicity hypothesis. Nat Rev Nephrol. 2009;5(12):713–21.

36. Li Y, Liu Y, Liu S, Gao M, Wang W, Chen K, et al. Diabetic vascular diseases: molecular mechanisms and therapeutic strategies. Signal Transduct Target Ther. 2023;8(1):152.
37. Chade AR. Small vessels, big role: renal microcirculation and progression of renal injury. Hypertension. 2017;69(4):551–63.
38. Suh SH, Kim SW. Dyslipidemia in patients with chronic kidney disease: an updated overview. Diabetes Metab J. 2023;47(5):612–29.
39. Huh JH, Han KD, Cho YK, Roh E, Kang JG, Lee SJ, et al. Remnant cholesterol and the risk of cardiovascular disease in type 2 diabetes: a nationwide longitudinal cohort study. Cardiovasc Diabetol. 2022;21(1):228.
40. Das Pradhan A, Glynn RJ, Fruchart JC, MacFadyen JG, Zaharris ES, Everett BM, et al. Triglyceride lowering with pemafibrate to reduce cardiovascular risk. N Engl J Med. 2022;387(21):1923–34.
41. Malick WA, Waksman O, Do R, Koenig W, Pradhan AD, Stroes ESG, et al. Clinical trial design for triglyceride-rich lipoprotein-lowering therapies: JACC focus seminar 3/3. J Am Coll Cardiol. 2023;81(16):1646–58.
42. Brandts J, Ray KK. Novel and future lipid-modulating therapies for the prevention of cardiovascular disease. Nat Rev Cardiol. 2023;20(9):600–16.
43. Beckman JA, Paneni F, Cosentino F, Creager MA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II. Eur Heart J. 2013;34(31):2444–52.
44. Biondi-Zoccai GG, Abbate A, Liuzzo G, Biasucci LM. Atherothrombosis, inflammation, and diabetes. J Am Coll Cardiol. 2003;41(7):1071–7.
45. Dangas GD, Farkouh ME, Sleeper LA, Yang M, Schoos MM, Macaya C, et al. Long-term outcome of PCI versus CABG in insulin and non-insulin-treated diabetic patients: results from the FREEDOM trial. J Am Coll Cardiol. 2014;64(12):1189–97.
46. Muniyappa R, Montagnani M, Koh KK, Quon MJ. Cardiovascular actions of insulin. Endocr Rev. 2007;28(5):463–91.
47. Sliwa K, Lyons JG, Carrington MJ, Lecour S, Marais AD, Raal FJ, et al. Different lipid profiles according to ethnicity in the Heart of Soweto study cohort of de novo presentations of heart disease. Cardiovasc J Afr. 2012;23(7):389–95.
48. Lu X, Peloso GM, Liu DJ, Wu Y, Zhang H, Zhou W, et al. Exome chip meta-analysis identifies novel loci and East Asian-specific coding variants that contribute to lipid levels and coronary artery disease. Nat Genet. 2017;49(12):1722–30.
49. de Vries JK, Balder JW, Pena MJ, Denig P, Smit AJ. Non-LDL dyslipidemia is prevalent in the young and determined by lifestyle factors and age: The LifeLines cohort. Atherosclerosis. 2018;274:191–8.

Publisher's Note