Diabetology & Metabolic Syndrome

RESEARCH

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The prognostic value of remnant cholesterol to adverse renal outcomes in patients with type 2 diabetes

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Abstract

Background Type 2 diabetes (T2DM) is known to have detrimental effects on renal health. Our study aimed to investigate the relationship between remnant cholesterol (remnant-C) and adverse renal outcomes in patients with T2DM.

Methods We utilized data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which included 10,196 participants with T2DM to investigate the relationship between remnant-C and adverse renal outcomes by performing Kaplan–Meier survival analysis, Cox proportional regression and Restricted cubic spline (RCS) analysis. Finally, several sensitivity analyses were conducted to assess the robustness of our findings.

Results Over a 7-year follow-up period, 2039 patients (23.2%) developed albuminuria, 5824 patients (57.1%) experienced worsening renal function, and 280 patients (2.7%) progressed to renal failure. After adjusting for multiple confounding factors, we found that remnant-C was significantly associated with the development of albuminuria ($P=0.007$) and worsening renal function ($P=0.002$). However, there was no discernible connection between remnant-C and renal faiure ($P=0.621$). In sensitivity analyses, the association between remnant-C and the risk of adverse renal outcomes remained robust.

Conclusion Our findings highlight the association between remnant-C and the risk of adverse renal outcomes in patients with T2DM. This easily calculable index can provide valuable information to physicians for predicting the risk of adverse renal outcomes in patients with T2DM.

Keywords Type 2 diabetes, Remnant cholesterol, Adverse renal outcomes

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Introduction

The escalating prevalence of diabetes and its complications constitutes a significant threat to global health. In 2021, the global population living with diabetes reached 529 million, corresponding to an age-standardized prevalence rate of 6.1% [1]. The kidney emerges as one of the primary target organs susceptible to microvascular damage in diabetes. Approximately 50% of patients with type 2 diabetes will develop diabetic kidney disease (DKD). Clinically, DKD is characterized by increased urinary albumin excretion, impaired renal function, or a combination of both [2, 3]. In several developed countries, including the United States, DKD stands as a leading cause of ESRD [4]. Concerning diabetes-related complications, DKD exerts a significant financial burden and a profound impact on the daily lives of those affected. The high prevalence of DKD, along with the associated disabilities and mortality, imposes substantial health and socioeconomic costs, particularly in countries like China [5, 6]. Therefore, a paramount objective is the development of effective strategies for the prevention and management of DKD in individuals with diabetes.

Remnant cholesterol, often referred to as the cholesterol content within triglyceride-rich lipoproteins (TRLs), primarily comprising intermediate density lipoprotein and very low-density lipoprotein [7], plays a critical role in the development of major adverse cardiovascular events (MACEs). Elevated serum levels of remnant-C have been associated with MACEs, as they facilitate increased penetration into the arterial wall [8]. Multiple studies have consistently demonstrated that the risk of MACEs in both primary and secondary prevention of cardiovascular disease (CVD) is heightened in individuals with higher circulating remnant-C levels [9–12]. However, the relationship between remnant-C and the risk of adverse renal outcomes has been less clear, with previous studies yielding inconsistent results [13–18]. Some investigations have shown connections between remnant-C levels and the risk of proteinuria and chronic kidney disease (CKD) [13–15], while others failed to establish such correlations [16–18]. This ambiguity in the impact of remnant cholesterol on CKD could be attributed to variations in sample sizes, disparities in study populations, differences in metabolic characteristics, intricate in vivo regulatory mechanisms, and the extent of adjustments for confounding factors. Considering the association between remnant-C and CKD, it is reasonable to postulate that remnant-C may also play a role in the development of adverse renal outcomes in individuals with diabetes. While previous research has demonstrated the predictive value of remnant-C concentration in the progression of DKD in type 1 diabetes [19], the relationship between remnant-C and adverse renal outcomes remains largely unexplored in type 2 diabetes.

In this extensive retrospective cohort study, our primary aim was to investigate whether remnant-C, a promising non-invasive biomarker associated with nutrition, could serve as a predictive indicator for incident adverse renal outcomes in T2DM using data from the ACCORD trial.

Methods

Study design and participants

In our study, we conducted a retrospective analysis of data from the ACCORD trial, which was funded by the National Heart, Lung, and Blood Institute. The ACCORD trial adopted a multicenter, randomized, and double 2×2 factorial design approach with the aim of elucidating the impact of three distinct medical treatment strategies. These strategies encompassed the glycemia trial, the lipid trial and the blood pressure trial, and sought to assess their effects on the morbidity and mortality of the study participants. The trial included a total of 10,251 middle-aged and older individuals diagnosed with type 2 diabetes, with a mean glycated hemoglobin level of 8.3% and a median diabetes duration of 10 years. Recruitment for the ACCORD trial took place between June 2001 and October 2005 at 77 research sites located across the United States and Canada. All participants were characterized by a high risk of CVD events, either due to the presence of clinical CVD, a high likelihood of CVD, or the presence of two or more high-risk factors for CVD. The specific inclusion and exclusion criteria for the study can be found in the original ACCORD study [20]. Participants who were missing the baseline remnant-C values were excluded from our study. It's important to note that the use of the ACCORD dataset in this study has been approved by the National Heart, Lung, and Blood Institute and the institutional review board of Xiangya Hospital, Central South University, ensuring adherence to ethical and regulatory standards.

Data collection and outcomes

The collected data encompassed a range of variables, including demographics (such as age, sex, race, education levels, smoking habits, alcohol consumption, and body mass index), common clinical indicators (including blood pressure, HbA1c, duration of diabetes, history of cardiovascular disease, blood lipid profiles, heart rate, and treatment regimens), and traditional kidney risk factors (serum creatinine, estimated glomerular filtration rate, and urinary albumin levels). To compute remnant-C levels, we utilized the following formula: remnant-C = Total Cholesterol (TC) - Low-Density Lipoprotein Cholesterol (LDL-C) - High-Density Lipoprotein Cholesterol (HDL-C). Among the initial cohort of 10,251 patients with type 2 diabetes, individuals lacking remnant-C values were excluded, resulting in the analysis of 10,196 patients with

T2DM in the current study. Our study focused on three specific adverse renal outcomes, each previously defined based on ACCORD criteria: the development of albuminuria, indicated by a urinary albumin level equal to or exceeding 30 mg/dL; the occurrence of worsening renal function, defined as a doubling of serum creatinine levels or a decrease in estimated glomerular filtration rate by more than 20 mL/min/m^2; progressing to renal failure, defined as the occurrence of end-stage renal disease or serum creatinine levels exceeding 3.3 mg/dL. Kidney microvascular events were prespecified outcomes in ACCORD, and the original definitions are used [21].

Statistical analysis

In our study, we used either mean (standard deviation) or median (interquartile range) to describe continuous variables and proportions (percentage) for categorical variables to provide an overview of the demographic information. To compare groups, the analysis of variance (ANOVA) or Kruskal-Wallis test was employed for continuous variables, while the chi-squared ($\chi 2$) test was used to compare categorical variables. Participants were stratified into four distinct remnant-C groups, denoted as quartile 1, quartile 2, quartile 3, and quartile 4, based on the interquartile range of remnant-C values within the entire cohort. To elucidate the relationship between remnant-C and various adverse renal outcomes, Kaplan-Meier estimates were utilized to calculate the survival probabilities of adverse renal outcomes based on remnant-C quartiles. Differences in these estimates were then compared using the log-rank test, which assessed whether there were significant disparities in outcomes among the quartiles. To assess the association between remnant-C and the incidence of adverse renal outcomes, we applied Cox proportional hazard models. In the establishment of multivariable models, variables with a *P*-value<0.05 in the univariate analyses, as well as those clinically linked to adverse renal outcomes, were included in the multivariable analyses. We employed three multivariate models with progressive adjustments to account for potential confounding factors related to adverse renal outcomes. Model 1 was adjusted for age, sex, education levels, race, systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking, alcohol consumption, and body mass index (BMI). Model 2 included the covariates from model 1 and added glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), duration of diabetes, serum creatinine, and urinary albumin (log-transformed). Model 3 further adjusted for the history of CVD and the treatment regimens. Furthermore, we employed restricted cubic spline analysis, which allowed for the exploration of both linear and nonlinear associations. Finally, several sensitivity analyses were conducted to assess the robustness of our findings. First, we excluded 2747 patients who had used fenofibrate at baseline to weaken the impact of fenofibrate on outcomes. Second, we excluded 3585 participants who had a history of CVD at baseline. In addition, to deal with missing baseline covariates, we used imputation methods such as single imputation. All analyses were conducted using R version 4.3.0. A two-sided *P*-value<0.05 was considered statistically significant in our analysis.

Baseline characteristics by quartiles of remnant-C

In Table 1, we presented the baseline characteristics of the 10,196 participants included in the study. The average age of the participants was 62.77 years, 61.5% were male, and 62.5% identified as White. The average body mass index was 32.23 kg/m^2 and additional baseline characteristics are detailed in Table 1. Regarding baseline blood lipid levels, our study found that the mean TC was 183.31 mg/dL, triglycerides (TG) median was 155.00 mg/dL, LDL-C averaged 104.9 mg/dL, and HDL-C was found to have an average of 41.87 mg/dL. Notably, the remnant-C was observed to be 31.00 mg/dL. We stratified the baseline characteristics of the participants based on quartiles of remnant-C levels. It was important to highlight that baseline remnant-C levels were associated with various demographic and clinical factors, including age, race, smoking status, alcohol consumption, education levels, BMI, duration of diabetes, SBP, DBP, heart rate, use of ACEI, HbA1c, fasting plasma glucose, blood lipid profiles (TC, TG, LDL-C, HDL-C), serum potassium, serum creatinine, eGFR, urinary albumin, urinary creatinine, urinary albumin-to-creatinine ratio (UACR), glycemia trial, blood pressure trial and lipid trial.

The risk of adverse renal outcomes was related with quartiles of remnant-C levels

The risk of adverse renal outcomes based on quartiles of remnant-C levels were illustrated in Fig. 1, as determined by Kaplan-Meier survival analysis. Notably, the figure indicated that patients with lower levels of remnant-C had a higher survival probability, which suggested a more favorable kidney prognosis for this group. To further assess the statistical significance of these disparities, we employed the log-rank test. The results of this test demonstrated that individuals with higher levels of remnant-C had a significantly increased risk of albuminuria ($P < 0.001$) and worsening renal function ($P < 0.001$) when compared to those with lower levels. However, the association between remnant-C and renal failure was found to be statistically insignificant ($P = 0.37$).

Baseline remnant-C levels and adverse renal outcomes

In our study, we conducted the Cox proportional regression analysis using three different models with progressive adjustments to assess the risk of adverse renal

Table 1 Subject baseline characteristics by quartiles of remnant-C levels

Variable	Overall (*n* = 10196)	Quartile 1 (*n* = 2609)	Quartile 2 (*n* = 2599)	Quartile 3 (*n* = 2572)	Quartile 4 (*n* = 2416)	*P* value
Remnant-C, mg/dL	31.00 (21.00–46.00)	17.00 (13.00-19.00)	26.00 (24.00–29.00)	38.00 (34.00–42.00)	60.00 (53.00–71.00)	< 0.001
Age, years	62.77 ± 6.63	63.44 ± 6.86	62.98 ± 6.73	62.85 ± 6.49	61.72 ± 6.30	< 0.001
Sex						0.704
Male	6268 (61.5%)	1592 (61.0%)	1581 (60.8%)	1593 (61.9%)	1502 (62.2%)	
Female	3928 (38.5%)	1017 (39.0%)	1018 (39.2%)	979 (38.1%)	914 (37.8%)	
Race						< 0.001
Non-white	3825 (37.5%)	1423 (54.5%)	1034 (39.8%)	791 (30.8%)	577 (23.9%)	
White	6371 (62.5%)	1186 (45.5%)	1565 (60.2%)	1781 (69.2%)	1839 (76.1)	
Education levels						< 0.001
Less than high school	1502 (14.7%)	452 (17.3%)	400 (15.4%)	373 (14.5%)	277 (11.5%)	
High school graduate or GED	2692 (26.4%)	721 (27.7%)	670 (25.8%)	655 (25.5%)	646 (26.7%)	
Some college	3343 (32.8%)	774 (29.7%)	862 (33.2%)	844 (32.8%)	863 (35.7%)	
College degree or higher	2652 (26.0%)	660 (25.3%)	665 (25.6%)	698 (27.2%)	629 (26.0%)	
BMI, kg/m^2	32.23 ± 5.40	30.96 ± 5.58	32.28 ± 5.41	32.74 ± 5.24	32.99 ± 5.11	< 0.001
Duration of diabetes, years	10.80 ± 7.59	12.37 ± 8.14	10.98 ± 7.62	10.23 ± 7.39	9.52 ± 6.38	< 0.001
Smoking	4281 (48.3%)	1169 (51.4%)	1113 (48.6%)	1057 (47.0%)	942 (45.7%)	0.001
Alcohol consumption	0.96 ± 2.68	0.95 ± 2.57	0.89 ± 2.55	1.02 ± 2.77	0.96 ± 2.81	0.384
Blood pressure, mmHg						
Systolic	136.35 ± 17.11	136.92 ± 17.25	136.46 ± 17.02	135.52 ± 17.22	136.50 ± 16.92	0.026
Diastolic	74.88 ± 10.66	73.87 ± 10.58	74.80 ± 10.64	75.03 ± 10.60	75.90 ± 10.75	< 0.001
Heart rate, bpm	72.68 ± 11.75	71.82 ± 11.62	72.17 ± 11.58	72.77 ± 11.75	74.06 ± 11.96	< 0.001
History of CVD	3586 (35.2%)	879 (33.7%)	890 (34.2%)	921 (35.8%)	896 (37.1%)	0.050
Medication use						
ARB	1705 (16.8%)	421 (16.1%)	445 (17.2%)	409 (16.0%)	430 (17.9%)	0.237
ACEI	5538 (54.5%)	1452 (55.7%)	1194 (46.0%)	1124 (43.9%)	1158 (48.1%)	0.011
HbA1c, %	8.30 ± 1.06	8.26 ± 1.05	8.25 ± 1.05	8.30 ± 1.03	8.40 ± 1.09	< 0.001
Plasma concentration						
Total cholesterol, mg/dL	183.31 ± 41.85	166.20 ± 34.52	176.55 ± 35.65	184.81 ± 37.95	207.46 ± 47.50	< 0.001
TG, mg/dL	155.00 (106.00-229.00)	83.00 (67.00–95.00)	131.00 (119.00-144.00)	189.00 (172.00-209.00)	308.00 (265.00-397.00)	< 0.001
LDL-C, mg/dL	104.90 ± 33.91	100.95 ± 29.54	107.36 ± 32.47	106.91 ± 34.83	104.38 ± 38.20	< 0.001
HDL-C, mg/dL	41.87 ± 11.62	49.19 ± 13.26	42.88 ± 10.26	39.66 ± 9.16	35.23 ± 8.35	< 0.001
Fasting plasma glucose (mg/dL)	175.20 ± 56.18	160.97 ± 54.37	170.77 ± 53.40	177.35 ± 53.77	193.04 ± 58.49	< 0.001
Serum potassium (mmol/L)	4.47 ± 0.47	4.47 ± 0.47	4.46 ± 0.41	4.49 ± 0.44	4.49 ± 0.56	0.038
Serum creatinine (mg/dL)	0.91 ± 0.23	0.92 ± 0.21	0.91 ± 0.24	0.92 ± 0.23	0.90 ± 0.25	0.004
eGFR (ml/min/1.73 m^2)	91.05 ± 27.15	92.44 ± 23.76	90.87 ± 25.43	88.85 ± 24.78	92.09 ± 33.83	< 0.001
Urinary albumin (mg/dL)	1.59 (0.72–4.96)	1.43 (0.65–4.20)	1.53 (0.72–4.46)	1.56 (0.73–5.10)	1.92 (0.81–6.82)	< 0.001
Urinary creatinine (mg/dL)	124.37 ± 66.18	125.97 ± 67.80	126.40 ± 67.94	123.29 ± 63.15	121.63 ± 65.56	0.033
Urinary albumin to creatinine ratio (mg/g)	14.00 (7.00–47.00)	13.00 (6.00–40.00)	14.00 (7.00–42.00)	14.00 (7.00–47.00)	17.00 (8.00–62.00)	< 0.001
Glycemia trial						0.071
Standard glucose control	5092 (49.9%)	1270 (48.7%)	1351 (52.0%)	1289 (50.1%)	1182 (48.9%)	
Intensive glucose control	5104 (50.1%)	1339 (51.3%)	1248 (48.0%)	1283 (49.9%)	1234 (51.1%)	
Blood pressure trial						< 0.001
None	5482 (53.8%)	1190 (45.6%)	1433 (55.1%)	1534 (59.6%)	1325 (54.8%)	
Standard blood pressure control	2359 (23.1%)	712 (27.3%)	584 (22.5%)	530 (20.6%)	533 (22.1%)	
Intensive blood pressure control	2355 (23.1%)	707 (27.1%)	582 (22.4%)	508 (19.8%)	558 (23.1%)	
Lipid trial						< 0.001
None	4714 (46.2%)	1419 (54.4%)	1166 (44.9%)	1038 (40.4%)	1091 (45.2%)	
Standard lipid control	2735 (26.8%)	607 (23.3%)	715 (27.5%)	769 (29.9%)	644 (26.7%)	
Intensive lipid control	2747 (26.9%)	583 (22.3%)	718 (27.6%)	765 (29.7%)	681 (28.2%)	

Data are presented as mean ± sd or as median (range) or as n (%). The quartile ranges were quartile 1 (3–21 mg/dL), quartile 2 (22–31 mg/dL), quartile 3 (32–46 mg/dL), quartile 4 (47–474 mg/dL). GED, General Education Development

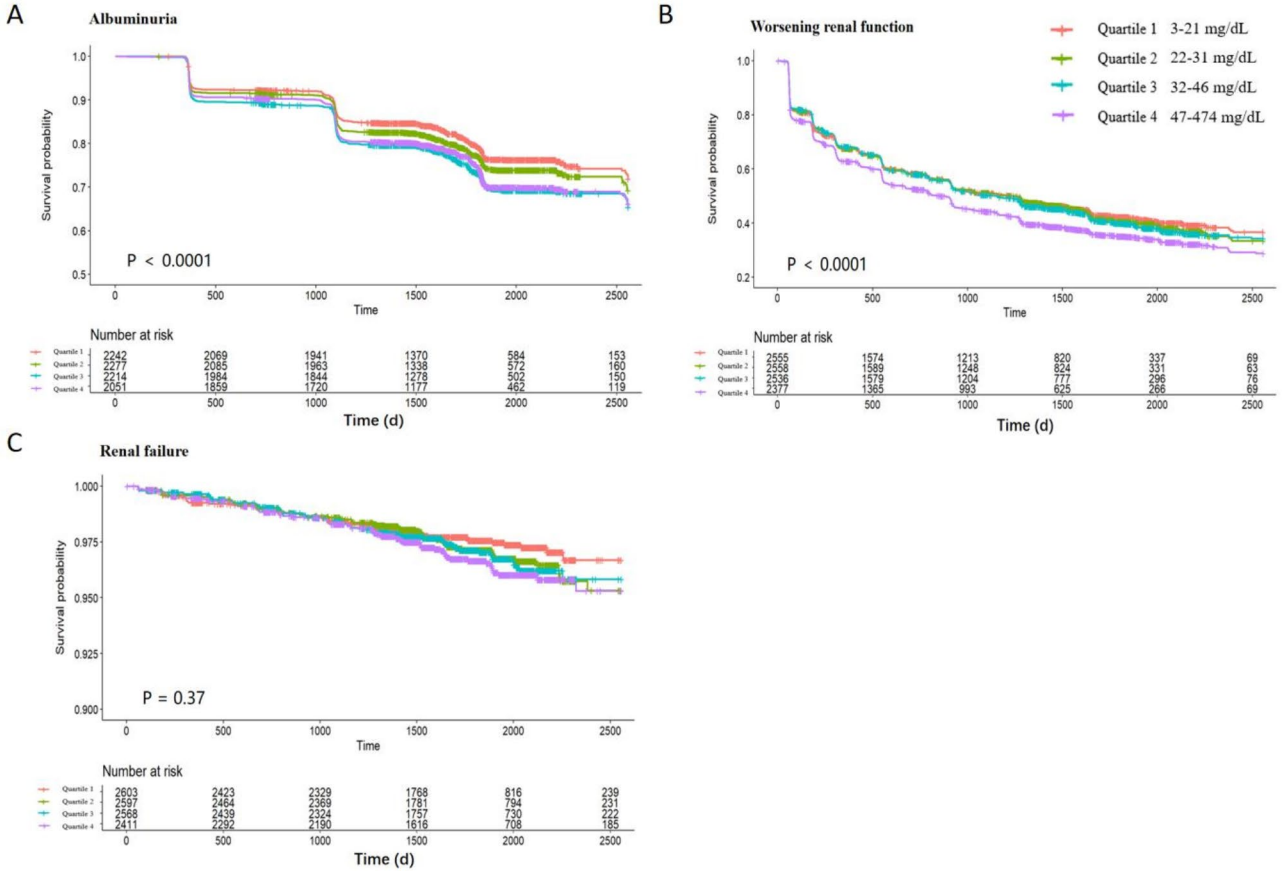

Fig. 1 Kaplan - Meier survival analysis for adverse renal outcomes according to quartiles of remnant-C levels. **A**. Albuminuria; **B**. Worsening renal function; **C**. Renal failure

outcomes. With full adjustments made in Model 3 in table 2, our study revealed the baseline remnant-C levels were associated with the risk of albuminuria [HR 1.23 (95% CI 1.06–1.43), $P = 0.007$] and worsening renal function [HR 1.15 (95% CI 1.05–1.25), $P = 0.002$] between quartile 1 and quartile 4, but not the risk of renal failure [HR 1.11 (95% CI 0.74–1.64), $P = 0.621$]. Moreover, as the quartiles of remnant-C increased, the risk of albuminuria (P for trend = 0.001) and worsening renal function (P for trend < 0.001) also increased, revealing a graded association between remnant-C levels and the risk of albuminuria and worsening renal function, while it was not significant for renal failure (P for trend = 0.649). Furthermore, when remnant-C levels were treated as a continuous variable, a 1-standard deviation increase in remnant-C was associated with a 6% higher risk of albuminuria and an 9% higher risk of worsening renal function ($P = 0.010$ and $P < 0.001$, respectively) after adjusting for all potential confounders. However, there was no significant association between remnant-C as a continuous variable and the risk of renal failure ($P = 0.455$). Our results indicated that the remnant-C could be served as a promising indicator for adverse renal outcomes. Significant differences in albuminuria and worsening renal function were still observed between quartile 1 and quartile 4, but not renal failure in the model 3. These findings were consistent with Kaplan-Meier curves and log rank test. Compared with patients with a lower remnant-C levels, those with a higher remnant-C levels had a higher probability of poor patient outcomes ($P < 0.05$). Overall, our study revealed a significant association between baseline remnant-C levels and adverse renal outcomes, suggesting that it may serve as a promising prognostic marker for patients with type 2 diabetes.

The linear or nonlinear relationship between remnant-C and adverse renal outcomes

In this study, we aimed to elucidate the linear or nonlinear relationship between remnant-C and various adverse renal outcomes. To achieve this, we employed restricted cubic spline analysis to explore the associations. Our findings revealed that there was a linear relationship between remnant-C and worsening renal function (P for nonlinear = 0.2760) and renal faiure (P for nonlinear = 0.9784), as depicted in Fig. 2. However, in the case of albuminuria, we observed a nonlinear relationship

Table 2 Risk of incident adverse renal outcomes for baseline remnant-C levels

	Model 1		Model 2		Model 3	
Remnant-C	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Albuminuria						
Quartile 1	Ref		Ref		Ref	
Quartile 2	1.18 (1.03–1.35)	0.020	1.16 (1.01–1.33)	0.040	1.14 (0.99–1.31)	0.075
Quartile 3	1.45 (1.27–1.66)	< 0.001	1.36 (1.18–1.56)	< 0.001	1.32 (1.15–1.52)	< 0.001
Quartile 4	1.40 (1.22–1.62)	< 0.001	1.26 (1.08–1.46)	0.003	1.23 (1.06–1.43)	0.007
Per 1 SD	1.10 (1.06–1.15)	< 0.001	1.06 (1.01–1.11)	0.009	1.06 (1.01–1.11)	0.010
P for trend		< 0.001		< 0.001		0.001
Worsening renal function						
Quartile 1	Ref		Ref		Ref	
Quartile 2	1.00 (0.93–1.09)	0.951	1.00 (0.93–1.09)	0.920	0.96 (0.89–1.04)	0.357
Quartile 3	1.03 (0.95–1.12)	0.461	1.06 (0.98–1.15)	0.158	1.01 (0.93–1.10)	0.775
Quartile 4	1.19 (1.09–1.29)	< 0.001	1.19 (1.09–1.30)	< 0.001	1.15 (1.05–1.25)	0.002
Per 1 SD	1.09 (1.06–1.12)	< 0.001	1.08 (1.05–1.11)	< 0.001	1.09 (1.06–1.12)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001
Renal failure						
Quartile 1	Ref		Ref		Ref	
Quartile 2	1.07 (0.74–1.55)	0.732	1.08 (0.74–1.57)	0.702	1.06 (0.73–1.55)	0.763
Quartile 3	1.17 (0.80–1.69)	0.416	1.08 (0.74–1.58)	0.699	1.06 (0.72–1.55)	0.783
Quartile 4	1.34 (0.93–1.95)	0.120	1.13 (0.76–1.67)	0.551	1.11 (0.74–1.64)	0.621
Per 1 SD	1.09 (0.98–1.20)	0.109	1.05 (0.93–1.18)	0.457	1.05 (0.93–1.18)	0.455
P for trend		0.103		0.576		0.649

Model 1: adjusted for age, sex, race, education levels, BMI, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure

Model 2: adjusted for model 1 covariables plus Hba1c, fasting plasma glucose, duration of diabetes, serum creatinine, urinary albumin

Model 3: adjusted for model 2 covariables plus the history of CVD and treatment regimens

(*P* for nonlinear = 0.0237). This implied that the risk of this particular adverse renal outcome does not follow a consistent linear pattern but rather exhibits a more complex relationship with remnant-C levels.

Sensitivity analyses

The association between remnant-C and the risk of adverse renal outcomes in sensitivity analyses remained robust. A consistent association was observed when (1) excluding 2747 patients who had used fenofibrate at baseline (Figure S1 and Table S1); (2) excluding 3586 patients who had a history of CVD at baseline (Figure S2 and Table S2); (3) Furthermore, after education levels, BMI, duration of diabetes, alcohol consumption status, smoking status, systolic pressure, diastolic pressure, HbA1c, UACR were imputed, the results remained consistent after imputation (Table S3).

Discussion

To elucidate the relationship between remnant-C levels and adverse renal outcomes in patients with type 2 diabetes, our study conducted a retrospective analysis of data from the ACCORD trial. Our findings revealed a significant association between baseline remnant-C levels and the risk of adverse renal outcomes in individuals with type 2 diabetes. Notably, this relationship remained independent of well-established risk factors, such as serum creatinine, urinary protein, and treatment with ARB or ACEI. Our study demonstrated that remnant-C could accurately predict early adverse renal outcomes in patients with type 2 diabetes. However, it was important to note that the predictive power of remnant-C for late-stage renal adverse outcomes remained an area of future investigation.

A growing body of evidence underscores the significance of remnant-C as a potent atherosclerotic cholesterol component within triglyceride-rich lipoproteins. It has been well-documented to exhibit a strong correlation with cardiovascular outcomes, supported by previous research [12, 22, 23]. While previous studies have successfully established an association between low-density lipoprotein cholesterol and atherosclerotic cardiovascular disease, it is important to note that despite the effective control of LDL-C levels within an optimal range, recurrent ASCVD events still occur. This phenomenon has led to the hypothesis that remnant-C may be a contributing factor to this residual risk [24, 25].

Regarding kidney health, the relationship between remnant-C levels and chronic kidney disease has been a subject of inconsistency in previous studies. Some investigations have reported that elevated levels of remnant-C and its constituents, including intermediate density lipoprotein cholesterol and very low-density lipoprotein cholesterol, are associated with an increased risk

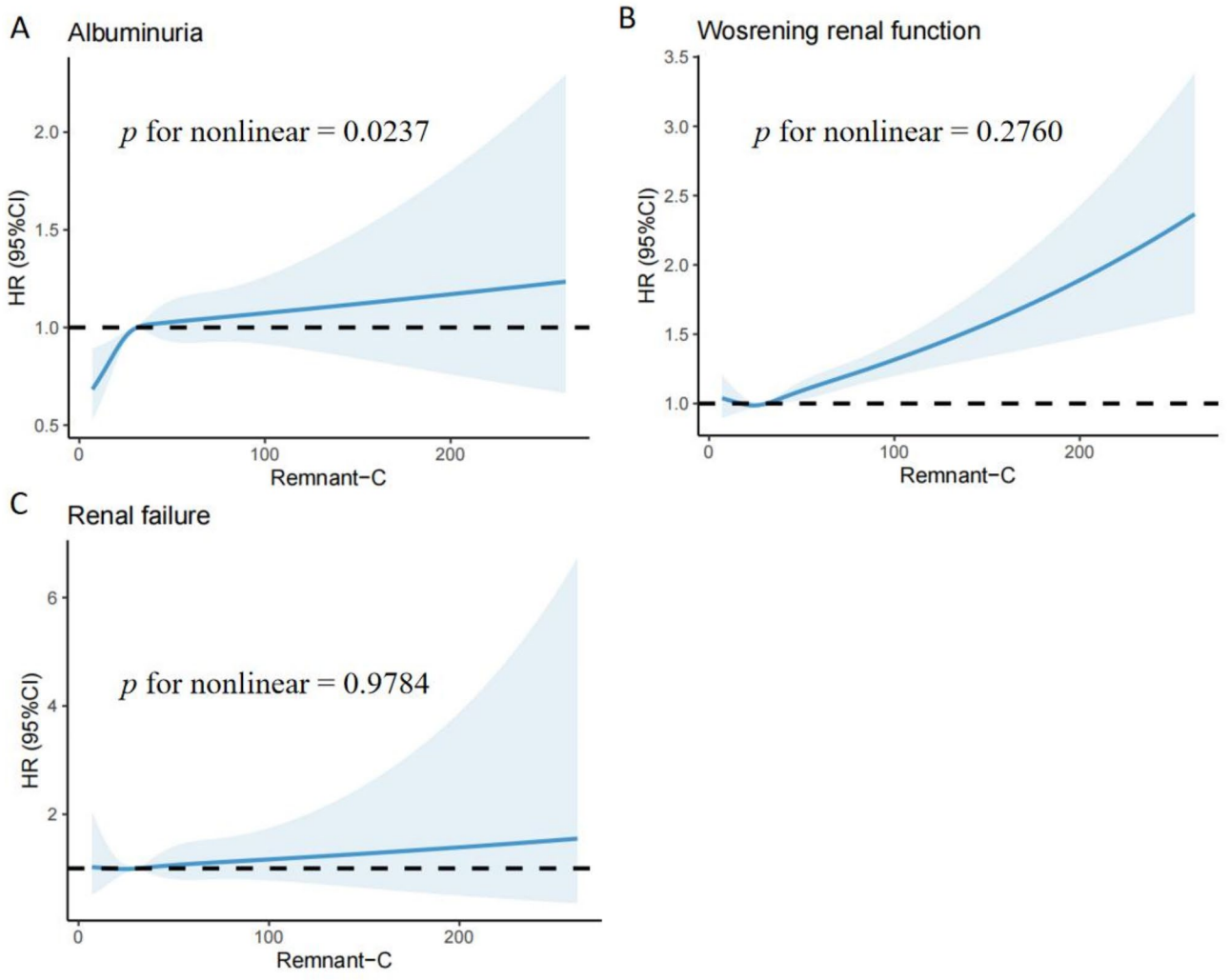

Fig. 2 The linear or nonlinear relationship between remnant-C and adverse renal outcomes by performing Restricted cubic spline analysis. (**A**) Albuminuria; (**B**) Worsening renal function; (**C**) Renal failure

of proteinuria and CKD [13–15]. However, other studies have failed to find a significant correlation between remnant-C and CKD [16–18]. In recent years, additional studies have provided evidence that remnant-C levels serve as an independent risk factor for various kidney-related outcomes, such as DKD progression [19], a decline in eGFR [26] and the development of CKD [27–29]. These findings collectively suggest a close association between remnant-C and adverse renal outcomes. It is important to note that previous research in this area has its limitations, and the conclusions drawn from these studies warrant further validation through future research. Nevertheless, the emerging body of evidence underscores the significance of remnant-C not only in cardiovascular health but also in kidney health, making it a critical area for continued investigation and clinical relevance.

Previous studies indicated that remnant-C is a powerful lipid component that contributes to atherosclerosis. Remnant-C can act on the arterial wall, leading to atherosclerosis and endothelial dysfunction through low-grade inflammation and oxidative stress, and then leading to the development of CKD and ASCVD. Varbo et al. revealed a close association between remnant-C and low-grade systemic inflammation, reflected by elevated C-reactive protein (CRP) [30, 31]. It was worth noting that both eGFR and declining albuminuria were associated with CRP and inflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in diabetes [32, 33]. However, further investigation is needed to determine whether systemic inflammation or other potential unknown mechanisms between remnant-C and adverse renal outcomes.

This study set out to investigate whether remnant-C could serve as a predictor of adverse renal outcomes in

individuals with type 2 diabetes. The findings from our research strongly support that remnant-C is indeed a valuable predictor for early renal adverse outcomes. After adjusting for confounding factors, our study reveal that remnant-C is significantly associated with albuminuria and worsening renal function. As commonly known, eGFR and albumin-to-creatinine ratio (ACR) are traditional markers used to assess the risk of chronic kidney disease. Regular screening for these markers is essential to monitor renal function in individuals with type 2 diabetes, as they are independently and synergistically related to the progression to end-stage renal disease and increased mortality. However, by the time these markers become abnormal, advanced structural kidney damage may already be present. Therefore, there is a critical need for novel biomarkers that can identify early renal adverse outcomes. Our research results indicate that remnant-C can effectively predict these early adverse renal outcomes, potentially filling a gap in existing biomarkers and allowing for early intervention in individuals with higher remnant-C levels. It's important to note that our study did not find a significant association between remnant-C and the occurrence of renal failure. However, it's worth mentioning that the follow-up duration in our study was limited, and the majority of patients did not experience these specific outcome events. Consequently, statistical significance could not be established in this regard. Further research with a longer follow-up period is necessary to explore the potential relationship between remnant-C and late-stage renal adverse outcomes. Nevertheless, our study provides robust evidence that remnant-C levels are reliable predictors of early adverse renal outcomes, which can be of significant clinical importance.

The combination of a large sample size and the availability of high-quality subject information, along with the utilization of multiple statistical methods, allowed our study to establish independent associations between remnant-C and adverse renal outcomes, providing reliable conclusions. However, it's important to acknowledge the limitations of our study. Firstly, despite the inclusion of most recognized risk factors for adverse renal outcomes in multivariable regression models, the presence of potential confounding factors cannot be entirely ruled out. Additionally, it's worth noting that our research findings are observational in nature. While they strongly suggest a link between remnant-C levels and adverse renal outcomes, further prospective intervention studies are needed to conclusively establish the causal effect of remnant-C levels on these outcomes. Furthermore, the question of whether reducing remnant-C levels is beneficial for patients remains unanswered. This is a critical area for future research, as understanding the potential therapeutic implications of modifying remnant-C levels could have a significant impact on the management and treatment of individuals with type 2 diabetes at risk for adverse renal outcomes. Finally, considering the variability of proteinuria, serum creatinine, and eGFR, the definition of outcomes should take into account their dynamic changes rather than single absolute values to define the outcomes more rigorously.

Efforts have been made to establish a "lipid fingerprint" using lipomics to identify diabetes-related complications at an earlier stage [34, 35]. However, the specific lipids or lipoproteins that play the most critical role in the pathogenesis of CKD in diabetes remain to be definitively determined. Clear evidence demonstrating that statins, a common type of lipid-lowering medication, can effectively protect the kidneys of patients with diabetes is lacking [36, 37]. Jun et al. found that fibrate drugs can reduce albuminuria, but the precise mechanisms underlying their renal protective effects remain unclear [38, 39].

Our study offers novel and valuable evidence that remnant-C can serve as a promising predictor of the risk of adverse renal outcomes in patients with type 2 diabetes. Future research endeavors are necessary to build upon these findings and shed more light on the relationship between remnant-C and adverse renal outcomes. Additionally, investigating the renal effects of lipid-lowering therapy in this context is an important avenue for further exploration. Large prospective studies will play a critical role in deepening our understanding of the intricate interplay between remnant-C, renal health, and potential therapeutic interventions. our research has laid the foundation for addressing this important issue, and future investigations have the potential to contribute significantly to the care and management of patients with type 2 diabetes at risk for adverse renal outcomes.

Conclusion

Our study investigated the relationship between remnant-C levels and adverse renal outcomes in individuals with type 2 diabetes. Our findings reveal that baseline remnant-C levels are associated with adverse renal outcomes, suggesting remnant-C's potential as a risk-stratification tool. Further research is needed to verify these associations and assess the benefits of interventions targeting remnant-C levels. Such studies could guide clinical practice and improve the management of diabetes patients at risk for renal complications.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01617-8.

Supplementary Material 1: **Figure S1**: Kaplan - Meier survival analysis for adverse renal outcomes according to quartiles of remnant-C levels among the participants who didn't use fenofibrate.

Supplementary Material 2: **Figure S2**: Kaplan - Meier survival analysis

for adverse renal outcomes according to quartiles of remnant-C levels among the participants who didn't experience CVD at baseline.

Supplementary Material 3: **Table S1**: Risk of incident adverse renal outcomes for baseline remnant-C levels among the participants who didn't use fenofibrate at baseline.

Supplementary Material 4: **Table S2**: Risk of incident adverse renal outcomes for baseline remnant-C levels among the participants who didn't experience CVD at baseline.

Supplementary Material 5: **Table S3**: Risk of incident adverse renal outcomes for baseline remnant-C levels after using median imputation and mode imputation.

Acknowledgements
We are thankful for the contributions the ACCORD group made in data collection and sharing.

Author contributions
ZZP, JXP and PY contributed to study design. JXP contributed to data acquisition. PY, JXP and QJY contributed to data analysis. PY, LH, JXP, QJY and ZZP contributed to drafting of the manuscript. LJT contributed to supervision and mentorship. The final version of the manuscript was read and approved by all authors.

Funding
This project was supported by the Major Program of the National Natural Science Foundation of China (82090024) and the Natural Science Foundation of Hunan province China (2022JJ40790).

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

Declarations

Ethics approval and consent to participate
The use of the ACCORD dataset in this study has been approved by the National Heart, Lung, and Blood Institute and the Medical Ethics Committee of Xiangya Hospital of Central South University (NO. 202210011).

Competing interests
The authors declare no competing interests.

Received: 18 November 2024 / Accepted: 29 January 2025
Published online: 12 February 2025

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