Lipids in Health and Disease

RESEARCH

Open Access

Association of the remnant cholesterol to high-density lipoprotein cholesterol ratio with mortality in peritoneal dialysis patients

Zebin Wang[1†], Sibing Huang[1†], Na Tian[2], Qingdong Xu[3], Xiaojiang Zhan[4], Fenfen Peng[5], Xiaoyang Wang[6], Ning Su[7], Xiaoran Feng[8], Xingming Tang[9], Xianfeng Wu[10], Qian Zhou[11], Jianbo Liang[1], Jiao Li[1,12*] and Yueqiang Wen[1*]

Abstract

Background In individuals receiving continuous ambulatory peritoneal dialysis (CAPD), remnant cholesterol (RC) and high-density lipoprotein cholesterol (HDL-C) levels significantly influence clinical outcomes. Current clinical practice might benefit from assessing these two lipid markers in combination when evaluating cardiovascular disease (CVD) and all-cause mortality. Therefore, this research sought to examine how the RC/HDL-C ratio correlates with both CVD and all-cause mortality rates among individuals receiving CAPD treatment.

Methods Between January 1, 2005 and December 31, 2016, a multi-center retrospective analysis of 2006 CAPD patients from five peritoneal dialysis hospitals in China was conducted. Participants were split into two subgroups in accordance with the baseline serum RC/HDL-C ratio restricted cubic spline cutoff value. The correlations between mortality and RC/HDL-C ratio were examined through case-specific hazard modeling.

Results The observation period documented 549 all-cause fatalities, with cardiovascular deaths accounting for 269 cases. The Kaplan-Meier analysis revealed statistically significant divergence in both all-cause mortality (log rank test $P<0.001$) and CVD mortality (log rank test $P=0.003$). Elevated RC/HDL-C ratios showed increased hazard ratios (HR) for all-cause mortality (1.335, 95% CI, 1.112–1.603, $P=0.002$) and CVD mortality (1.319, 95% CI, 1.013–1.717, $P=0.040$) compared to lower ratio counterparts. Nevertheless, no statistically meaningful association was found between CVD mortality and either RC (HR: 1.296, 95% CI, 0.992–1.691, $P=0.057$) or HDL-C (HR: 0.887, 95% CI, 0.680–1.157, $P=0.376$).

Conclusion The RC/HDL-C ratio independently predicts mortality in CAPD patients, persisting as a significant prognostic marker after multivariable adjustment.

Keywords Lipids, Cholesterol, High-density lipoprotein, Peritoneal dialysis, Cardiovascular disease, Mortality

†Zebin Wang and Sibing Huang contributed equally to this work.

*Correspondence:
Jiao Li
gzlijiao@163.com
Yueqiang Wen
yueqiangwen@163.com

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

Introduction

End-stage renal illness severely affects health care systems and is prevalent worldwide [1]. One of the primary options for end-stage renal illness, which affects approximately 11% of dialysis patients overall, is continuous ambulatory peritoneal dialysis (CAPD) [2]. Cardiovascular complications represent the primary cause of mortality in individuals with chronic kidney disease (CKD) [3].

Peritoneal dialysis recipients exhibit distinct lipid metabolism derangements serving as validated predictors of cardiovascular risk. Characteristic presentations include elevated total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C), with concurrent reductions in high-density lipoprotein cholesterol (HDL-C) levels. One of the most prevalent forms of dyslipidemia in peritoneal dialysis patients is hypertriglyceridemia [4, 5]. Contemporary treatment strategies for peritoneal dialysis patients LDL-C reduction as the primary intervention for dyslipidemia management. However, some research has indicated that a significant cardiovascular risk remains even when LDL-C reaches guideline-recommended targets. Furthermore, pharmacological interventions targeting HDL-C elevation demonstrate no significant clinical efficacy in patients receiving intensive statin regimens, suggesting that elevated remnant cholesterol (RC) concentrations may underlie residual cardiovascular risk [6, 7]. RC is triglyceride-rich lipoprotein cholesterol comprising very low-density lipoprotein cholesterol (VLDL-C) and intermediate-density lipoprotein cholesterol (IDL-C) in the fasting periods as well as VLDL-C, IDL-C, and chylomicron in the postprandial state. RC is a significant cardiovascular disease (CVD) risk factor [8]. Emerging evidence demonstrates associations between increased RC concentrations and elevated stroke risk [9, 10], with parallel correlations observed for atherosclerotic cardiovascular conditions [11, 12]. Furthermore, among individuals on peritoneal dialysis, RC demonstrates independent associations with all-cause mortality and cardiovascular-related fatalities [13]. Reduced HDL-C levels have also been correlated with the occurrence of CVD in the aged population [14]. Moreover, the development of CKD is linked to low plasma HDL-C levels [15]. The RC/HDL-C ratio acts as a marker for intracranial atherosclerosis [16] and myocardial injury following percutaneous coronary intervention in diabetes populations [17]. Furthermore, elevated RC/HDL-C ratios demonstrate robust associations with incident nonalcoholic fatty liver disease (NAFLD) risk. Compared to traditional lipid biomarkers, the composite RC/HDL-C metric enhances NAFLD detection accuracy [18]. As a new biomarker, the RC/HDL-C ratio demonstrates clinical significance and is easily accessible. It can be widely used in clinical and epidemiologic studies to assess a patient's CVD risk. Therefore, combining RC and HDL-C may enhance predict the prognosis of CAPD patients.

However, a thorough examination of the associations between the RC/HDL-C ratio and mortality outcomes in CAPD patients is needed to enhance clinical understanding of metabolic parameter optimization and prognostic evaluation techniques, as there have been no studies to date indicating a relationship between mortality and the ratio. This cohort study, utilizing data from multiple peritoneal dialysis centers in China, was designed to investigate the potential ability of the RC/HDL-C ratio in forecasting mortality among CAPD patients.

Study design and population

This multi-center cohort analysis included patients with ongoing CAPD selected from a multicenter database (The Ever-green Tree Nephrology Group [ETNG]) in China from January 1, 2005, to May 31, 2016. Age ≥ 18 years and ≤ 80 years at the start of CAPD and survival for ≥ three months following initial CAPD therapy were the inclusion criteria. Patients with malignant diseases were excluded. The study ultimately included 2006 patients (Fig. 1).

All patients were monitored until May 31, 2017, at which point they were either censored, moved to another dialysis center, switched to hemodialysis (HD) therapy, or lost to follow-up. CVD mortality encompassed fatal events attributed to acute myocardial ischemia, heart failure, hemorrhagic/thromboembolic cerebrovascular events, life-threatening arrhythmias, and sudden cardiac death.

This investigation strictly adhered to the provisions of the Helsinki Declaration. All research protocols received formal approval from the Ethics Review Board of Guangzhou Medical University's Second Affiliated Hospital (Approval No. 2024-hg-ks-10). Given the observational nature of this retrospective analysis involving only anonymized clinical data, the institutional ethics committee granted a waiver of informed consent requirements, confirming the absence of both interventional procedures and participant risk exposure. All study participant data were obtained from hospital inpatient information and used anonymously.

Lipid measurements

Blood samples were taken after participants had fasted overnight. The CHOD-PAP technique was used to detect TC, whereas enzyme colorimetry was used to measure TG. LDL-C concentrations were quantified via homogeneous enzymatic colorimetric assays, while HDL-C levels were assessed using selective inhibition methodology. The following is how RC was calculated and examined as a continuous variable: RC = TC – LDL-C – HDL-C, with the RC/HDL-C ratio was obtained by dividing RC by

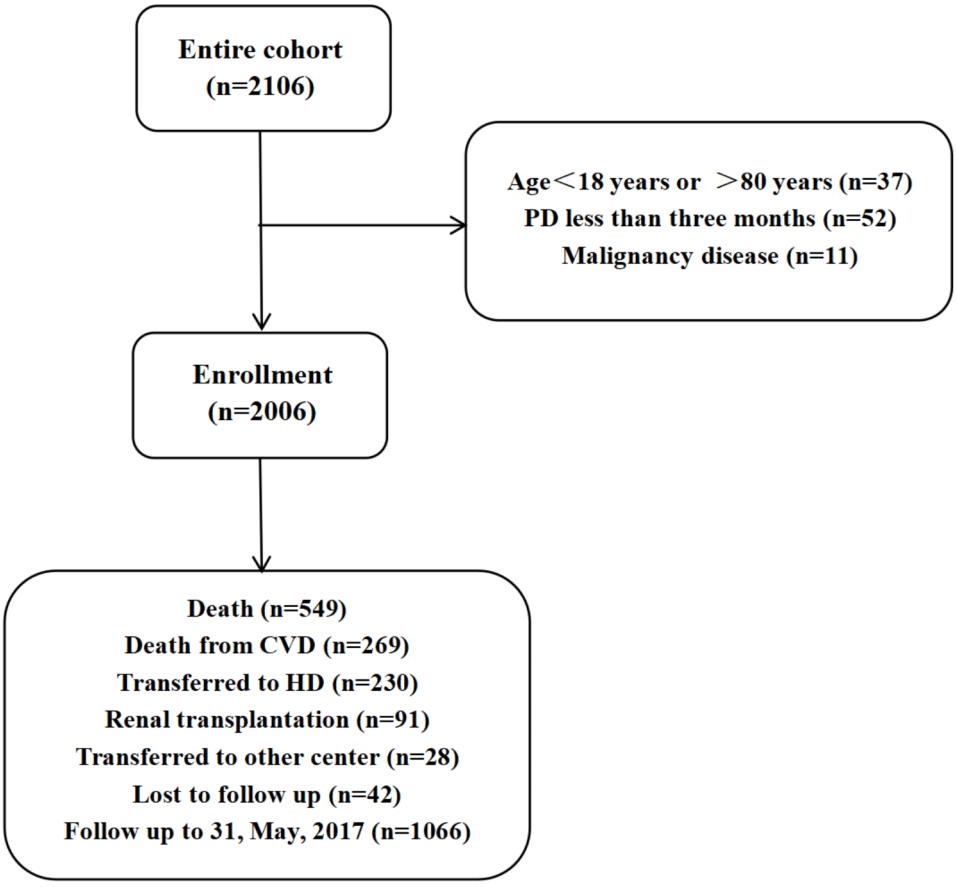

Fig. 1 Flow chart of the participants in the study cohort. PD, peritoneal dialysis; HD, hemodialysis

HDL-C. This equation has been widely employed in prior studies despite the absence of standardized RC quantification protocols because it can be acquired from conventional lipid profiles [19–21]. Baseline lipid profiles were acquired within the first one to three months after the start of CAPD.

Baseline investigations

The demographic baseline data encompassed variables such as age, sex, complications, and medication history. In addition, baseline biochemical indices were documented during the commencement of CAPD. These included body mass index (BMI), blood pressure, lipid profile, serum uric acid, platelet count, serum albumin, hemoglobin, serum creatinine, calcium, sodium, potassium, phosphorus, total Kt/V for urea (Kt/V), fasting blood glucose and renal residual function (RRF). Within three months of the start, baseline data were gathered, and medication use was documented in accordance with prescriptions.

Statistical analysis

Relationships of the RC/HDL-C ratio with mortality outcomes were assessed via restricted cubic spline (RCS) modeling. The RCS function with five knots was applied. Through RCS analyses, a cutoff RC/HDL-C ratio of 0.56 was established as the reference value. Study participants were classified into two groups: Group 1 (RC/HDL-C ratio <0.56) and Group 2 (RC/HDL-C ratio ≥ 0.56). The median (25th to 75th percentile) was used to reflect the skewed distribution of all continuous variables, whereas frequencies and percentages were applied to report categorical data. Non-normally distributed continuous measures underwent nonparametric analysis via the Mann-Whitney U method. Categorical variables comparisons utilized chi-square testing. A Kaplan–Meier curve was used to analyze all-cause and CVD deaths, with differences between group quantified through log-rank comparative testing.

A univariate Cox proportional hazards regression analysis was utilized to examine the relationships between risk variables and mortality. To assess the proportional hazards assumption in the unadjusted Cox analysis, the Schoenfeld residual test was conducted, and this assumption was satisfied for both CVD and all-cause mortality. Qualified covariates were used to develop a multivariate Cox regression model. The duration of risk in the Cox regression models ranged from the start of the trial to

Table 1 Baseline patient characteristics by categories of RC/ HDL-C ratio

	Total	RC/HDL-C ratio <0.56	RC/HDL-C ratio ≥0.56	*P* value
	(*n* = 2006)	(*n* = 1011)	(*n* = 995)	
Demographic data				
Age (Y)	51 (40,62)	49 (39,60)	52 (40,63)	<0.001
Male sex (%)	1097 (54.7)	552 (54.6)	545 (54.8)	0.937
BMI (kg/m2)	21.7 (19.8,24.1)	21.3 (19.7,23.8)	22.1 (20.1,24.4)	<0.001
Systolic BP (mmHg)	142 (130,155)	143 (132,159)	141 (130,153)	0.007
Diastolic BP (mmHg)	85 (78,93)	86 (79,94)	84 (78,92)	0.003
Comorbid				
Hypertension (%)	1435 (71.5)	716 (70.8)	719 (72.3)	0.475
Diabetes Mellitus (%)	416 (20.7)	192 (19.0)	224 (22.5)	0.052
Prior cardiovascular disease (%)	295 (14.7)	114 (11.3)	181 (18.2)	<0.001
Treatments				
CCB (%)	1526 (76.1)	759 (75.1)	767 (77.1)	0.291
ACEI/ARB use (%)	827 (6.0)	388 (38.4)	439 (44.1)	0.009
β-blockers (%)	783 (39.0)	390 (38.6)	393 (39.5)	0.672
Aspirin (%)	198 (9.9)	91 (9.0)	107 (10.8)	0.188
Insulin (%)	279 (13.9)	137 (13.6)	142 (14.3)	0.641
Diuretic (%)	138 (6.9)	73 (7.2)	65 (6.5)	0.543
Statin (%)	223 (11.1)	106 (10.5)	117 (11.8)	0.364
Laboratory variables				
WBC(*109/L)	6.2 (5.0,7.7)	5.9 (4.7,7.2)	6.6 (5.3,8.1)	<0.001
Platelet(*109/L)	191 (146,242)	177 (131,227)	205 (160,261)	<0.001
Hemoglobin(g/L)	90 (75,108)	87 (73,105)	93 (77,110)	<0.001
Albumin (g/L)	35.9 (32.1,39.3)	35.9 (32.0,39.4)	35.9 (32.3,39.2)	0.709
Triglycerides (mmol/L)	1.3 (0.9,1.9)	1.0 (0.8,1.4)	1.8 (1.4,2.5)	<0.001
RC (mmol/L)	0.62 (0.40,0.98)	0.41 (0.28,0.53)	0.97 (0.71,1.37)	<0.001
HDL -C(mmol/L)	1.10 (0.90,1.40)	1.31 (1.08,1.58)	0.95 (0.79,1.12)	<0.001
RC/HDL-C	0.55 (0.32,0.97)	0.32 (0.21,0.43)	0.98 (0.72,1.48)	<0.001
Creatinine (μmol/L)	720 (552,951)	730 (564,963)	715 (542,939)	0.078
Uric acid (μmol/L)	411 (345,484)	407 (338,487)	417 (351,483)	0.091
Sodium(mmol/L)	140.0 (138.0,142.0)	140.0 (138.0,142.0)	140.0 (137.8,142.2)	0.299
Calcium (mmol/L)	2.1 (2.0,2.3)	2.1 (1.9,2.3)	2.2 (2.0,2.3)	<0.001
Phosphorus (mmol/L)	1.6 (1.3,2.0)	1.7 (1.4,2.0)	1.6 (1.3,2.0)	0.001
Potassium (mmol/L)	4.1 (3.5,4.7)	4.2 (3.6,4.8)	3.9 (3.4,4.5)	<0.001
FBG (mmol/L)	4.8 (4.2,5.7)	4.7 (4.1,5.4)	4.9(4.3,6.0)	<0.001
Total Kt/V	2.2 (1.8,2.7)	2.2 (1.8,2.6)	2.3 (1.9,2.7)	0.010
RRF (mL/min/1.73 m^2)	3.3 (1.8,5.4)	3.2 (1.8,5.2)	3.3 (1.9,5.6)	0.035

All continuous variables were skewed distribution, the values for continuous variables were given as P50 (P25, P75). BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; WBC, white blood cell; RC, remnant cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG: fasting blood glucose; Total Kt/V, K, clearance of urea; t, dialysis time; V, volume of distribution of urea; RRF, renal residual function

all-cause and CVD death, as well as moving to hemodialysis therapy, kidney transplantation, other center's care, or the study's conclusion on May 31, 2017. Competing risk analysis was utilized to consider the impact of the previously mentioned follow-up outcomes on mortality. To minimize the possibility of reverse causality, participants with a past experience of CVD or those who passed away within six months before the follow-up were excluded from the multivariate Cox regression analysis. Subgroup analyses were executed to evaluate potential modifications in the RC/HDL-C-mortality association across clinically relevant subpopulations. The subgroup classification criteria included age threshold (< 60 vs. ≥ 60 years), sex, hypertensive history (yes/no), diabetes status (present/absent), and TG concentrations categorized at 1.7 mmol/L. All computational procedures were executed through SPSS 26.0 software and R (R-4.3.0), and $P < 0.05$ indicated statistical significance.

Table 2 Incidence rate of death according to RC/ HDL-C ratio

Outcomes	RC/HDL-C ratio		
	Total	RC/HDL-C ratio<0.56	RC/HDL-C ratio ≥ 0.56
All-cause mortality			
Deaths, n	549	226	323
Deaths, per 1000 person years	87.4	36.0	51.4
CVD mortality			
Deaths, n	269	111	158
Deaths, per 1000 person years	42.8	17.7	25.2

The incidence rate was calculated by dividing the proportion of events by the total effective observation time in the risk, which is converted to the number of episodes per 1000 years. RC, remnant cholesterol; HDL-C, high-density lipoprotein cholesterol

Results

Baseline characteristics

After excluding 37 patients under 18 or over 80 years old, 52 patients who had not been monitored for more than three months, and 11 patients who had malignant diseases, the final analysis included 2006 CAPD patients (Fig. 1).

There were no differences in the distributions of the primary and input data when we compared the two variables (Table S1).

The analyzed cohort included 2,006 participants, demonstrating a median age of 51 years (IQR 40–62). Males accounted for 54.7% of participants, while 416 (20.7%) had diabetes, and 295 (14.7%) had CVD. The median RC/HDL-C ratio was 0.55 (0.32, 0.97). The RCS analyses guided the selection of reference groups; these analyses determined the optimal reference category for RC/HDL-C in all-cause mortality assessment, establishing 0.56 as the critical subgroup threshold (Fig. S1). Patient characteristics by baseline RC/HDL-C are shown in Table 1. Higher RC/HDL-C was linked to greater usage of angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), older age, and a greater risk of CVD. Higher RC/HDL-C was linked to increases in BMI, white blood cell, platelet, hemoglobin, TG, fasting blood glucose levels, serum calcium levels, total Kt/V, and RRF but decreased blood pressure and serum potassium and serum phosphorus levels.

The RC/HDL-C ratio and mortality

The median follow-up period spanned 21.7 months (IQR 19.9–24.1). Throughout the following period, 549 (27.4%) all-cause deaths, 230 (11.5%) patients were moved to HD, 91 patients (4.5%) received renal transplants, 28 patients (1.4%) were moved to other peritoneal dialysis clinics, and 42 patients (2.1%) were excluded due to loss of contact (Fig. 1). Among the 549 deaths, 269 (49.0%) were caused by CVD, 59 (10.7%) by infections, 111 (20.2%) by other causes, and 110 (20.0%) by unknown causes. The low RC/HDL-C group exhibited 226 deaths (36.0 per 1000 person-years), whereas the high-ratio group demonstrated 323 deaths (51.4 per 1000 person-years) (Table 2). The Kaplan–Meier cumulative morbidity curves used in the survival analysis revealed that the higher RC/HDL-C group had greater all-cause mortality (log-rank test $P<0.0001$) and CVD mortality (log-rank test $P=0.003$) than the lower RC/HDL-C group did (Fig. 2). Multivariable-adjusted Cox regression modeling demonstrated elevated hazards for all-cause mortality (HR: 1.335; 95%CI, 1.112–1.603) and CVD mortality (HR:

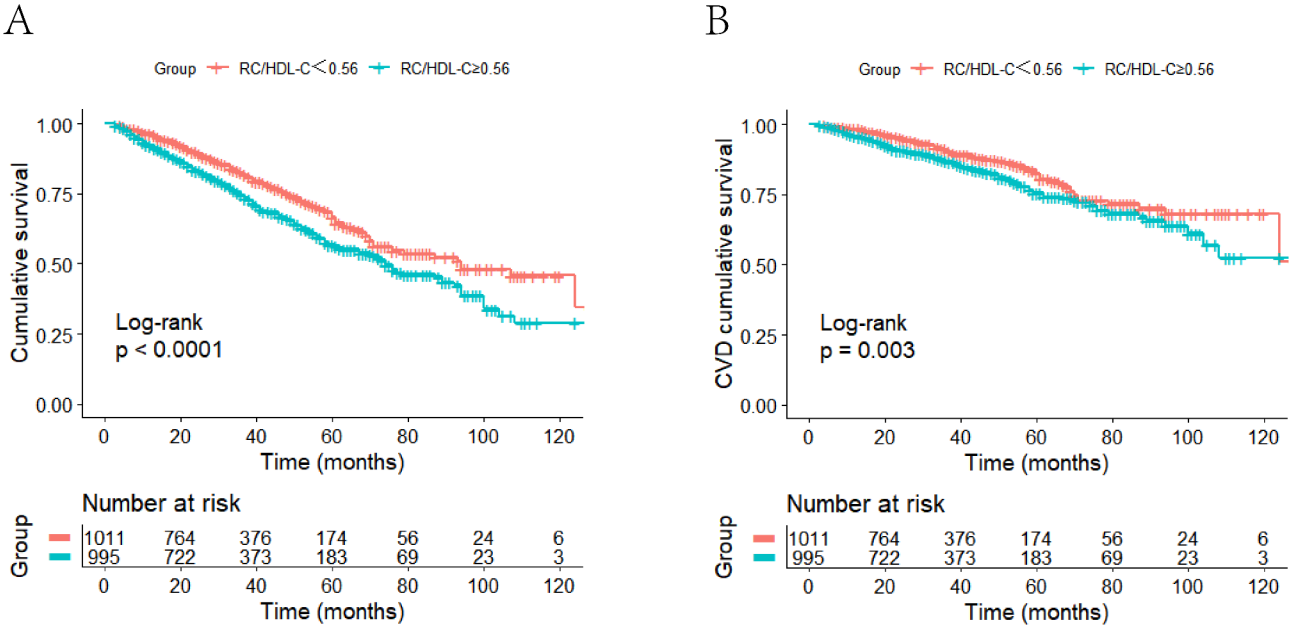

Fig. 2 Kaplan-Meier curves of CAPD patients with different levels of RC/HDL-C ratio all-cause mortality (**A**) and CVD mortality (**B**)

Table 3 RC/HDL-C ratio predicts the prognosis of all-cause and CVD mortality in CAPD patients

All-cause mortality	HR (95%CI)	*P* value
Univariate	1.449 (1.222,1.718)	<0.001
Multivariable	1.335 (1.112,1.603)	0.002
Patients without prior cardiovascular disease	1.427 (1.152,1.768)	0.001
Patients with follow-up period >6 months	1.338 (1.105,1.620)	0.003
CVD mortality		
Univariate	1.441 (1.130,1.838)	0.003
Multivariable	1.319 (1.013,1.717)	0.040
Patients without prior cardiovascular disease	1.436 (1.053,1.957)	0.022
Patients with follow-up period >6 months	1.352 (1.027,1.780)	0.032

Reference group was the lower RC/HDL-C group (RC/HDL-C<0.56);

Unless stated, model adjusted for age, sex, body mass index, comorbidities, medication use, and laboratory variables. HR, hazards ratio

1.319; 95%CI, 1.013–1.717) in the elevated RC/HDL-C cohort compared to lower-ratio counterparts. The statistical models incorporated comprehensive adjustments for comorbidity profiles, pharmacotherapy regimens, demographic variables (age/sex), and laboratory biomarkers. The results of the RC/HDL-C study remained largely unchanged after excluding patients who had a history of CVD or those who passed away within six months of follow-up (Table 3).

In the competing risk analysis, the cumulative incidence curve between different RC/HDL-C groups was significant for all-cause mortality ($P<0.001$). Nevertheless, there was no difference in metastasis to HD treatment ($P>0.05$), kidney transplantation ($P>0.05$), transfer to different facilities ($P>0.05$), or loss to follow-up ($P>0.05$). All-cause and CVD mortality results were comparable (Fig. 3).

Table 4 HDL-C, RC, RC/HDL-C ratio based on Cox regression model

All-cause mortality	HR (95%CI)	*P* value
RC	1.331 (1.106, 1.603)	0.003
HDL	0.992 (0.826, 1.190)	0.929
RC/HDL-C ratio	1.335 (1.112,1.603)	0.002
CVD mortality		
RC	1.296 (0.992,1.691)	0.057
HDL-C	0.887 (0.680,1.157)	0.376
RC/HDL-C ratio	1.319 (1.013,1.717)	0.040

Reference group was the lower RC/HDL-C group (RC/HDL-C<0.56);

Unless stated, model adjusted for age, sex, body mass index, comorbidities, medication use, and laboratory variables. HR, hazards ratio; RC, remnant cholesterol; HDL-C, high-density lipoprotein cholesterol

Comparison with RC and HDL-C

To examine the comparative prognostic performance of the RC/HDL-C ratio versus isolated RC and HDL-C measurements in CADP patients, cohorts were stratified using RCS-derived thresholds for baseline serum RC and HDL-C, employing consistent stratification criteria aligned with the RC/HDL-C grouping methodology. After controlling for comorbidities, medications, sex, age, and biochemical tests in multifactorial Cox stepwise regression analyses, elevated RC levels demonstrated significant associations with increased all-cause mortality risk in CAPD recipients (HR: 1.331, 95%CI, 1.106–1.603), though no differential CVD mortality risk was observed between high and low RC subgroups. Notably, HDL-C concentrations showed no statistically meaningful correlations with either CVD or all-cause mortality endpoints in this population (Table 4).

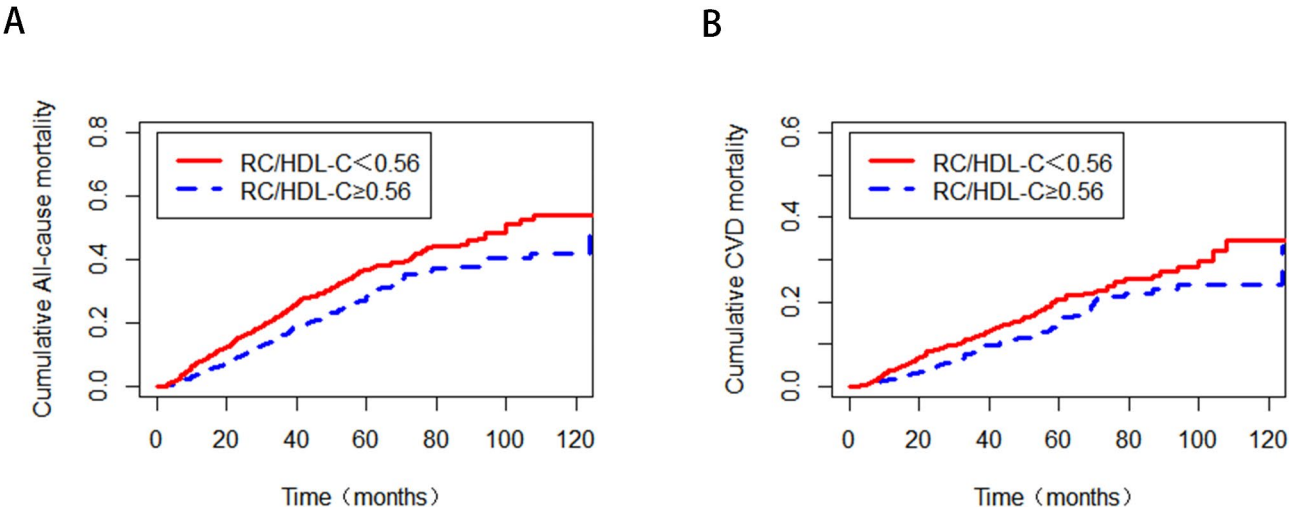

Fig. 3 Competing risk models. **A**: Estimated cumulative incidence curves between the all-cause mortality and other competing events for each RC/HDL-C group. **B**: Estimated cumulative incidence curves between CVD mortality and other competing events for each RC/HDL-C group

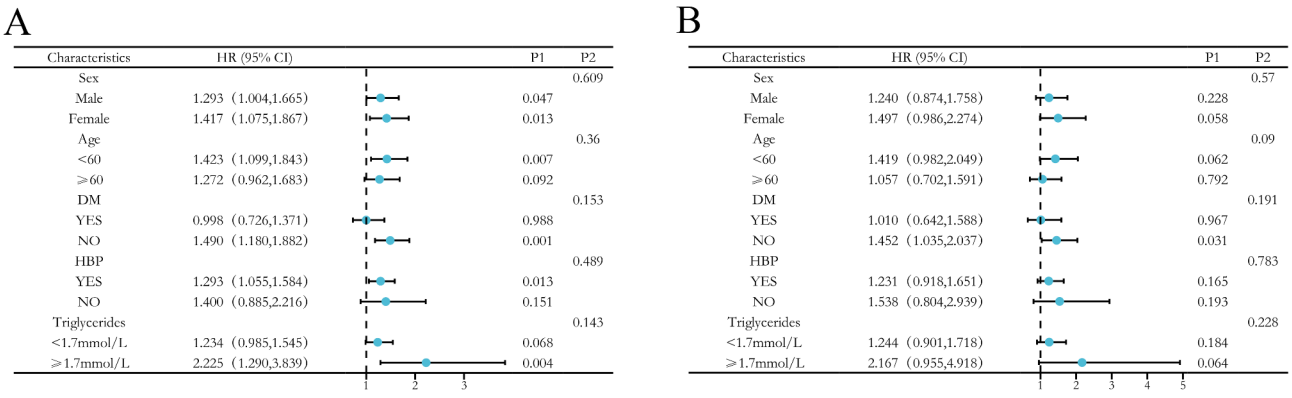

Fig. 4 Forest plots of the relationship between RC/HDL-C and all-cause mortality (**A**) and CVD mortality (**B**) in different subgroups. Note: The P1 value corresponds to the relationship between RC/HDL-C and cardiovascular disease mortality or all-cause mortality in different subgroups. The P2 value corresponds to the interaction test between the RC/HDL-C and the subgroups variable of interest. HR, hazard ratio; CI, confidence interval

Subgroup analyses

Several subgroups in this study, such as males or females, those with or without diabetes mellitus, those with or without hypertension, those with or without high triglyceride levels, and those who are old (≥ 60 years) or young (< 60 years), were conducted to examine relationship between the RC/HDL-C ratio and cardiovascular/all-cause mortality. Cox proportional hazards regression with forest plot visualization was utilized to quantify these relationships, revealing no statistically significant interaction effects across subgroups (Fig. 4).

Discussion

This multi-center analysis revealed elevated RC/HDL-C ratios demonstrated strong correlations with heightened risks of all-cause and CVD mortality in CAPD patients. Notably, combining HDL-C and RC enhanced predictive accuracy for CVD mortality in the CAPD population compared to individual biomarker assessment.

Dyslipidemia is a validated cardiovascular risk indicator in community populations and is also prevalent among individuals with CAPD. Compared to HD patients, the lipid composition of CAPD patients is more atherosclerotic, characterized by higher levels of TC and LDL-C, along with a more significant increase in triglyceride levels [5]. One potential explanation is that patients with CAPD absorb a large amount of glucose from the peritoneal dialysis fluid, which increases insulin levels and promotes the production and release of hepatic lipoproteins [22]. It has been shown that statin-mediated LDL-C reduction lacks prognostic benefits for dialysis patients [23]. Therefore, to better understand the true significance of dyslipidemia in CAPD patients, a combination of the characteristics of the lipid profile of CAPD patients and additional confounding factors need to be considered.

RC is an unconventional lipid indicator. In general, elevated RC levels are directly correlated with elevated non-fasting triglyceride levels. Additionally, increased triglyceride levels are excellent indicators of enhanced RC and are a solid predictor of a greater risk of cardiovascular disease [24]. However, given that most body cells can easily metabolize triglycerides, it is doubtful that triglycerides alone cause CVD. Instead, it appears more likely that RC is the catalyst for the progression of atherosclerosis [8, 24, 25]. Emerging evidence demonstrates significant associations between elevated RC concentrations and adverse cardiovascular outcomes in diabetic populations [26]. This relationship extends to peritoneal dialysis recipients, where heightened RC levels correlate with increased mortality risks [13]. Notably, an investigation involving 5,414 participants revealed that elevated RC concentrations independently predict mortality among patients with ischemic heart disease [20]. Noncardiovascular conditions like cancer and inflammatory disorders that are linked to higher mortality rates have also been linked to RC [27–29]. It is possible that RC can penetrate the artery wall's intima and become stuck there, causing inflammation and vascular injury [7, 30]. Nevertheless, elevated RC levels demonstrate associations with systemic low-grade inflammatory states, in contrast to elevated LDL-C levels [21]. In addition to causing inflammation, RC may also increase the likelihood of a poor prognosis by interfering with endothelium function, altering the connections between monocytes and endothelial cells, as well as encouraging the production of foam cells [8, 31, 32]. A worldwide standard for the precise safe range of RC is not available. A postprandial RC of ≥ 0.9 mmol/L or a fasting RC of ≥ 0.8 mmol/L, according to some pertinent studies, is regarded as a high RC range [33]. To create a uniform clinical standard, more investigations are needed. Owing to its strong anti-inflammatory, antioxidant, and thrombogenic effects, HDL-C is typically regarded as "good" cholesterol [34]. According to a recent observational and Mendelian randomization study [35], reduced HDL-C levels could be a direct cause for elevated CVD risk.

Reduced HDL-C concentrations in plasma have been established as an independent predictor for progression to advanced CKD (stages 4–5). HDL-C has been recognized as a lipid parameter that impacts CKD progression [15]. Renal disease affects HDL-C composition and function, which may contribute to the loss of its atheroprotective properties. Thus, this study did not find a relationship between HDL-C and CVD or all-cause mortality in CAPD patients [36].

When considered collectively, RC is a lipid marker linked to low-grade systemic inflammation and atherosclerosis progression. A reduced HDL-C level is linked to many risk factors and is an atheroprotective lipoprotein. The prognosis of CAPD patients may be more accurately predicted by the combined assessment of RC and HDL-C. Through thorough multivariable adjustment, this multicenter cohort study examined 2,006 CAPD cases to confirm the RC/HDL-C ratio's predictive ability for mortality risk. The findings demonstrated that this new biomarker can independently predict death from all causes and CVD.

A recent study of 615 patients undergoing coronary angiography identified a relationship between serum RC/HDL-C ratios and both advancement and seriousness of coronary artery disease [37]. Furthermore, analysis of 658 ischemic stroke survivors demonstrated the RC/HDL-C ratio's better predictive capacity for cerebral atherosclerotic stenosis compared to isolated lipid parameters [16]. Moreover, an analysis of studies has shown that the RC/HDL-C ratio acts as a valuable indicator for NAFLD and diabetes complications. When diagnosing NAFLD, the conjunction of RC and HDL-C performs noticeably better than traditional lipid indicators [17, 18]. Our results show that RC/HDL-C has greater prognostic value for cardiovascular death than RC or HDL-C alone, and it predicts both all-cause and CVD mortality in the CAPD group.

How RC/HDL-C predicts mortality in CAPD patients remains unknown. The following are potential mechanisms. First, the RC/HDL-C ratio represents a composite indicator reflecting either elevated RC levels, diminished HDL-C concentrations, or concurrent dysregulation of both lipid parameters. RC is a TG-rich lipoprotein cholesterol, and plasma HDL-C concentration variations exhibit an inverse relationship with TG levels, demonstrating reciprocal metabolic regulation between these lipid parameters [38]. Mechanistic studies suggest that the decrease in HDL-C levels in the presence of cholesterol ester transfer protein results from the interchange of TG and cholesterol ester in TG-rich lipoproteins and the more rapid breakdown of smaller, TG-rich HDL-C [39, 40]. RC/HDL-C indicates how atherogenic and anti-cardiovascular risk factors are balanced. Second, several clinically critical poor outcomes are linked to chronic inflammation, a prevalent consequence in individuals with CAPD [41]. RC has a proinflammatory effect [42]. In this study, along with CVD mortality, inflammatory conditions like pneumonia and peritonitis were prominent contributors to patient deaths. Unlike to LDL-C, elevated RC levels demonstrate associations with persistent low-grade systemic inflammation [21]. According to specific theories, RC contributes significantly to the development of CKD using chronic inflammation, and the correlation between RC and CKD is, in part, mediated by inflammatory indicators, including increased leukocytes and high-sensitivity CRP [43]. On the other hand, HDL-C has been extensively demonstrated to have anti-inflammatory qualities [44]. Finally, metabolic syndrome (MetS), which is prevalent among CAPD patients, is linked to elevated hazard of overall mortality in this population [45, 46]. The RC/HDL-C ratio may serve as a potential predictor for CVD and all-cause mortality in CAPD patients, potentially mediated by insulin resistance (IR), a central factor in the development of MetS. Some studies have proposed the TG/HDL-C ratio as an effective surrogate biomarker for IR [47, 48]. The TG-enriched composition of RC suggests its ratio to HDL-C may exhibit a direct relationship with IR. However, no research has established a link between the two. Hence, more investigations are needed to determine whether the RC/HDL-C ratio and IR are related.

The high-level RC/HDL-C group in this study also had lower blood pressure and greater hemoglobin, total Kt/V, and RRF values than the low-level group. The following represent some potential causes for this. Initially, contrary to earlier research, hemoglobin was higher in this study's high RC/HDL-C group, where mortality was higher [49]. Hemoglobin levels could fluctuate over the follow-up period, which could be the cause. The patients' hemoglobin profile is not completely represented by their hemoglobin levels at baseline. With respect to testing procedures, hypertriglyceridemia might result in a misleading increase in hemoglobin due to increased blood turbidity [50]. Second, a connection may exist between the lipid profile and RRF preservation in CAPD patients, as evidenced by the fact that RRF was greater in this study's high RC/HDL-C group. Additionally, greater ACEI/ARB use in this patient population could help protect against RRF. Nevertheless, further research is still needed to establish causation. Furthermore, total Kt/V comprises both renal and peritoneal Kt/V. The high total Kt/V among patients with high RC/HDL-C levels may have resulted from greater renal Kt/V in this patient group due to high RRF. Research has indicated a substantial correlation between increased systolic blood pressure and decreased HDL-C but increased TG and RC [51]. However, the development of hypertension is multifactorial, and the baseline values in this study did not

exclude the effects of various medications and other factors. Thus, additional investigation will be necessary to confirm this relationship.

This study establishes that the RC/HDL-C ratio acts as a new prognostic biomarker for mortality risk in CAPD patients. This biomarker facilitates mortality risk stratification in peritoneal dialysis recipients and provides a novel avenue for future research on lipid management in the maintenance dialysis population. Clinicians should closely monitor the lipid profile of CAPD patients, focusing on more than just traditional lipids such as TG and LDL-C. In the CAPD population, patients presenting with high RC and low HDL-C require enhanced medical care and monitoring during follow-up and a more personalized treatment plan. The RC/HDL-C ratio acts as an effective and straightforward predictor of mortality risk in this population, offering an early signal for prompt patient intervention.

Strengths and limitations

This study's strengths include its sizeable multicenter sample size, high level of data completeness, and precise covariates that enable adjustment for possible confounding variables. There are a few noteworthy limitations. First, additional prospective studies are necessary, as this research was retrospective and could only demonstrate a correlation, rather than a causal connection, between the RC/HDL-C and adverse outcomes. Second, this research considered only baseline data and did not measure dynamic changes in indicators, which cannot adequately reflect trends in blood parameters. Furthermore, this study indirectly calculates RC levels instead of employing direct measurements of active RC. Nevertheless, indirect calculation techniques are inexpensive and often employed in clinical and research contexts. Owing the unavailability of data on markers representing residual cardiovascular risk, such as apolipoprotein B and ultrasensitive C-reactive protein, these markers were excluded from the analysis. Finally, the fact that all qualifying patients were from China raises the possibility that the results cannot be applied to other ethnic populations.

Conclusions

Ultimately, this research revealed that, among CAPD patients, a higher serum RC/HDL-C ratio independently predicts both all-cause and CVD mortality. For individuals with CAPD, the RC/HDL-C ratio can be regarded as a practical and affordable marker for determining mortality. This investigation provides valuable insights into lipid management in the maintenance dialysis population. Monitoring the RC/HDL-C in a clinical setting may allow early identification of mortality risk in the CAPD population.

Abbreviations

RC	Remnant cholesterol
HDL-C	High-density lipoprotein cholesterol
CAPD	Continuous ambulatory peritoneal dialysis
CVD	Cardiovascular disease
CKD	Chronic kidney disease
TC	Total cholesterol
TG	Triglyceride
LDL-C	Low-density lipoprotein cholesterol
VLDL	Very low-density lipoprotein
IDL	Intermediate-density lipoprotein
NAFLD	Nonalcoholic fatty liver disease
HD	Hemodialysis
BMI	Body mass index
RRF	Renal residual function
IR	Insulin resistance
MetS	Metabolic syndrome

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02522-9.

Supplementary Material 1

Acknowledgements

The authors are grateful for all the participants in this study.

Author contributions

ZBW: Project development, Manuscript writing; SBH: Data analysis, Manuscript revision; NT: Data collection; QDX: Provide statistical support; XJZ: Data collection; FFP: Data collection; XYW: Data collection; NS: Data collection; XRF: Data analysis; XMT: Assist in data analysis; XFW: Manuscript editing; QZ: Data collection; JBL: Data management; JL: Project development, Manuscript editing, Funding. YQW: Data management, Manuscript editing, Funding. All authors have read and approved the manuscript.

Funding

This study was supported by the grants: Guangzhou Key Discipline of Urology; Second Affiliated Hospital of Guangzhou Medical University Fund Project (2021-LCYJ-04). Clinical Research Project of the Second Affiliated Hospital of Guangzhou Medical University (2021-LCYJ-DZX-03, 2022-LCYJ-YYDZX-03). The open research funds from the Sixth Affiliated Hospital of Guangzhou Medical University, Qingyuan People's Hospital (202201-304). Guangdong Basic and Applied Basic Research Foundation (2023A1515011721， 2024A1515011439).

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the Second Affiliated Hospital of Guangzhou Medical University (approval number 2024-hg-ks-10) and the 1964 Helsinki Declaration as well as its later amendments or comparable ethical standards.

Consent for publication

All the authors gave their consent to publication.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Nephrology, The Second Affiliated Hospital, Guangzhou Medical University, Guangzhou 510260, China
[2]Department of Nephrology, General Hospital of Ningxia medical university, Yinchuan, China

[3]Department of Nephrology, Jiangmen Central Hospital, Jiangmen, China
[4]Department of Nephrology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China
[5]Department of Nephrology, Zhujiang Hospital, Southern Medical University, Guangzhou, China
[6]Department of Nephrology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou University, No.1, Jianshe East Road, Zhengzhou, China
[7]Department of Hematology, The Sixth Affiliated Hospital of Sun Yat-Sen University, No.26, Yuancun Erheng Road, Guangzhou 510655, PR China
[8]Department of Nephrology, Jiujiang NO. 1 People's Hospital, Jiangxi, China
[9]Department of Nephrology, Dongguan Songshan Lake Tungwah Hospital, No.7, Kefa Road, Dongguan 523000, China
[10]Department of Nephrology, Affiliated Sixth People's Hospital, Shanghai Jiao Tong University, Shanghai, China
[11]Department of Medical Statistics, Clinical Trials Unit, The First Affiliated Hospital, Sun Yat- sen University, Guangzhou, China
[12]Department of Geriatrics, The Second Affiliated Hospital, Guangzhou Medical University, Guangzhou, China

Received: 15 December 2024 / Accepted: 11 March 2025
Published online: 21 March 2025

References

1. Sharma S, Sarnak MJ, Epidemiology. The global burden of reduced GFR: ESRD, CVD and mortality. Nat Rev Nephrol. 2017;13:447–8.
2. Cho Y, Bello AK, Levin A, Lunney M, Osman MA, Ye F, et al. Peritoneal Dialysis use and practice patterns: an international survey study. Am J Kidney Dis Off J Natl Kidney Found. 2021;77:315–25.
3. Matsushita K, Ballew SH, Wang AY-M, Kalyesubula R, Schaeffner E, Agarwal R. Epidemiology and risk of cardiovascular disease in populations with chronic kidney disease. Nat Rev Nephrol. 2022;18:696–707.
4. Thobani A, Jacobson TA. Dyslipidemia in patients with kidney disease. Cardiol Clin. 2021;39:353–63.
5. Mikolasevic I, Žutelija M, Mavrinac V, Orlic L. Dyslipidemia in patients with chronic kidney disease: etiology and management. Int J Nephrol Renov Dis. 2017;10:35–45.
6. Investigators AIM-HIGH, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, et al. Niacin in patients with low HDL cholesterol levels receiving intensive Statin therapy. N Engl J Med. 2011;365:2255–67.
7. Chapman MJ, Ginsberg HN, Amarenco P, Andreotti F, Borén J, Catapano AL, et al. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. Eur Heart J. 2011;32:1345–61.
8. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet Lond Engl. 2014;384:626–35.
9. Wang Y, Zha F, Han Y, Cai Y, Chen M, Yang C, et al. Nonlinear connection between remnant cholesterol and stroke risk: evidence from the China health and retirement longitudinal study. Lipids Health Dis. 2023;22:181.
10. Li W, Huang Z, Fang W, Wang X, Cai Z, Chen G, et al. Remnant cholesterol variability and incident ischemic stroke in the general population. Stroke. 2022;53:1934–41.
11. Yu D, Wang Z, Zhang X, Qu B, Cai Y, Ma S, et al. Remnant cholesterol and cardiovascular mortality in patients with type 2 diabetes and incident diabetic nephropathy. J Clin Endocrinol Metab. 2021;106:3546–54.
12. 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;76:2712–24.
13. Deng J, Tang R, Chen J, Zhou Q, Zhan X, Long H, et al. Remnant cholesterol as a risk factor for all-cause and cardiovascular mortality in incident peritoneal Dialysis patients. Nutr Metab Cardiovasc Dis. 2023;33:1049–56.
14. de Freitas EV, Brandão AA, Pozzan R, Magalhães ME, Fonseca F, Pizzi O, et al. Importance of high-density lipoprotein-cholesterol (HDL-C) levels to the incidence of cardiovascular disease (CVD) in the elderly. Arch Gerontol Geriatr. 2011;52:217–22.
15. Weldegiorgis M, Woodward M. Elevated triglycerides and reduced high-density lipoprotein cholesterol are independently associated with the onset of advanced chronic kidney disease: a cohort study of 911,360 individuals from the united Kingdom. BMC Nephrol. 2022;23:312.
16. Yang W-S, Li R, Shen Y-Q, Wang X-C, Liu Q-J, Wang H-Y, et al. Importance of lipid ratios for predicting intracranial atherosclerotic stenosis. Lipids Health Dis. 2020;19:160.
17. Zeng R-X, Li S, Zhang M-Z, Li X-L, Zhu C-G, Guo Y-L, et al. Remnant cholesterol predicts periprocedural myocardial injury following percutaneous coronary intervention in poorly-controlled type 2 diabetes. J Cardiol. 2017;70:113–20.
18. Zou Y, Hu C, Kuang M, Chai Y. Remnant cholesterol/high-density lipoprotein cholesterol ratio is a new powerful tool for identifying non-alcoholic fatty liver disease. BMC Gastroenterol. 2022;22:134.
19. Cordero A, Alvarez-Alvarez B, Escribano D, García-Acuña JM, Cid-Alvarez B, Rodríguez-Mañero M, et al. Remnant cholesterol in patients admitted for acute coronary syndromes. Eur J Prev Cardiol. 2023;30:340–8.
20. Jepsen A-MK, Langsted A, Varbo A, Bang LE, Kamstrup PR, Nordestgaard BG. Increased remnant cholesterol explains part of residual risk of All-Cause mortality in 5414 patients with ischemic heart disease. Clin Chem. 2016;62:593–604.
21. Varbo A, Freiberg JJ, Nordestgaard BG. Extreme nonfasting remnant cholesterol vs extreme LDL cholesterol as contributors to cardiovascular disease and all-cause mortality in 90000 individuals from the general population. Clin Chem. 2015;61:533–43.
22. Tsimihodimos V, Dounousi E, Siamopoulos KC. Dyslipidemia in chronic kidney disease: an approach to pathogenesis and treatment. Am J Nephrol. 2008;28:958–73.
23. Ghayda RA, Lee JY, Yang JW, Han CH, Jeong GH, Yoon S, et al. The effect of Statins on all-cause and cardiovascular mortality in patients with non-dialysis chronic kidney disease, patients on dialysis, and kidney transplanted recipients: an umbrella review of meta-analyses. Eur Rev Med Pharmacol Sci. 2021;25:2696–710.
24. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA. 2007;298:299–308.
25. Varbo A, Benn M, Tybjærg-Hansen A, Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol. 2013;61:427–36.
26. Cao Y-X, Zhang H-W, Jin J-L, Liu H-H, 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;19:104.
27. Li M, Liu Q, Shi M, Fu M, He G. Association between remnant cholesterol and the risk of 4 site-specific cancers: evidence from a cross-sectional and Mendelian randomization study. Lipids Health Dis. 2024;23:256.
28. Tian Y, Wu Y, Qi M, Song L, Chen B, Wang C, et al. Associations of remnant cholesterol with cardiovascular and cancer mortality in a nationwide cohort. Sci Bull. 2024;69:526–34.
29. Fabre B, Fernandez Machulsky N, Olano C, Jacobsen D, Gómez ME, Perazzi B, et al. Remnant cholesterol levels are associated with severity and death in COVID-19 patients. Sci Rep. 2022;12:17584.
30. Bernelot Moens SJ, Verweij SL, Schnitzler JG, Stiekema LCA, Bos M, Langsted A, et al. Remnant cholesterol elicits arterial wall inflammation and a multi-level cellular immune response in humans. Arterioscler Thromb Vasc Biol. 2017;37:969–75.
31. Nakajima K, Tanaka A. Postprandial remnant lipoproteins as targets for the prevention of atherosclerosis. Curr Opin Endocrinol Diabetes Obes. 2018;25:108–17.
32. Tada H, Nohara A, Inazu A, Mabuchi H, Kawashiri M-A. Remnant lipoproteins and atherosclerotic cardiovascular disease. Clin Chim Acta Int J Clin Chem. 2019;490:1–5.
33. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J. 2016;37:2999–3058.
34. Kronenberg F. HDL in CKD-The devil is in the detail. J Am Soc Nephrol JASN. 2018;29:1356–71.
35. Chen J-X, Li Y, Zhang Y-B, Wang Y, Zhou Y-F, Geng T, et al. Nonlinear relationship between high-density lipoprotein cholesterol and cardiovascular disease: an observational and Mendelian randomization analysis. Metabolism. 2024;154:155817.
36. Pavanello C, Ossoli A. HDL and chronic kidney disease. Atheroscler Plus. 2023;52:9–17.
37. Pan L, Jiang W, Liao L, Li W, Wang F. Association between the remnant cholesterol to high-density lipoprotein cholesterol ratio and the risk of coronary artery disease. Coron Artery Dis. 2024;35:114–21.

38. Lamarche B, Després JP, Pouliot MC, Prud'homme D, Moorjani S, Lupien PJ, et al. Metabolic heterogeneity associated with high plasma triglyceride or low HDL cholesterol levels in men. Arterioscler Thromb J Vasc Biol. 1993;13:33–40.
39. Lamarche B, Uffelman KD, Carpentier A, Cohn JS, Steiner G, Barrett PH, et al. Triglyceride enrichment of HDL enhances in vivo metabolic clearance of HDL Apo A-I in healthy men. J Clin Invest. 1999;103:1191–9.
40. Horowitz BS, Goldberg IJ, Merab J, Vanni TM, Ramakrishnan R, Ginsberg HN. Increased plasma and renal clearance of an exchangeable pool of Apolipoprotein A-I in subjects with low levels of high density lipoprotein cholesterol. J Clin Invest. 1993;91:1743–52.
41. Cho Y, Hawley CM, Johnson DW. Clinical causes of inflammation in peritoneal Dialysis patients. Int J Nephrol. 2014;2014:909373.
42. Henein MY, Vancheri S, Longo G, Vancheri F. The role of inflammation in cardiovascular disease. Int J Mol Sci. 2022;23:12906.
43. Yuan Y, Hu X, Zhang S, Wang W, Yu B, Zhou Y, et al. Remnant cholesterol, preinflammatory state and chronic kidney disease: association and mediation analyses. Ren Fail. 2024;46:2361094.
44. Calabresi L, Gomaraschi M, Simonelli S, Bernini F, Franceschini G. HDL and atherosclerosis: insights from inherited HDL disorders. Biochim Biophys Acta. 2015;1851:13–8.
45. Lo WK. Metabolic syndrome and obesity in peritoneal Dialysis. Kidney Res Clin Pract. 2016;35:10–4.
46. Sanguankeo A, Upala S. Metabolic syndrome increases mortality risk in Dialysis patients: A systematic review and Meta-Analysis. Int J Endocrinol Metab. 2018;16:e61201.
47. Young KA, Maturu A, Lorenzo C, Langefeld CD, Wagenknecht LE, Chen Y-DI, et al. The triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio as a predictor of insulin resistance, β-cell function, and diabetes in Hispanics and African Americans. J Diabetes Complications. 2019;33:118–22.
48. Zhang M, Zhou J, Liu Y, Sun X, Luo X, Han C, et al. Risk of type 2 diabetes mellitus associated with plasma lipid levels: the rural Chinese cohort study. Diabetes Res Clin Pract. 2018;135:150–7.
49. Molnar MZ, Mehrotra R, Duong U, Kovesdy CP, Kalantar-Zadeh K. Association of hemoglobin and survival in peritoneal Dialysis patients. Clin J Am Soc Nephrol CJASN. 2011;6:1973–81.
50. Shi X, Feng K. Hypertriglyceridemia interferes with hemoglobin detection and calibration methods. Clin Lab. 2024;70.
51. Robinson BM, Tong L, Zhang J, Wolfe RA, Goodkin DA, Greenwood RN, et al. Blood pressure levels and mortality risk among Hemodialysis patients in the Dialysis outcomes and practice patterns study. Kidney Int. 2012;82:570–80.

Publisher's note