Association of the remnant cholesterol to high-density lipoprotein cholesterol ratio with mortality in chronic obstructive pulmonary disease: a mediation analysis of body mass index

Shurun Zuo, Haiquan Li, Lei Ma, Yongliang Du, Yonghong Xu*

Department of Respiratory and Critical Care Medicine, The Second Affiliated Hospital of Xuzhou Medical University, Xuzhou, China

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***Corresponding author:**
Yonghong Xu
Department of Respiratory and
Critical Care Medicine
The Second Affiliated Hospital
Xuzhou Medical University
Xuzhou, 221000, China
E-mail: yh250819@163.com

Abstract

Introduction: The remnant cholesterol to high-density lipoprotein cholesterol ratio (RC/HDL-C) reflects atherogenic lipid burden. We investigated its association with mortality in patients with chronic obstructive pulmonary disease (COPD) and the mediating role of body mass index (BMI).

Material and methods: This cross-sectional study included 1,307 COPD patients from NHANES 2007–2018. Multivariable Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Restricted cubic splines (RCS) were employed to assess dose-response relationships. Mediation analysis was conducted to quantify the extent to which BMI mediated the association between RC/HDL-C and mortality.

Results: During a median follow-up of 104 months, 226 all-cause and 74 cardiovascular deaths occurred. After adjusting for potential confounders, elevated RC/HDL-C was independently associated with higher risks of all-cause (HR = 2.16, 95% CI: 1.64–2.86) and cardiovascular mortality (HR = 3.30, 95% CI: 2.19–4.99). Mediation analysis indicated that BMI exerted a suppression effect on the association with all-cause mortality, masking 11.0% of the RC/HDL-C-associated risk. However, no significant mediating effect of BMI was observed for cardiovascular mortality. Stratified analyses indicated that these associations were more pronounced in patients younger than 65 years.

Conclusions: RC/HDL-C is independently associated with all-cause and cardiovascular mortality in COPD patients. While higher BMI partially suppresses the association between RC/HDL-C and all-cause mortality, no mediating effect is observed for cardiovascular mortality. The associations were more pronounced in younger patients, suggesting potential value for risk stratification in this subgroup.

Key words: chronic obstructive pulmonary disease, remnant cholesterol, high-density lipoprotein cholesterol, mortality, mediation analysis.

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death globally, placing a significant burden on public health systems [1, 2]. Although COPD is characterized by airflow limitation, it is es-

sentially a complex syndrome involving systemic inflammation [3]. Cardiovascular disease (CVD) is one of the most common and fatal comorbidities in COPD patients [4]. Studies have shown that the risk of cardiovascular events in COPD patients is 2–3 times higher than in the general population, and cardiovascular death is the leading cause of death among patients with mild to moderate COPD [5]. Therefore, early identification and management of cardiovascular risk are crucial for improving the long-term prognosis of COPD patients.

Dyslipidemia is a recognized independent risk factor for cardiovascular diseases [6, 7]. However, traditional lipid markers, such as low-density lipoprotein cholesterol (LDL-C), may have limitations in assessing cardiovascular risk in COPD patients [8]. Research indicates that even in patients with controlled LDL-C levels, there remains a higher residual cardiovascular risk, primarily due to triglyceride-rich lipoprotein remnants (remnant cholesterol – RC) [9, 10]. In recent years, the ratio of remnant cholesterol to high-density lipoprotein cholesterol (RC/HDL-C) has been confirmed as a novel composite lipid marker that more sensitively reflects the imbalance between atherogenic load and anti-atherosclerotic capacity. This ratio has been shown to have superior predictive value for adverse cardiovascular events in the general population compared to traditional lipid parameters [11, 12]. However, there is a lack of research exploring the association between RC/HDL-C and long-term mortality risk in COPD populations. COPD patients have a unique metabolic profile, often characterized by enhanced systemic inflammation and concurrent nutritional depletion [13]. Notably, the "obesity paradox" has been widely reported in COPD patients, where a higher body mass index (BMI) is often associated with better survival rates [14]. Given that elevated RC/HDL-C levels are usually accompanied by metabolic syndrome and increased BMI, it remains unclear whether BMI might mask or mediate the effect of RC/HDL-C on mortality risk. This complex pathophysiological mechanism makes the assessment of lipid-related risks in COPD patients particularly challenging.

Therefore, this study used data from the National Health and Nutrition Examination Survey (NHANES) from 2007 to 2018, aiming to: (1) assess the association between the RC/HDL-C ratio and all-cause as well as cardiovascular mortality risk in COPD patients; (2) use mediation analysis to explore the potential role of BMI in mediating the relationship between RC/HDL-C and mortality risk. The findings of this study may provide new epidemiological evidence for cardiovascular risk stratification and personalized management in COPD patients.

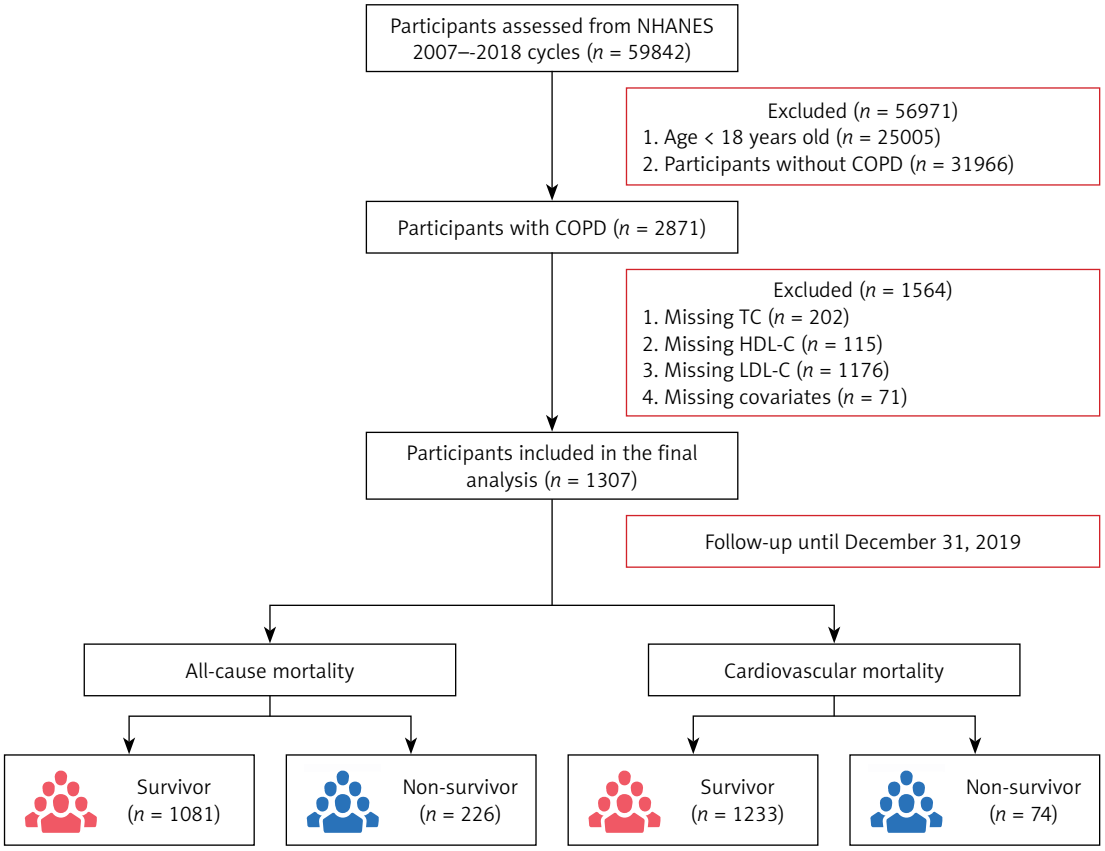

Figure 1. Flowchart of participant selection from NHANES 2007–2018

Material and methods

Study design and population

The data for this study were sourced from the NHANES. NHANES is a cross-sectional study designed to assess the health and nutritional status of U.S. adults and children, conducted by the National Center for Health Statistics (NCHS) using a stratified, multi-stage probability sampling design. This study included survey data from six cycles spanning 2007 to 2018. All participants provided informed consent, and the study protocol was approved by the NCHS Research Ethics Review Board.

The selection process for study participants is shown in Figure 1. Initially, a total of 59,842 participants were identified. The exclusion criteria were as follows: (1) age < 18 years (n = 25,005); (2) participants not diagnosed with COPD (n = 31,966). COPD diagnosis was based on a forced expiratory volume in the first second to forced vital capacity ratio (FEV_1/FVC) < 0.70, or a self-reported physician diagnosis of COPD, indicated by an affirmative response to the question "Has a doctor ever told you that you have COPD?" (variable MCQ160O = 1). Among the remaining 2,871 COPD patients, further exclusions were made for missing baseline lipid data, including total cholesterol (TC) missing (n = 202), HDL-C missing (n = 115), LDL-C missing (n = 1,176), and missing key covariate data (n = 71). Ultimately, 1,307 COPD patients were included in the analysis for this study.

Assessment of RC/HDL-C ratio and covariates

The exposure variable in this study was the RC/HDL-C. Serum TC, HDL-C, and triglycerides (TG) were measured enzymatically using standard automated biochemical analyzers in accordance with the NHANES laboratory procedures. LDL-C was calculated using the Friedewald equation for participants with TG levels ≤ 400 mg/dl [15]. RC was calculated using the formula: RC = TC – (HDL-C + LDL-C). The RC/HDL-C ratio was then computed. In this study, RC/HDL-C was analyzed as a continuous variable. Additionally, participants were divided into quartiles based on the distribution of RC/HDL-C (Q1–Q4): Q1 (< 0.25), Q2 (0.25–0.41), Q3 (0.41–0.68), and Q4 (≥ 0.68), with Q1 serving as the reference group.

The selection of covariates was based on previous literature and clinical relevance, including: sociodemographic characteristics such as age, sex, race, marital status, education level, and the poverty-income ratio (PIR); lifestyle factors such as smoking and alcohol consumption; anthropometric and laboratory measurements, including body mass index (BMI), white blood cell count (WBC), blood urea nitrogen (BUN), uric acid (UA), glycated hemoglobin (HbA1c), and estimated glomerular filtration rate (eGFR); comorbidities including hypertension, diabetes, cardiovascular diseases (CVDs, including congestive heart failure, coronary artery disease, angina, and myocardial infarction), stroke, cancer, and the use of lipid-lowering medications.

Outcome ascertainment

The outcome variables in this study were all-cause mortality and cardiovascular mortality. Mortality data were obtained by linking NHANES records with the National Death Index (NDI). This linkage was performed by the NCHS using a probabilistic matching algorithm based on identifying information such as Social Security Number (SSN), first and last name, and date of birth. Although this matching process is highly reliable, there remains a minor possibility of missing mortality events due to incomplete identifying records, mismatched information, or deaths occurring outside the United States. The follow-up time began from the baseline survey date and continued until the date of death or the end of follow-up (December 31, 2019), with the earliest event being considered. Cardiovascular death was defined according to the International Classification of Diseases, 10th edition (ICD-10), with the coding range including I00-I09, I11, I13, I20-I51, and I60-I69.

Statistical analysis

For baseline characteristics, continuous variables are presented as medians (interquartile range, IQR), and group comparisons were performed using the Mann-Whitney U test. Categorical variables are presented as frequencies (percentages), and group comparisons were performed using the χ^2 test. Kaplan-Meier survival curves were plotted, and the log-rank test was used to assess survival differences between different RC/HDL-C quartile groups. A multivariable Cox proportional hazards regression model was constructed to calculate hazard ratios (HRs) and their 95% confidence intervals (CIs) to evaluate the independent association between RC/HDL-C and mortality risk. The model was adjusted for confounding factors, including demographic characteristics, lifestyle factors, and clinical comorbidities. A restricted cubic splines (RCS) model with 4 knots (at the 5th, 35th, 65th, and 95th percentiles) was used to explore whether there was a nonlinear dose-response relationship between RC/HDL-C and mortality risk. Subgroup analysis was conducted to assess potential modifying effects of stratifying factors such as age, sex, BMI, and comorbidities, and interaction p-values (p for

interaction) were calculated using the likelihood ratio test. Additionally, mediation analysis was performed to explore the mediating role of BMI in the relationship between RC/HDL-C and mortality risk, with the total effect decomposed into direct effects (ADE) and indirect effects (ACME), and the

Table I. Baseline characteristics of COPD patients stratified by all-cause and cardiovascular mortality status

Variables	All-cause mortality			Cardiovascular mortality		
	Survivor (*n* = 1081)	Non-survivor (*n* = 226)	*P*-value	Survivor (*n* = 1233)	Non-survivor (*n* = 74)	*P*-value
Age [years]	56 (42, 67)	70 (60, 75)	< 0.001	58 (44, 69)	69 (59, 74)	< 0.001
Sex, *n* (%)			< 0.001			0.008
Male	604 (55.87)	156 (69.03)		706 (57.26)	54 (72.97)	
Female	477 (44.13)	70 (30.97)		527 (42.74)	20 (27.03)	
Race, *n* (%)			0.015			0.398
Mexican American	104 (9.62)	9 (3.98)		108 (8.76)	5 (6.76)	
Other Hispanic	77 (7.12)	16 (7.08)		84 (6.81)	9 (12.16)	
Non-Hispanic White	637 (58.93)	155 (68.58)		747 (60.58)	45 (60.81)	
Non-Hispanic Black	183 (16.93)	36 (15.93)		207 (16.79)	12 (16.22)	
Other race	80 (7.40)	10 (4.42)		87 (7.06)	3 (4.05)	
Marriage, *n* (%)			0.074			0.837
Married	667 (61.70)	125 (55.31)		748 (60.67)	44 (59.46)	
Never married	414 (38.30)	101 (44.69)		485 (39.33)	30 (40.54)	
Education, *n* (%)			0.032			0.196
Less than high school	111 (10.27)	25 (11.06)		124 (10.06)	12 (16.22)	
High school or equivalent	491 (45.42)	122 (53.98)		578 (46.88)	35 (47.30)	
College or above	479 (44.31)	79 (34.96)		531 (43.07)	27 (36.49)	
Smoking, *n* (%)	726 (67.16)	187 (82.74)	< 0.001	854 (69.26)	59 (79.73)	0.057
Alcohol use, *n* (%)	717 (66.33)	156 (69.03)	0.433	822 (66.67)	51 (68.92)	0.689
CVDs, *n* (%)	174 (16.10)	65 (28.76)	< 0.001	212 (17.19)	27 (36.49)	< 0.001
Hypertension, *n* (%)	467 (43.20)	137 (60.62)	< 0.001	554 (44.93)	50 (67.57)	< 0.001
Diabetes, *n* (%)	189 (17.48)	68 (30.09)	< 0.001	228 (18.49)	29 (39.19)	< 0.001
Stroke, *n* (%)	75 (6.94)	20 (8.85)	0.314	90 (7.30)	5 (6.76)	0.861
Cancer, *n* (%)	139 (12.86)	44 (19.47)	0.009	169 (13.71)	14 (18.92)	0.209
Lipid-lowering, *n* (%)	301 (27.84)	65 (28.76)	0.780	345 (27.98)	21 (28.38)	0.941
PIR	2.0 (1.1, 3.8)	1.6 (1.0, 2.5)	< 0.001	1.9 (1.1, 3.7)	1.5 (0.9, 2.3)	0.029
BMI [kg/m^2]	27.3 (23.9, 31.7)	26.3 (22.6, 30.9)	0.035	27.1 (23.7, 31.6)	27.6 (24.6, 34.8)	0.099
HbA1c [%]	5.6 (5.3, 6.0)	5.8 (5.4, 6.3)	< 0.001	5.6 (5.3, 6.0)	6.0 (5.5, 6.6)	< 0.001
TG [mg/dl]	106 (74, 152)	113 (82, 159)	0.111	106 (74, 151)	139 (100, 216)	< 0.001
TC [mg/dl]	182 (158, 212)	191 (162, 223)	0.016	184 (159, 213)	195 (154, 228)	0.386
LDL-C [mg/dl]	103 (82, 127)	112 (86, 137)	0.002	103 (82, 127)	120 (87, 144)	0.019
HDL-C [mg/dl]	54 (47, 66)	46 (35, 59)	< 0.001	54 (46, 66)	37 (30, 52)	< 0.001
WBC [10^3/µl]	6.8 (5.6, 8.3)	7.2 (5.9, 8.9)	0.017	6.8 (5.6, 8.4)	7.3 (6.3, 9.1)	0.022
BUN [mg/dl]	13.0 (10.0, 16.0)	14.0 (10.0, 18.8)	0.011	13.0 (10.0, 16.0)	15.0 (10.0, 20.8)	0.006
UA [µmol/l]	327 (274, 387)	342 (286, 416)	0.001	327 (274, 387)	393 (315, 470)	< 0.001
eGFR [ml/min/1.73 m^2]	89 (74, 103)	78 (62, 92)	< 0.001	88 (72, 102)	80 (59, 89)	< 0.001
RC [mg/dl]	20.95 (13.94, 29.97)	29.06 (20.04, 39.41)	< 0.001	21.90 (14.82, 31.10)	28.64 (18.69, 46.10)	< 0.001
RC/HDL-C	0.39 (0.24, 0.63)	0.58 (0.35, 0.93)	< 0.001	0.40 (0.24, 0.66)	0.66 (0.38, 1.36)	< 0.001

CVDs – cardiovascular diseases (including coronary heart disease – angina – myocardial infarction – and heart failure), PIR – poverty-income ratio, BMI – body mass index, HbA1c – glycated hemoglobin, TG – triglycerides, TC – total cholesterol, LDL-C – low-density lipoprotein cholesterol, WBC – white blood cell count, BUN – blood urea nitrogen, UA – uric acid, eGFR – estimated glomerular filtration rate, RC/HDL-C – remnant cholesterol to high-density lipoprotein cholesterol ratio, COPD – chronic obstructive pulmonary disease.

proportion of mediation was calculated. All data analyses were conducted using R software (Version 4.2.3). A two-tailed *p*-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 1,307 COPD patients were included with a median follow-up of 104 months. During the follow-up, 226 all-cause (17.3%) and 74 cardiovascular (5.7%) deaths occurred (Table I). For all-cause mortality, non-survivors were older (median: 70 vs. 56 years), had higher proportions of males and smokers, lower education and income levels, and greater burdens of cardiometabolic and inflammatory comorbidities (all $p < 0.05$). Baseline lipid-lowering therapy use was similar between the survivor and non-survivor groups (27.84% vs. 28.76%, $p = 0.780$). In addition, RC levels and the RC/HDL-C ratio (0.58 vs. 0.39) were significantly higher in the deceased group (both $p < 0.001$). Regarding cardiovascular mortality, non-survivors similarly presented with older age, male predominance, and higher rates of metabolic comorbidities. Variables such as BMI, smoking status, cancer history, and lipid-lowering medication use (28.38% vs. 27.98%, $p = 0.941$) showed no significant differences between the two groups. The deceased group exhibited higher levels of TG, RC, and the RC/HDL-C ratio (0.66 vs. 0.40) (all $p < 0.001$). The between-group difference in the RC/HDL-C ratio was more pronounced than in the all-cause mortality analysis.

Association of RC/HDL-C ratio with mortality risks

Kaplan-Meier survival curves demonstrated a significant decline in both all-cause and cardiovascular mortality cumulative survival rates as the RC/HDL-C quartiles increased (Figure 2, Log-rank $p < 0.001$). Multivariable Cox regression analysis further confirmed that (Table II), after fully adjusting for confounding factors, RC/HDL-C remained an independent risk factor for mortality. For all-cause mortality, each 1-unit increase in RC/HDL-C was associated with a 1.16-fold increase in risk (HR = 2.16, 95% CI: 1.64–2.86); compared to the Q1 group, the risks of death in the Q3 (HR = 1.85) and Q4 (HR = 2.72) groups were significantly higher (p for trend < 0.001). Similarly, in the cardiovascular mortality analysis, RC/HDL-C showed a stronger risk association (HR = 3.30, 95% CI: 2.19–4.99), with patients in the highest quartile (Q4) having a 2.29 times higher risk than those in the lowest quartile (HR = 2.29, 95% CI: 1.06–4.97, p for trend < 0.001).

Dose-response analysis

Using an RCS model, we further explored the association between continuous changes in RC/HDL-C and mortality risk (Figure 3). The analysis showed that, after adjusting for all confounders, RC/HDL-C levels were significantly positively correlated with both all-cause mortality (p-overall < 0.001) and cardiovascular mortality (p-overall < 0.001). Nonlinearity testing indicated that the associations between RC/HDL-C and all-cause mortality (p-nonlinear = 0.095) and cardiovascular mortality (p-nonlinear = 0.466) were not statistically significant, suggesting that mortality risk increases approximately linearly with increasing RC/HDL-C levels in COPD patients.

Subgroup analysis

To assess the robustness of the results, we conducted stratified analyses by age, sex, BMI,

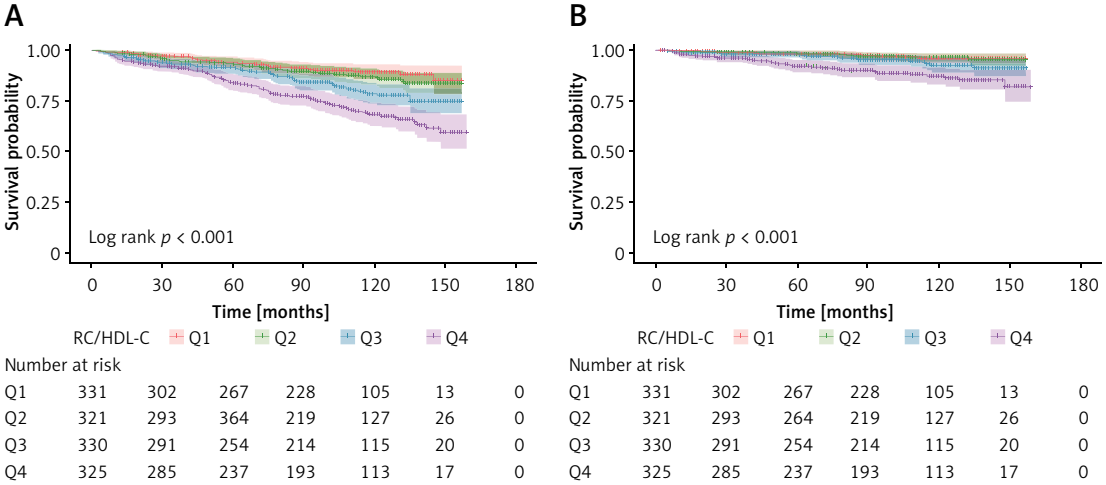

Figure 2. Kaplan-Meier survival curves for COPD patients according to quartiles of RC/HDL-C ratio. **A** – All-cause mortality. **B** – Cardiovascular mortality

Table II. Multivariable Cox proportional hazards models for the association between RC/HDL-C ratio and mortality risks in patients with COPD

Variables	Groups	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All-cause mortality							
RC/HDL-C	Continuous	2.29 (1.83–2.87)	< 0.001	2.38 (1.82–3.11)	< 0.001	2.16 (1.64–2.86)	< 0.001
	Q1 (< 0.25)	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
	Q2 (0.25–0.41)	1.23 (0.78–1.97)	0.374	1.24 (0.77–1.98)	0.370	1.21 (0.75–1.94)	0.441
	Q3 (0.41–0.68)	1.93 (1.26–2.96)	0.003	1.90 (1.22–2.96)	0.005	1.85 (1.18–2.90)	0.007
	Q4 (≥ 0.68)	3.14 (2.10–4.69)	< 0.001	3.06 (1.99–4.70)	< 0.001	2.72 (1.75–4.22)	< 0.001
P for trend			< 0.001		< 0.001		< 0.001
Cardiovascular mortality							
RC/HDL-C	Continuous	3.65 (2.68–4.96)	< 0.001	3.86 (2.61–5.70)	< 0.001	3.30 (2.19–4.99)	< 0.001
	Q1 (< 0.25)	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
	Q2 (0.25–0.41)	0.99 (0.41–2.38)	0.982	1.01 (0.42–2.45)	0.98	0.92 (0.37–2.28)	0.865
	Q3 (0.41–0.68)	1.82 (0.84–3.95)	0.128	1.62 (0.72–3.61)	0.241	1.58 (0.70–3.56)	0.271
	Q4 (≥ 0.68)	3.89 (1.93–7.83)	< 0.001	3.00 (1.41–6.39)	0.004	2.29 (1.06–4.97)	0.015
P for trend			< 0.001		< 0.001		< 0.001

Model 1: unadjusted. Model 2: adjusted for age, sex, race, marriage, education, smoking, alcohol use, PIR, BMI. Model 3: adjusted for Model 2 covariates plus hypertension, CVDs, diabetes, stroke, cancer, lipid-lowering medications, HbA1c, BUN, WBC, UA, eGFR. CVDs – cardiovascular diseases (including coronary heart disease – angina – myocardial infarction – and heart failure), PIR – poverty-income ratio, BMI – body mass index, HbA1c – glycated hemoglobin, WBC – white blood cell count, BUN – blood urea nitrogen, UA – uric acid, eGFR – estimated glomerular filtration rate, COPD – chronic obstructive pulmonary disease, RC/HDL-C – remnant cholesterol to high-density lipoprotein cholesterol ratio.

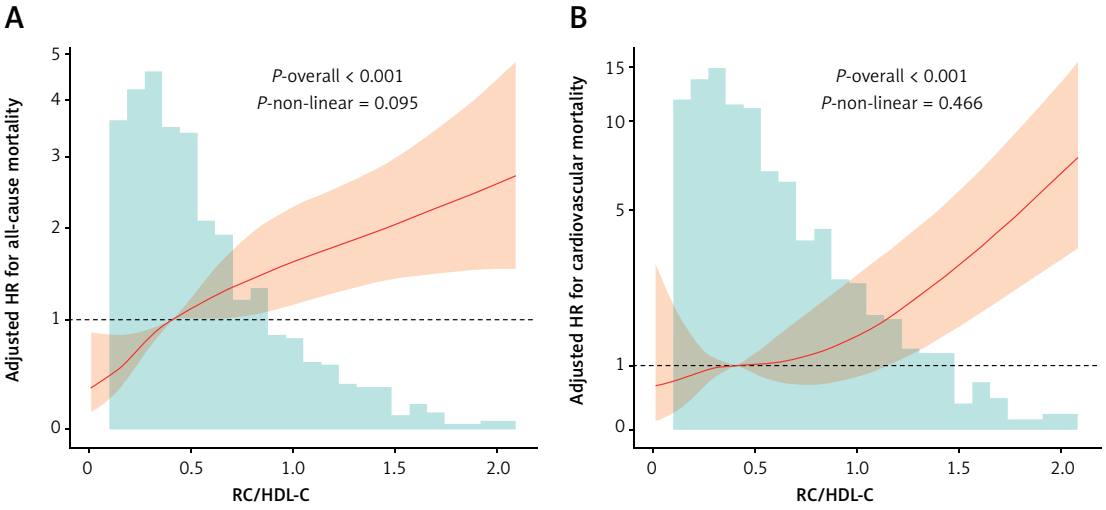

Figure 3. Restricted cubic spline (RCS) analysis of the dose-response relationship between RC/HDL-C ratio and mortality risk. **A** – All-cause mortality. **B** – Cardiovascular mortality

lifestyle factors, comorbidities, and lipid-lowering medications (Table III). The positive association between the RC/HDL-C ratio and mortality risk remained consistent across most subgroups. Significant interactions were observed regarding age, cancer, and cardiovascular disease history. For all-cause mortality, the association with elevated RC/HDL-C was stronger in younger patients (< 65 years) compared to older patients (HR = 2.87 vs. 1.72, *p* for interaction = 0.047), and in patients without cancer (*p* for interaction = 0.025). For cardiovascular mortality, similar heterogeneity was observed: the association was stronger in younger patients (HR = 5.37, *p* for interaction = 0.011), patients without a prior history of cardiovascular disease (HR = 4.19, *p* for interaction = 0.034), and those without cancer (HR = 4.16, *p* for interaction = 0.016). In the corresponding older or comorbid groups, the associations were weaker or statistically non-significant. Clinically, these interactions indicate that the mortality risk associated with lipid dysregulation is more prominent in young-

Table III. Stratified subgroup analyses of the association between RC/HDL-C ratio and mortality

Variables	All-cause mortality			Cardiovascular mortality		
	HR (95% CI)	*P*-value	*P* for interaction	HR (95% CI)	*P*-value	*P* for interaction
All patients	2.16 (1.64–2.86)	< 0.001		3.30 (2.19–4.99)	< 0.001	
Age			0.047			0.011
< 65	2.87 (1.98–4.16)	< 0.001		5.37 (3.04–9.49)	< 0.001	
≥ 65	1.72 (0.94–2.61)	0.072		1.80 (0.91–3.58)	0.098	
BMI			0.944			0.223
< 25	3.21 (1.75–5.89)	< 0.001		5.24 (3.00–7.95)	< 0.001	
25–30	2.15 (1.22–3.80)	0.008		3.30 (1.32–8.23)	0.011	
≥ 30	2.25 (1.39–3.63)	< 0.001		4.81 (2.18–6.65)	< 0.001	
Sex			0.149			0.222
Male	1.89 (1.38–2.59)	< 0.001		3.01 (1.89–4.78)	< 0.001	
Female	3.16 (1.57–6.34)	0.001		5.77 (1.86–9.90)	0.002	
Smoking			0.946			0.272
Yes	2.11 (1.57–2.84)	< 0.001		3.71 (2.38–5.77)	< 0.001	
No	5.21 (1.94–9.95)	0.001		6.12 (1.28–11.37)	0.023	
Alcohol use			0.399			0.781
Yes	2.25 (1.62–3.13)	< 0.001		4.43 (2.12–6.57)	< 0.001	
No	2.02 (1.07–3.80)	0.029		3.48 (1.08–5.21)	0.037	
Hypertension			0.333			0.278
Yes	1.78 (1.22–2.58)	0.003		2.86 (1.63–5.01)	< 0.001	
No	2.98 (1.92–4.62)	< 0.001		6.32 (3.01–9.29)	< 0.001	
CVDs			0.083			0.034
Yes	1.56 (0.84–2.90)	0.162		1.70 (0.74–3.90)	0.210	
No	2.53 (1.85–3.46)	< 0.001		4.19 (2.58–6.81)	< 0.001	
Diabetes			0.674			0.403
Yes	2.07 (1.30–3.30)	0.002		2.91 (1.49–5.68)	0.002	
No	2.34 (1.60–3.43)	< 0.001		4.09 (2.17–7.70)	< 0.001	
Stroke			0.912			0.664
Yes	2.14 (0.56–8.22)	0.266		3.07 (0.23–6.00)	0.396	
No	1.94 (1.48–2.55)	< 0.001		3.06 (2.06–4.55)	< 0.001	
Cancer			0.025			0.016
Yes	1.22 (0.53–2.84)	0.580		1.66 (0.36–7.72)	0.457	
No	2.40 (1.79–3.23)	< 0.001		4.16 (2.68–6.45)	< 0.001	
Lipid-lowering			0.996			0.542
Yes	2.89 (1.63–5.13)	< 0.001		4.13 (1.75–9.77)	0.001	
No	2.05 (1.47–2.86)	< 0.001		3.35 (1.98–5.66)	< 0.001	

CVDs – cardiovascular diseases (including coronary heart disease – angina – myocardial infarction – and heart failure), BMI – body mass index, RC – remnant cholesterol, HDL-C – high-density lipoprotein cholesterol, RC/HDL-C – remnant cholesterol to high-density lipoprotein cholesterol ratio.

er populations and in individuals without severe competing risks, such as advanced age or malignancy. Additionally, stratification by lipid-lowering therapy showed that the association between RC/HDL-C and mortality remained significant in both the treated and non-treated groups, without significant interaction (p for interaction = 0.996 for all-cause and 0.542 for cardiovascular mortality). This confirms that the observed lipid-associated risk persists regardless of baseline lipid-lowering medication use.

Mediation analysis of BMI

To further elucidate the potential mechanism of BMI in mediating the association between RC/HDL-C and mortality risk, we conducted mediation analysis (Figure 4). For all-cause mortality, the re-

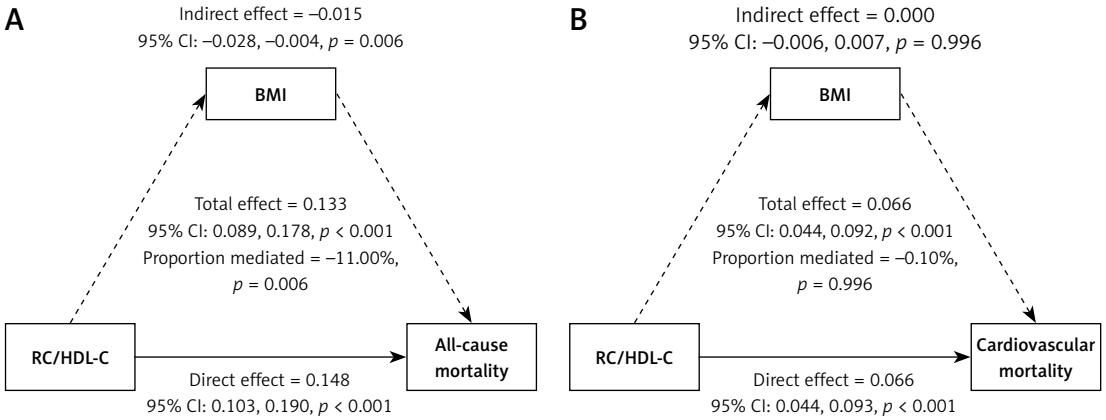

Figure 4. Mediation analysis of BMI in the association between RC/HDL-C ratio and mortality. **A** – All-cause mortality showing a suppression effect of BMI. **B** – Cardiovascular mortality showing only a direct effect

sults demonstrated a "suppression effect." Specifically, while the overall association (total effect) between RC/HDL-C and mortality was positive and significant (β = 0.133, $p < 0.001$), BMI mediated a negative indirect path (β = –0.015, $p = 0.006$). This indicates that the higher BMI typically accompanying elevated lipids provides a partial survival advantage in COPD patients, masking approximately 11.0% of the RC/HDL-C-related all-cause mortality risk. After accounting for this BMI-mediated suppression, the direct effect of RC/HDL-C on all-cause mortality remained significant (β = 0.148, $p < 0.001$). In contrast, for cardiovascular mortality, BMI did not exhibit a mediating role (indirect effect ≈ 0, $p = 0.996$). The association between RC/HDL-C and cardiovascular mortality was almost entirely driven by the direct effect (β = 0.066, $p < 0.001$). This suggests that the cardiovascular risk associated with elevated remnant cholesterol acts directly and is not mitigated by the patient's body weight.

Discussion

This study, based on data from NHANES 2007–2018, confirmed a significant independent positive correlation between the RC/HDL-C ratio and both all-cause and cardiovascular mortality risk in COPD patients. The results show a linear increase in mortality risk as RC/HDL-C levels rise in COPD patients. Mediation analysis further revealed the complex role of BMI: for all-cause mortality, BMI exerted a significant "suppression effect", buffering part of the harmful effects of lipid abnormalities; however, for cardiovascular mortality, RC/HDL-C exhibited a purely direct pathogenic effect, independent of BMI. Additionally, subgroup analysis showed that the association between RC/HDL-C and mortality risk was more pronounced in younger (< 65 years) and cardiovascular disease-free COPD patients, highlighting its potential value for early risk identification.

RC/HDL-C, a novel lipid marker reflecting the balance between atherogenic load (represented by RC) and anti-atherosclerotic capacity (represented by HDL-C), has gained attention in recent years [16, 17]. Previous studies, such as the Kailuan prospective cohort study by Tan *et al*., found that high RC/HDL-C was positively correlated with the risk of atherosclerotic cardiovascular disease (ASCVD), and this marker showed a stronger association with myocardial infarction and stroke compared to traditional lipid markers [18]. Pan *et al*.'s study also confirmed that RC/HDL-C was positively associated with the severity of coronary artery disease (CAD), being an independent risk factor for high Gensini scores and multi-vessel disease [19]. Furthermore, Zhang *et al*. found that elevated RC/HDL-C was closely associated with the risk of type 2 diabetes in elderly populations [20]. This study extends the application of this marker to COPD, and the findings align with previous studies in the general population or high cardiovascular risk populations, confirming its value as a marker of poor prognosis. However, unlike purely cardiovascular studies, COPD patients often experience systemic inflammation and metabolic disorders, along with the unique "obesity paradox" phenomenon [21, 22]. We found that even after adjusting for inflammatory markers (WBC), metabolic comorbidities (diabetes, hypertension), and traditional cardiovascular risk factors, RC/HDL-C remained significantly associated with mortality risk, indicating that it captures residual cardiovascular risk not covered by traditional risk models in COPD patients. Notably, our subgroup analysis demonstrated that the risk associated with elevated RC/HDL-C persists even in patients receiving lipid-lowering drugs. This strongly highlights the concept of "residual cardiovascular risk". While traditional statin therapies effectively lower LDL-C, they are often less effective at reducing triglyceride-rich lipoprotein remnants, leaving sta-

tin-treated patients exposed to ongoing atherogenic harm driven by high RC levels [23].

This study innovatively highlights the dual role of BMI in the relationship between lipids and mortality risk. COPD is a chronic inflammatory condition that is often associated with weight loss and muscle wasting, and a higher BMI is generally considered to indicate better nutritional reserves and muscle mass, which have been associated with better survival in the context of the "obesity paradox" [24, 25]. Our mediation analysis indicated that, for all-cause mortality, BMI exhibited a significant "suppression effect" (mediation proportion –11.0%). This means that although high RC/HDL-C levels are associated with metabolic disturbances, their commonly associated higher BMI (reflecting greater nutritional reserves) may partially attenuate the positive association between RC/HDL-C and mortality [26, 27]. This finding suggests that clinicians should not overlook the potential risks associated with lipid abnormalities when assessing overweight COPD patients. However, for cardiovascular mortality, no mediating effect of BMI was observed. This suggests that the potential harm of RC/HDL-C to the cardiovascular system is largely direct. Regardless of whether a patient is underweight or obese, triglyceride-rich lipoprotein remnants (remnant cholesterol) may penetrate the vascular endothelium, be taken up by macrophages to form foam cells, and contribute to vascular inflammation and plaque rupture [28, 29]. These findings challenge the notion that obesity offsets cardiovascular metabolic risk and highlight the importance of improving lipid profiles (reducing RC and increasing HDL-C) in the management of cardiovascular complications in COPD.

Our subgroup analysis provides important insights into the clinical relevance of the RC/HDL-C ratio. The association between this marker and cardiovascular mortality risk was stronger in younger patients (< 65 years), with a higher HR (up to 5.37) compared with older patients. This may be because the mortality of younger COPD patients is less influenced by age-related competing risks and comorbidities, and high RC/HDL-C may reflect earlier and more severe metabolic and vascular dysfunction [30]. Additionally, in patients without a history of cardiovascular disease, the HR for RC/HDL-C was significantly higher than in those with established CVD (4.19 vs. 1.70). This finding has important public health implications: RC/HDL-C has the potential to become an "early warning signal" and a tool for primary prevention screening in COPD patients. For younger, seemingly cardiovascularly healthy COPD patients, elevated levels of this marker may indicate a high latent risk of mortality [31]. Given that RC/HDL-C is easy to calculate and does not require additional testing costs (it can be derived from standard lipid profiles), it may be considered for inclusion in routine risk assessment for COPD patients to help identify high-risk individuals early.

This study has several limitations. First, the observational design precludes causal inferences, and reliance on baseline lipid profiles cannot account for temporal fluctuations due to subsequent lifestyle modifications or medical interventions. Second, RC was estimated using a standard mathematical formula rather than the gold-standard ultracentrifugation; while this approach is highly practical for large epidemiological cohorts, potential estimation bias exists. Third, despite rigorous adjustments, residual confounding remains. The lack of data on specific COPD treatment regimens, genetic factors, and comprehensive etiological parameters (e.g., exact smoking pack-years, occupational exposures, indoor biomass smoke, and exacerbation history) restricted our ability to explore their complex interactions with lipid-associated mortality risks. Finally, the US-based demographic necessitates cautious extrapolation to other populations. Future prospective studies should incorporate direct lipid measurements, longitudinal tracking of clinical variables and specific therapies, and diverse multi-ethnic cohorts to fully establish the causal mechanisms and clinical applicability of the RC/HDL-C ratio.

In conclusion, the RC/HDL-C ratio is independently associated with all-cause and cardiovascular mortality in COPD patients. Its association with all-cause mortality is partially mediated by BMI, whereas no evidence of mediation by BMI was observed for cardiovascular mortality. Notably, the association between RC/HDL-C and adverse outcomes was more pronounced in younger and middle-aged COPD patients, as well as those without a history of cardiovascular disease. In clinical practice, the RC/HDL-C ratio may contribute to more refined cardiovascular risk stratification in COPD patients and may support personalized comprehensive management strategies.

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Availability of data and materials

The datasets analyzed in this study are publicly available from the NHANES website of the Nation-

al Center for Health Statistics (https://www.cdc.gov/nchs/nhanes/).

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Ethical approval and consent to participate

NHANES was conducted with approval by the National Center for Health Statistics Ethics Review Board, and obtained informed written consent from all the individuals involved in the study (approval numbers: protocol #2005-06, protocol #2011-17, protocol #2018-01). This secondary analysis was conducted in accordance with the Declaration of Helsinki and relevant guidelines and regulations.

Conflict of interest

The authors declare no conflict of interest.

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