The role of systemic inflammation in mediating the association between red cell distribution width/albumin ratio and all-cause and cardiovascular mortality in cardiovascular disease patients with diabetes or prediabetes: insights from a large, population-based study

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Abstract

Introduction: The association between red cell distribution width-to-albumin ratio (RAR) and clinical outcomes in cardiovascular disease (CVD) patients with diabetes mellitus (DM) or pre-DM remains unclear, and its underlying mechanisms are not fully understood.
Material and methods: This population-dependent prospective cohort study enrolled 3224 United States (U.S.) participants from the National Health and Nutrition Examination Survey (NHANES) (2001–2018) who had both CVD and either DM or pre-DM. Using the National Death Index data, the cohort's mortality outcomes were tracked until December 31, 2019. Cox proportional hazard models and restricted cubic spline regressions were employed to investigate the associations between RAR and mortality outcomes. Notably, mediation analyses were performed to quantify the contribution of inflammatory markers, including neutrophils, monocytes, the neutrophil-to-lymphocyte ratio (NLR), and the systemic immune-inflammation index (SII), in the RAR-mortality relationship.
Results: During a median 78-month follow-up, 1,223 deaths occurred (483 cardiovascular-related). Elevated RAR was significantly associated with increased all-cause mortality (hazard ratio = 1.43, 95% CI: 1.31–1.56) and cardiovascular mortality (1.44, 1.28–1.62). NLR and SII exhibited significant mediating effects (8.8–10.79% for all-cause; 9.58–11.99% for cardiovascular mortality).
Conclusions: Elevated RAR was significantly associated with increased risk of all-cause mortality and cardiovascular mortality among patients with CVD and DM or pre-DM. Systemic inflammation significantly mediated these associations. RAR may serve as a practical prognostic marker in this high-risk population.

Key words: National Health and Nutrition Examination Survey, red cell distribution width/albumin ratio, mortality risk, inflammatory indicators, cardiovascular disease, diabetes, prediabetes.

Introduction

Despite significant advancements in treatment, cardiovascular disease (CVD) represents the primary cause of mortality and morbidity worldwide, posing a persistent public health challenge [1]. According to the Global Burden of Disease (GBD) Study 2023, which summarized CVD burden across 21 GBD regions, the global age-standardized mortality rate for CVD has decreased by 34.9%, from 358.4 to 233.2 per 100,000 individuals between 1990 and 2023. However, the absolute number of CVD-related deaths has risen dramatically, from 12.4 to 19.8 million in 1990 and 2022, driven by population growth, aging, and the prevalence of modifiable risk factors, including metabolic syndrome, smoking, and physical inactivity [2]. Nearly 80% of people with diabetes mellitus (DM) develop cardiovascular complications, and approximately 65% succumb to them; DM is related to a heightened risk of cardiovascular complications [3, 4]. Additionally, pre-DM is associated with increased CVD risk [5]. An effective reduction in all-cause mortality (ACM) and cardiovascular mortality (CVM) in CVD patients who have various glucose metabolism statuses requires the identification of remaining risk variables.

Chronic inflammation is fundamental to the onset and progression of CVD and significantly contributes to an unfavorable prognosis in patients who have glucose metabolism disorders. The combined effects of oxidative stress, insulin resistance, and dysregulated lipid metabolism amplify inflammatory responses [6]. Systemic low-grade inflammation underpins many chronic diseases and is particularly central to the obesity-insulin resistance-glucose metabolism disorder continuum [7]. This inflammatory and insulin-resistant state is a major pathogenic pathway for chronic diseases, including DM, nonalcoholic fatty liver disease (NAFLD), and CVD [8]. Shared inflammatory pathways explain the frequent coexistence of conditions such as hypertension, hyperlipidemia, and DM in the same patient [9, 10], further increasing the long-term risk of developing CVD. Consequently, systemic inflammation could be a key mediator in determining long-term outcomes for CVD patients who have DM or pre-DM.

Red cell distribution width (RDW), a hematological parameter reflecting blood cell size heterogeneity, has traditionally been used to diagnose anemia because of its affordability and accessibility. Nonetheless, RDW has been revealed to be related to chronic inflammation [11], closely linking it to the onset, progression, and adverse outcomes of various diseases, including heart failure, DM, and DM complications [12]. Similarly, the level of albumin (ALB), a key protein involved in nutrient transport and immune function regulation, has been shown to be inversely correlated with dysfunction, disease, and mortality risk [13–15], reflecting both nutritional status and systemic inflammation [16].

The RDW/ALB ratio (RAR) is an innovative composite metric that may represent a complex physiological state characterized by inflammation, oxidative stress, and nutritional imbalances. Emerging evidence has demonstrated a strong link between RAR and adverse findings in multiple disorders, particularly acute myocardial infarction (MI), atrial fibrillation, heart failure, stroke, DM and burn surgery [17–21]. The potential association between RAR and fatality in CVD patients who have DM or pre-DM has yet to be confirmed. This study sought to clarify the relationship between RAR and both ACM and CVM within this population, with a particular focus on whether inflammatory indicators serve as mediators in these associations.

Material and methods

Study population and design

Herein, we acquired data from the CDC's National Center for Health Statistics (NCHS). The NHANES survey is designed to determine the health and nutritional status of civilian, noninstitutionalized populations across the United States. All statistical analyses followed official NHANES guidelines and used a complex, stratified, multistage sampling design to ensure broad U.S. population representation [22]. The NCHS Research Ethics Review Board ethically authorized the NHANES study, with all participants signing informed consent [23]. The NHANES dataset is publicly accessible through the CDC website, and its longitudinal linkage to the National Death Index (NDI) facilitates comprehensive analyses of mortality outcomes [24].

This study utilized data collected across nine 2-year cycles between 2001 and 2018, with a focus on adults aged 20–85 years. All participants included in this analysis were from the U.S. The American Diabetes Association (ADA) criteria define DM, which includes self-reported diagnosis, the use of insulin or oral hypoglycemic agents, fasting blood glucose (FBG) levels ≥ 126 mg/dl, or and hemoglobin A_{1c} (HbA_{1c}) ≥ 6.5%. Pre-DM was recognized either through self-reported status or by an FBG of 100–125 mg/dl or an HbA_{1c} of 5.7–6.4% [25]. A standardized medical questionnaire was used to diagnose CVD, with participants reporting whether they had been informed of angina pectoris, congestive heart failure, coronary heart disease (CHD), MI, or stroke. The respondents affirming any of these conditions were classified as having CVD [26]. The cohort study included 3,224 adults diagnosed with both CVD and DM or pre-DM (Figure 1), following the exclusion of certain individuals with missing mortality data

(n = 3), missing RAR values (n = 333), or missing baseline medical condition data (n = 45). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines tailored for cohort studies.

Assessment of RAR

The RDW (%) was determined via a Coulter analyzer on peripheral blood samples obtained at mobile examination centers, whereas the serum ALB levels were measured via the bromocresol purple method. The RAR was calculated as the RDW divided by the ALB concentration, and its values were stratified into quartiles and considered a continuous exposure variable.

Assessment of mortality

The mortality status of the follow-up cohort was determined via the NHANES public-usage-related mortality file, updated until December 31, 2019, connected to the NDI by the NCHS, which employs a probability-matching algorithm. Our study identified disease-specific deaths on the basis of the 10th revision of the International Classification of Diseases (ICD-10). For our analysis, these deaths were categorized by the NCHS as heart diseases (054–064), malignant neoplasms (019–043), or all other causes (010) [27].

Covariates

This study gathered data on several covariates, including age, sex, race, education level, family income, body mass index (BMI), smoking and drinking status, and disease history (including hypertension, DM, stroke, and cardiac disease history). BMI was determined by dividing weight (kg) by height^2 (m^2). The participants were categorized by race as White, Black, Mexican, or Other. Educational level was grouped into below high school, high school or equivalent, and college or above. Family income was identified by the poverty-to-income ratio (PIR) and was divided into 0–1.0, 1.0–3.0, and > 3.0. Smoking status was categorized into never, former, and current smokers on the basis of questionnaire responses. Drinking status was classified into three levels: heavy, represented by females consuming ≥ 3 drinks daily and males ≥ 4, or engaging in binge drinking (4+ drinks on one occasion for females, 5+ for males) on ≥ 5 days monthly; moderate, represented by females consuming ≥ 2 drinks daily and males ≥ 3, or binge drinking on at least 2 days monthly; mild, defined as those not meeting heavy or moderate drinking criteria; and nondrinkers, or those with a daily binge drinking history [26]. A broad range of clinical indicators were evaluated in the NHANES laboratory, including metabolic markers such as

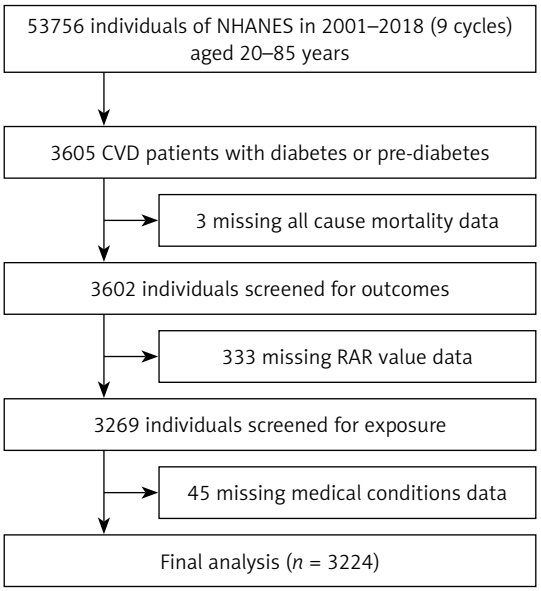

Figure 1. Flow chart of study participants

FBG, HbA_{1c}, triglyceride (TG), and cholesterol levels (total [TC], LDL-C, HDL-C). Hematologic parameters included leukocyte, lymphocyte, monocyte, neutrophil, red blood cell (RBC), hemoglobin, RDW, and platelet counts. Liver function was assessed through alanine (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), lactate dehydrogenase (LDH), and gamma-glutamyl transferase (GGT) levels. Estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), serum creatinine (Scr), and uric acid were used to measure kidney function. Several inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII, multiplied by the NLR), were also assessed.

Statistical analysis

The analysis incorporated the NHANES complex sampling design with sample weights, clustering, and stratification. Participants were divided into RAR quartiles (Q1: 0.226–0.307, Q2: 0.307–0.333, Q3: 0.333–0.367, Q4: 0.367–0.843). Continuous variables are presented as means ±standard deviations, and categorical variables as unweighted numbers with weighted percentages. Between-group differences were assessed using the Kruskal-Wallis test for continuous variables and the χ^2 test with Rao & Scott's correction for categorical variables.

Multivariate Cox proportional hazard models were used to evaluate associations between RAR and mortality outcomes, with progressive adjustment for potential confounders. Mediation analyses were performed to assess the indirect effects of inflammatory markers. Restricted cubic splines were applied to examine non-linear relationships. Statistical analyses were performed using R software, version 4.2.2 (R Foundation for Statistical

Table I. Patient demographics and baseline characteristics according to RAR quartiles

Characteristic	Quartiles of RAR					*P*-value[2]
	Overall Weighted *N* = 11,314,925 Unweighted *n* = 3224[1]	Q1 (0.226,0.307] Weighted *N* = 3,093,112 Unweighted *n* = 806[1]	Q2 (0.307,0.333] Weighted *N* = 2,886,883 Unweighted *n* = 790[1]	Q3 (0.333,0.367] Weighted *N* = 2,776,329 Unweighted *n* = 820[1]	Q4 (0.367,0.843] Weighted *N* = 2,558,601 Unweighted *n* = 808[1]	
Age [years]	66 ±12	65 ±12	66 ±12	67 ±12	67 ±13	< 0.001
Gender, *n* (%)						< 0.001
Male	1,848 (55.30)	535 (65.63)	448 (55.46)	468 (54.57)	397 (43.43%)	
Female	1,376 (44.70)	271 (34.37)	342 (44.54)	352 (45.43)	411 (56.57%)	
Race, *n* (%)						< 0.001
White	1,694 (73.52)	479 (78.39)	442 (77.57)	414 (71.50)	359 (65.25%)	
Black	741 (12.24)	89 (5.03)	150 (9.68)	227 (15.25)	275 (20.58%)	
Mexican	337 (4.47)	108 (5.31)	81 (3.73)	76 (3.99)	72 (4.82%)	
Other	452 (9.77)	130 (11.27)	117 (9.02)	103 (9.26)	102 (9.34%)	
Education, *n* (%)						0.13
Less than high school	538 (10.52)	145 (11.44)	120 (8.33)	137 (10.63)	136 (11.77%)	
High school graduate or equivalent	1,375 (42.56)	312 (39.74)	341 (41.44)	361 (43.25)	361 (46.48%)	
Some college or above	1,311 (46.92)	349 (48.82)	329 (50.24)	322 (46.12)	311 (41.75%)	
Smoking status, *n* (%)						0.078
Never	1,263 (38.57)	312 (35.88)	324 (41.37)	337 (40.13)	290 (36.98%)	
Former	1,348 (41.59)	364 (47.12)	309 (37.49)	328 (39.89)	347 (41.38%)	
Now	613 (19.84)	130 (17.00)	157 (21.14)	155 (19.98)	171 (21.64%)	
Alcohol, *n* (%)						0.015
Never	443 (13.40)	107 (12.15)	112 (14.60)	123 (14.72)	101 (12.13%)	
Former	919 (29.63)	223 (27.29)	232 (29.09)	221 (27.90)	243 (35.34%)	
Mild	964 (38.39)	265 (38.44)	246 (38.51)	250 (41.44)	203 (34.69%)	
Moderate	212 (8.14)	59 (9.26)	64 (11.19)	45 (5.62)	44 (5.94%)	
Heavy	272 (10.45)	87 (12.85)	47 (6.61)	68 (10.32)	70 (11.89%)	

Table I. Cont.

Characteristic	Quartiles of RAR					*P*-value[2]
	Overall Weighted *N* = 11,314,925 Unweighted *n* = 3224[1]	Q1 (0.226,0.307] Weighted *N* = 3,093,112 Unweighted *n* = 806[1]	Q2 (0.307,0.333] Weighted *N* = 2,886,883 Unweighted *n* = 790[1]	Q3 (0.333,0.367] Weighted *N* = 2,776,329 Unweighted *n* = 820[1]	Q4 (0.367,0.843] Weighted *N* = 2,558,601 Unweighted *n* = 808[1]	
Family poverty income ratio, *n* (%)						< 0.001
< 1	684 (16.58)	141 (12.37)	164 (14.09)	196 (19.01)	183 (22.08%)	
1–3	1,503 (47.94)	364 (44.09)	377 (49.59)	363 (46.47)	399 (52.52%)	
> 3	778 (35.48)	235 (43.54)	191 (36.32)	203 (34.52)	149 (25.40%)	
Hypertension, *n* (%)						0.003
No	755 (25.30)	219 (28.35)	196 (27.82)	197 (25.79)	143 (18.24%)	
Yes	2,469 (74.70)	587 (71.65)	594 (72.18)	623 (74.21)	665 (81.76%)	
Any DM, *n* (%)						< 0.001
Pre-DM	1,492 (50.32)	436 (57.97)	400 (54.69)	349 (45.57)	307 (41.28%)	
DM	1,732 (49.68)	370 (42.03)	390 (45.31)	471 (54.43)	501 (58.72%)	
BMI [kg/m^2]	32 ±7	30 ±6	31 ±7	32 ±7	34 ±9	< 0.001
Leukocytes [10^9/l]	7.70 ±3.59	7.22 ±2.33	7.54 ±2.53	8.12 ±5.60	8.01 ±2.95	< 0.001
Lymphocytes [10^9/l]	2.16 ±2.87	2.11 ±1.49	2.11 ±1.64	2.42 ±5.03	2.00 ±1.76	0.016
Monocytes [10^9/l]	0.63 ±0.22	0.59 ±0.18	0.62 ±0.19	0.64 ±0.25	0.66 ±0.26	0.001
Neutrophils [10^9/l]	4.63 ±1.73	4.25 ±1.45	4.53 ±1.59	4.75 ±1.69	5.06 ±2.07	< 0.001
RBC [10^{12}/l]	4.59 ±0.53	4.67 ±0.48	4.63 ±0.48	4.59 ±0.53	4.46 ±0.61	< 0.001
Hemoglobin [g/dl]	13.94 ±1.58	14.65 ±1.33	14.24 ±1.32	13.84 ±1.41	12.85 ±1.71	< 0.001
Red cell distribution width, %	13.78 ±1.45	12.66 ±0.58	13.32 ±0.61	13.91 ±0.73	15.53 ±1.75	< 0.001
Platelets [10^9/l]	231 ±72	227 ±64	233 ±68	226 ±71	241 ±85	0.10
ALT [IU/l]	24 ±31	26 ±15	25 ±50	24 ±32	20 ±14	< 0.001
AST [IU/l]	25 ±21	27 ±11	25 ±23	25 ±20	25 ±27	< 0.001
Albumin [g/l]	41.0 ±3.3	44.0 ±2.2	41.7 ±1.9	40.0 ±2.0	37.5 ±3.2	< 0.001
TBil [mg/dl]	0.66 ±0.31	0.76 ±0.31	0.66 ±0.27	0.61 ±0.29	0.59 ±0.33	< 0.001
GGT [IU/l]	34 ±47	35 ±43	29 ±33	36 ±56	37 ±53	0.092
TC [mg/dl]	180 ±45	184 ±46	182 ±45	179 ±42	172 ±45	< 0.001

Table I. Cont.

Characteristic	Quartiles of RAR					*P*-value[2]
	Overall Weighted *N* = 11,314,925 Unweighted *n* = 3224[1]	Q1 (0.226,0.307] Weighted *N* = 3,093,112 Unweighted *n* = 806[1]	Q2 (0.307,0.333] Weighted *N* = 2,886,883 Unweighted *n* = 790[1]	Q3 (0.333,0.367] Weighted *N* = 2,776,329 Unweighted *n* = 820[1]	Q4 (0.367,0.843] Weighted *N* = 2,558,601 Unweighted *n* = 808[1]	
TG [mg/dl]	137 ±87	136 ±87	145 ±97	128 ±70	141 ±92	0.36
LDL-cholesterol [mg/dl]	100 ±38	98 ±36	100 ±37	102 ±38	102 ±40	0.33
HDL-cholesterol [mg/dl]	49 ±15	49 ±15	49 ±15	48 ±14	49 ±16	0.71
LDH [IU/l]	144 ±36	137 ±30	141 ±31	146 ±37	155 ±44	< 0.001
eGFR [ml/min/1.73 m^2]	72 ±23	77 ±20	74 ±22	71 ±22	66 ±28	< 0.001
Scr [µmol/l]	97 ±56	88 ±26	91 ±32	95 ±44	116 ±95	< 0.001
Uric acid [mg/dl]	6.03 ±1.60	5.91 ±1.41	5.98 ±1.51	6.01 ±1.57	6.25 ±1.89	0.15
BUN [mg/dl]	18 ±9	16 ±7	18 ±7	18 ±9	20 ±12	< 0.001
FPG [mg/dl]	129 ±49	126 ±44	133 ±49	128 ±44	131 ±57	0.61
FINS [µIU/ml]	19 ±26	17 ±23	21 ±27	19 ±28	19 ±25	0.62
HbA_{1c}, %	6.40 ±1.27	6.16 ±1.07	6.38 ±1.26	6.55 ±1.31	6.57 ±1.41	< 0.001
NLR	2.60 ±1.51	2.28 ±1.07	2.47 ±1.26	2.66 ±1.58	3.09 ±1.94	< 0.001
SII	603 ±418	515 ±275	571 ±340	594 ±381	754 ±601	< 0.001
RAR	0.34 ±0.05	0.29 ±0.01	0.32 ±0.01	0.35 ±0.01	0.42 ±0.06	< 0.001
Follow-up time [months]	78 ±50	102 ±49	80 ±49	67 ±46	58 ±44	< 0.001
All-cause mortality						< 0.001
No	2,001 (66.55)	543 (71.64)	511 (70.87)	494 (63.81)	453 (58.70%)	
Yes	1,223 (33.45)	263 (28.36)	279 (29.13)	326 (36.19)	355 (41.30%)	
Cardiovascular mortality						0.005
No	2,741 (87.32)	704 (90.35)	670 (87.93)	694 (86.49)	673 (83.85%)	
Yes	483 (12.68)	102 (9.65)	120 (12.07)	126 (13.51)	135 (16.15%)	

[1]Mean ± SD; n (unweighted) (%). [2]Kruskal-Wallis rank-sum test for complex survey samples; χ^2 test with Rao & Scott's second-order correction. RAR – red cell distribution width to albumin ratio, PIR – poverty-to-income ratio, Pre-DM – prediabetes, DM – diabetes, BMI – body mass index, RBC – red blood cells, ALT – alanine aminotransferase, AST – aspartate transaminase, TBil – total bilirubin, GGT – γ-glutamyl transferase, TC – total cholesterol, TG – triglyceride, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein, LDH – lactate dehydrogenase, eGFR – estimated glomerular filtration rate, Scr – serum creatinine, BUN – blood urea nitrogen, FBG – fasting blood glucose, FINS – fasting insulin, HbA_{1c} – glycosylated hemoglobin A_{1c}, NLR – neutrophil to lymphocyte ratio, SII – systemic immune-inflammation index.

Computing, Vienna, Austria); EmpowerStats, version 2.0 (EmpowerStats, X&Y Solutions, Boston, MA, USA); and MSTATA software (www.mstata.com). A two-sided *p*-value < 0.05 was considered statistically significant.

Results

Participant baseline characteristics

Table I summarizes the participants' baseline features (n = 3224), with data stratified by RAR quartiles. The participants had a mean age of 66 years, with 55.3% being male. The average RAR was 0.34 ±0.05, with values ranging from 0.29 ±0.01 in Q1 to 0.32 ±0.01 in Q2, 0.35 ±0.01 in Q3, and 0.42 ±0.06 in Q4. Unlike those in the lowest quartile, the participants in the higher-RAR quartile were older; female; black; obese; alcohol consumers; and had a lower family PIR. Additionally, the participants in the highest quartile presented significantly higher leukocyte, neutrophil, lymphocyte, monocyte, RDW, systemic immune-inflammation index (SII), LDH, BUN, HbA_{1c} levels; significantly lower ALT, AST, ALB, total TBiL, TC, and eGFR levels; and a greater incidence of hypertension than did those in the lowest quartile. Of note, the oxidative stress-related indicators total bilirubin, uric acid, and current smoking were assessed. TBiL decreased significantly across RAR quartiles (p < 0.05), while uric acid and smoking showed upward trends without statistical significance. In addition, both LDL-C and HDL-C levels remained largely unchanged across RAR quartiles.

Further stratification among CVD patients with DM and pre-DM (Supplementary Table SI) showed that the DM group had a lower percentage of White participants (69.97% vs. 77.03%), lower education attainment (43.79% vs. 50.01%), a lower current smoking rate (15.61% vs. 24.01%), but higher rates of never and former alcohol consumption (all p < 0.05). The DM group also exhibited higher prevalence of hypertension, BMI, neutrophil count, RDW, GGT, LDL-C, BUN, and HbA_{1c}, but lower RBC, hemoglobin, HDL-C, and eGFR. Moreover, the DM group had a shorter follow-up time (75.51 vs. 81.89 months) and higher rates of ACM (37.24% vs. 29.70%) and CVM (14.32% vs. 11.07%) (all p < 0.05).

Correlations of RAR with ACM and CVM

Throughout an average follow-up of 78 months, 1223 (33.45%) participants out of 3224 died, with 483 deaths due to cardiovascular causes (12.68%). In a cubic spline regression analysis, RAR and both ACM and CVM were significantly positively associated (both p-values for nonlinearity < 0.05; Figures 2 A, B). The pre-DM and DM populations were analyzed separately, revealing that the nonlinear associations between RAR and both ACM and CVM persisted in CVD patients who had pre-DM (both p-values for nonlinearity < 0.05; Supplementary Figures S1 A, B). Specifically, in the pre-DM group, after adjusting for all covariates, each SD increase in RAR was associated with a higher risk of ACM (HR = 1.52, 95% CI: 1.28–1.82) and CVM (HR = 1.53, 95% CI: 1.28–1.82) (Supplementary Table SII). Among CVD patients with DM, RAR was nonlinearly related to ACM (p for nonlinearity = 0.015), whereas the association with CVM was approximately linear (p for nonlinearity = 0.17; Supplementary Figures S2 A, B). In the DM group, each SD increase in RAR corresponded to a higher risk of ACM (HR = 1.40, 95% CI: 1.27–1.55) and CVM (HR = 1.43, 95% CI: 1.24–1.65) (Supplementary Table SIII). These results indicate that the strength of the association between RAR and mortality outcomes was slightly greater in CVD patients with pre-DM than in those with DM.

The Cox proportional hazards regression analysis revealed that (Table II), in Model 1, each SD increase in RAR was positively connected with ACM (HR = 1.52, 95% CI: 1.42–1.62) and CVM (HR = 1.53, 95% CI: 1.40–1.67). In Model 2, these relationships remained significant for ACM (HR = 1.58,

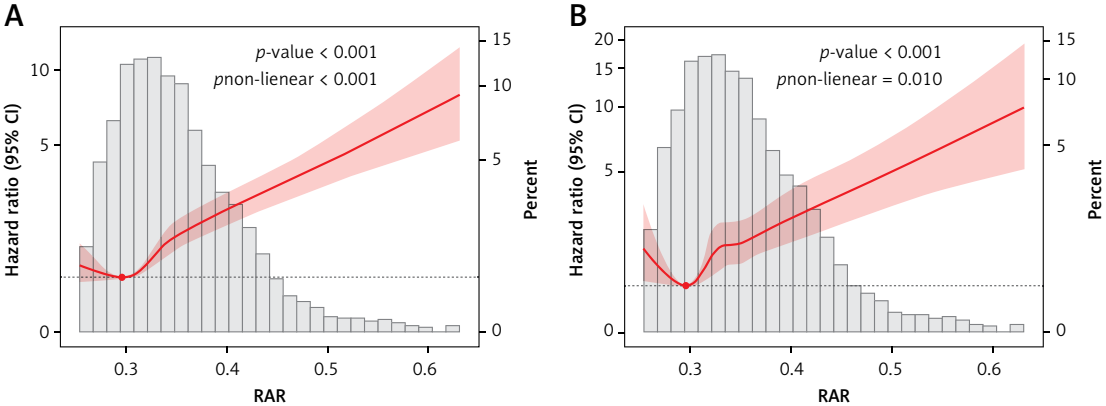

Figure 2. Association between RAR and ACM (**A**) and CVM (**B**) in CVD patients with DM or pre-DM visualized by restricted cubic splines. Hazard ratios were adjusted for age, sex, race, BMI, tobacco use, alcohol use, education, FPIR, hypertension, monocytes, red blood cells, platelets, GGT, uric acid, TC, HDL-C, eGFR, TBil, LDH and BUN

Table II. HRs (95% CIs) for mortality according to RAR quartiles

Parameter	HR (95% CI)		
	Model 1	Model 2	Model 3
All-cause mortality			
RAR per-SD change	1.52 (1.42, 1.62)	1.58 (1.45, 1.72)	1.43 (1.31, 1.56)
Q1 (0.226, 0.307)	1	1	1
Q2 (0.307, 0.333)	1.38 (1.11, 1.71)	1.33 (1.09, 1.62)	1.30 (1.07, 1.57)
Q3 (0.333, 0.367)	2.16 (1.74, 2.67)	1.94 (1.57, 2.40)	1.78 (1.45, 2.18)
Q4 (0.367, 0.843)	2.94 (2.36, 3.66)	3.07 (2.43, 3.88)	2.56 (2.01, 3.25)
P for trend	< 0.001	< 0.001	< 0.001
Cardiovascular mortality			
RAR per-SD change	1.53 (1.40, 1.67)	1.59 (1.42, 1.77)	1.44 (1.28, 1.62)
Q1 (0.226, 0.307)	1	1	1
Q2 (0.307, 0.333)	1.67 (1.22, 2.29)	1.59 (1.19, 2.13)	1.61 (1.20, 2.15)
Q3 (0.333, 0.367)	2.35 (1.72, 3.21)	2.06 (1.51, 2.81)	1.98 (1.44, 2.72)
Q4 (0.367, 0.843)	3.34 (2.45, 4.56)	3.43 (2.51, 4.69)	2.96 (2.08, 4.20)
P for trend	< 0.001	< 0.001	< 0.001

Model 1: Unadjusted. Model 2: Adjusted for age, sex, and race. Model 3: Adjusted for age, sex, race, BMI, tobacco use, alcohol use, education, FPIR, hypertension, monocytes, red blood cells, platelets, GGT, uric acid, TC, HDL, eGFR, TBil, LDH, and BUN.
RAR – red cell distribution width to albumin ratio, BMI – body mass index, FPIR – family poverty income ratio, GGT – γ-glutamyl transferase, TC – total cholesterol, HDL-C – high-density lipoprotein, eGFR – estimated glomerular filtration rate, TBil – total bilirubin, LDH – lactate dehydrogenase, BUN – blood urea nitrogen, HR – hazard ratio, CI – confidence interval, SD – standard deviation.

95% CI: 1.45–1.72) and CVM (HR = 1.59, 95% CI: 1.42–1.77). In Model 3, each SD increase in RAR was related to increased risks of ACM (HR = 1.43, 95% CI: 1.31–1.56) and CVM (HR = 1.44, 95% CI: 1.28–1.62). Participants in the highest RAR quartile (Q4) had an elevated risk of ACM (HR = 2.56, 95% CI: 2.01–3.25) and CVM (HR = 2.96, 95% CI: 2.08–4.20) in comparison to those in the lowest quartile (Q1), indicating a significant trajectory across quartiles (*p* for trend < 0.001). The Kaplan–Meier survival plots indicated that the higher-RAR quartile participants had significantly lower estimated survival rates regarding ACM and CVM than did those in the lowest quartile (Figures 3 A, B).

Stratified analyses

The stratified analysis results (Figures 4, 5) revealed that elevated RAR levels were related to increased risks for ACM and CVM in all strata. The outcomes revealed a strong correlation between increased RAR levels and ACM and CVM risk, regardless of age, sex, BMI, race, or DM status.

Correlations of inflammation with RAR and fatality

Table III outlines the connections between RAR and inflammation-related markers via multivariate logistic regression analysis. After all potential confounders were adjusted, RAR was positive-

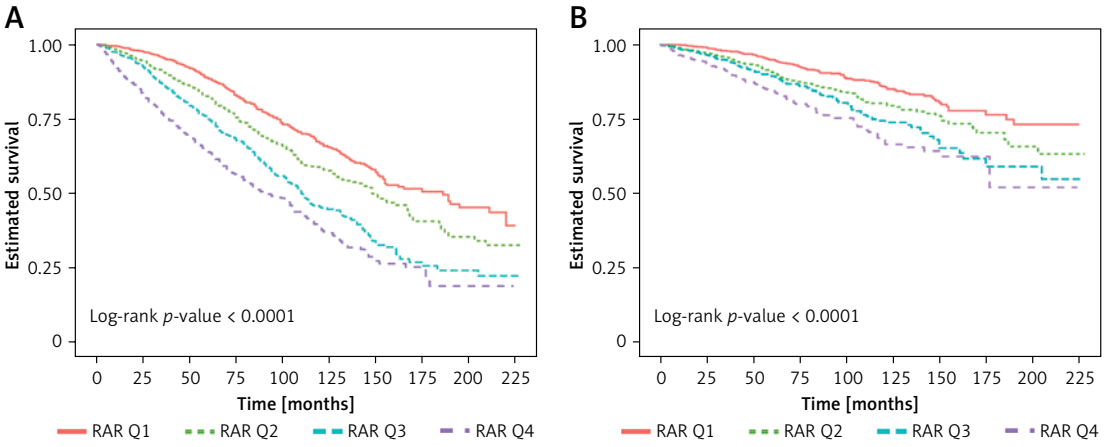

Figure 3. Kaplan-Meier curves of survival rate of participants according to RAR quartiles (**A** – all-cause mortality, **B** – cardiovascular mortality)

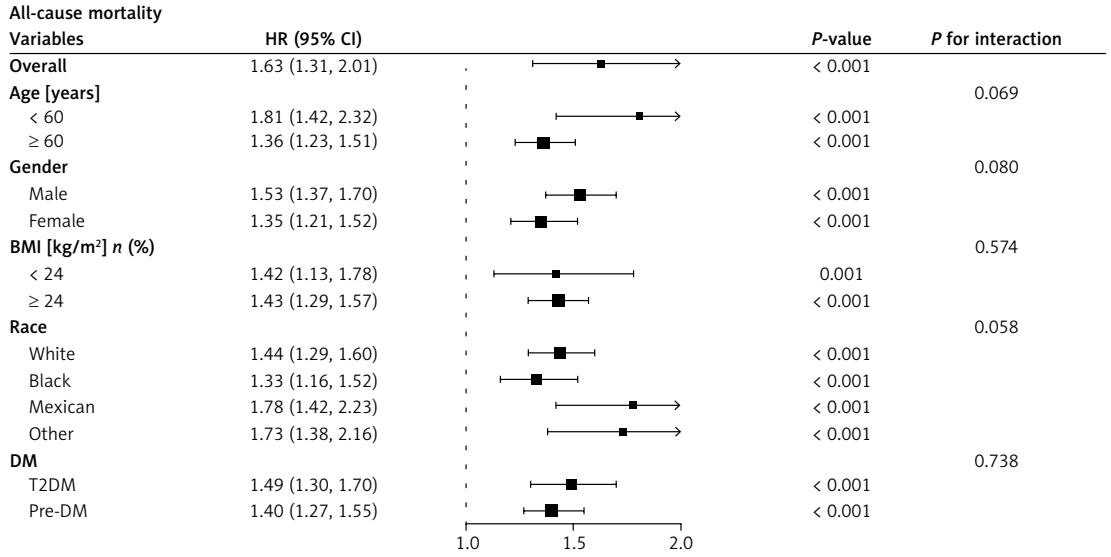

Figure 4. Stratified analyses of associations between RAR and all-cause mortality

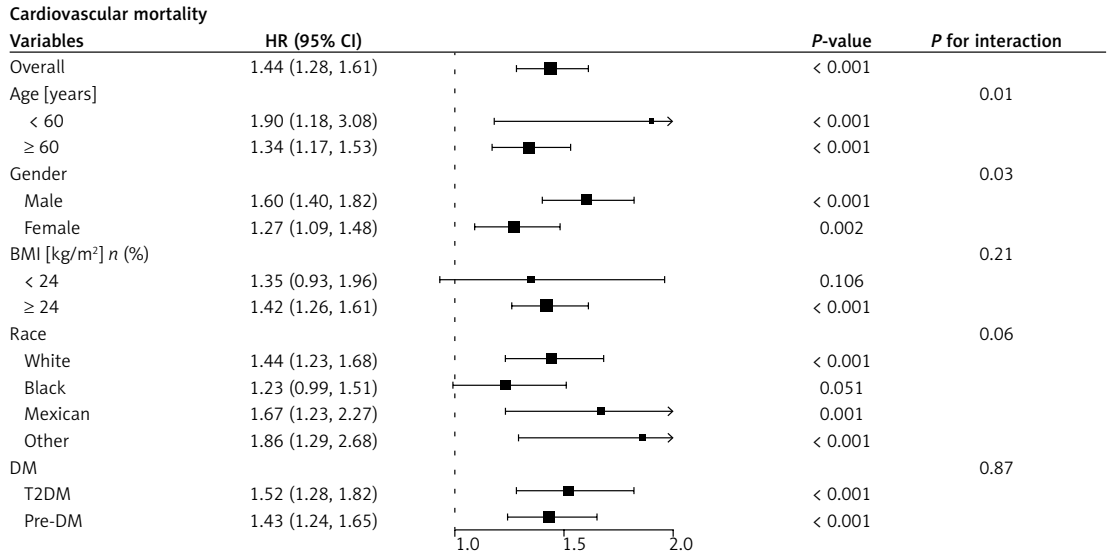

Figure 5. Stratified analyses of associations between RAR and cardiovascular mortality

ly associated with the NLR (β = 0.13, 95% CI = 0.10–0.16, $p < 0.01$) and the SII (β = 0.06, 95% CI = 0.04–0.07, $p < 0.01$). The Cox regression models in Table IV indicate that most inflammation-related indicators were positively associated with mortality, except lymphocytes for ACM and CVM.

Mediating effects of inflammation-related indicators

Mediation analysis was used to investigate the role of inflammatory indicators in mediating the association between RAR and both ACM and CVM (Supplementary Table SI). NLR mediated 8.8% of the association with ACM (Figure 6 A) and 10.79% of the association with CVM (Figure 7 A). SII mediated 9.58% of the association with ACM (Figure 6 B) and 11.99% of the association with CVM (Figure 7 B).

Discussion

This cohort study is the first to systematically investigate the associations between RAR and both ACM and CVM among CVD patients with DM or pre-DM. Restricted cubic spline analysis demonstrated a dose-dependent increase in mortality risk with rising RAR levels, and Cox proportional hazards regression further confirmed that elevated RAR remained independently associated with increased risks of ACM and CVM after adjustment for multiple confounders. Moreover, mediation analysis suggested that inflammation – particularly involving neutrophils, monocytes,

Table III. Association between standardized RAR and inflammation-related indicators

Parameter	β value	95% CI	*P*-value
Leukocytes			
Model 1	0.02	(0.00, 0.04)	0.01
Model 2	0.02	(0.01, 0.04)	0.01
Model 3	0.01	(0.00, 0.02)	0.21
Lymphocytes			
Model 1	–0.01	(–0.02, 0.00)	0.17
Model 2	–0.01	(–0.02, 0.00)	0.22
Model 3	–0.01	(–0.03, –0.00)	0.01
Monocytes			
Model 1	0.50	(0.33, 0.67)	< 0.01
Model 2	0.62	(0.44, 0.81)	< 0.01
Model 3	0.33	(0.18, 0.49)	< 0.01
Neutrophils			
Model 1	0.10	(0.07, 0.13)	< 0.01
Model 2	0.11	(0.08, 0.14)	< 0.01
Model 3	0.08	(0.05, 0.10)	< 0.01
NLR			
Model 1	0.14	(0.11, 0.17)	< 0.01
Model 2	0.15	(0.12, 0.19)	< 0.01
Model 3	0.13	(0.10, 0.16)	< 0.01
SII (per 100-unit increase)			
Model 1	0.06	(0.04, 0.07)	< 0.01
Model 2	0.06	(0.04, 0.07)	< 0.01
Model 3	0.06	(0.04, 0.07)	< 0.01

Model 1: Unadjusted. Model 2: Adjusted for age, sex, and race. Model 3: Adjusted for age, sex, race, BMI, tobacco use, alcohol use, education, FPIR, hypertension, red blood cells, platelets, GGT, uric acid, TC, HDL-C, eGFR, TBil, LDH, and BUN.
RAR – red cell distribution width-to-albumin ratio, NLR – neutrophil-to-lymphocyte ratio, SII – systemic immune-inflammation index, BMI – body mass index, FPIR – family poverty income ratio, GGT – γ-glutamyl transferase, TC – total cholesterol, HDL-C – high-density lipoprotein, eGFR – estimated glomerular filtration rate, TBil – total bilirubin, LDH – lactate dehydrogenase, BUN – blood urea nitrogen, HR – hazard ratio, CI – confidence interval, SD – standard deviation.

NLR, and SII – plays a significant mediating role in the relationship between RAR and prognosis. Notably, in patients with pre-DM and CVD, RAR had a nonlinear association with both ACM and CVM, whereas in patients with DM and CVD, the association between RAR and CVM was linear. This may reflect differences in inflammation and compensatory mechanisms [28], underscoring the need for early risk management.

Prior studies have investigated the link between RAR levels and adverse outcomes across various disease-specific cohorts and the general population, particularly in CVD and DM patients. Li *et al*. reported that in patients who have acute MI, a greater RAR was associated with a 23% increase in 30-day fatality (HR = 1.23, 95% CI: 1.09–1.39) and a 122% increase in 3-year mortality when the RAR was ≥ 4 [17]. RAR provides better mortality prediction than RDW or ALB alone and is correlated with the severity of CVD. Huang *et al*. analyzed the relationship between the RAR and carotid plaque formation in CHD patients with various glucose metabolic states and found that a higher RAR was associated with increased carotid plaque risk, especially in diabetic patients (OR = 1.28, 95% CI: 1.04–1.58) [20]. Hong *et al.* reported that both RDW (HR = 2.426, 95% CI: 1.557–3.778) and RAR (HR = 2.360, 95% CI: 1.414–3.942) were independent predictors of ACM in 860 patients with diabetic foot ulcers [29]. Similarly, our study found that higher RAR was associated with increased CVM (HR = 1.43, 95% CI: 1.28–1.62) and ACM (HR = 1.44, 95% CI: 1.31–1.56) in patients with CVD and diabetes or prediabetes. The broader inclusion in our study may further support the generalizability of RAR as a prognostic marker. Differences in study populations may explain the variation in HRs. In addition, RAR has been shown to be related to poor prognosis and mortality in burn surgery [21], acute pancreatitis [30], stroke [19], and the general population [31]. Altogether, these studies demonstrate a consistent association between higher RAR and adverse clinical outcomes in diverse diseases, and our study extends these findings specifically to the CVD population with DM or pre-DM.

Growing evidence suggests that oxidative stress plays a central role in the development and progression of cardiovascular disease in individuals with abnormal glucose metabolism [32]. TBiL, as an important endogenous antioxidant, not only improves insulin sensitivity and suppresses inflammation [33], but its decreased levels often indicate increased oxidative stress and a higher risk of cardiovascular and metabolic events [34]. In addition, studies have shown that elevated uric acid can promote oxidative stress and inflammatory responses, leading to endothelial dysfunction and injury, which further accelerates the development of atherosclerosis – especially in patients with diabetes [35]. Consistent with these observations, our study found that, among CVD patients with DM and pre-DM, higher RAR was associated with lower TBiL levels, increased uric acid, and a higher proportion of smokers. Moreover, our study further found that the proportion of smokers increased with higher RAR, suggesting a close association between RAR and oxidative stress [36, 37]. Meanwhile, higher RAR indicated more severe oxidative stress and an increased risk of mortality. This suggests that people with high RAR experience more pronounced oxidative stress and reduced antioxidant capacity, potentially increasing their mortality risk. Although LDL-C and HDL-C levels did not

Table IV. Association of inflammation-related indicators with all-cause mortality and cardiovascular mortality

Parameter	HR (95% CI)		
	Model 1	Model 2	Model 3
All-cause mortality			
Leukocytes	1.02 (1.01, 1.04)	1.02 (1.01, 1.03)	1.02 (1.01, 1.03)
Lymphocytes	1.04 (0.79, 1.14)	0.99 (0.97, 1.02)	0.99 (0.96, 1.02)
Monocytes	3.12 (2.41, 4.04)	2.21 (1.72, 2.85)	1.73 (1.33, 2.26)
Neutrophils	1.13 (1.08, 1.17)	1.17 (1.13, 1.21)	1.16 (1.11, 1.21)
NLR	1.20 (1.14, 1.26)	1.17 (1.12, 1.22)	1.14 (1.09, 1.19)
SII per 100-unit increase	1.05 (1.03, 1.08)	1.05 (1.03, 1.08)	1.06 (1.03, 1.09)
Cardiovascular mortality			
Leukocytes	1.01 (0.99, 1.03)	1.01 (1.01, 1.03)	1.01 (1.01, 1.03)
Lymphocytes	0.68 (0.52, 0.88)	0.87 (0.72, 1.06)	0.92 (0.78, 1.07)
Monocytes	3.43 (2.27, 5.20)	2.31 (1.57, 3.39)	1.94 (1.27, 2.96)
Neutrophils	1.11 (1.04, 1.18)	1.16 (1.09, 1.23)	1.15 (1.08, 1.23)
NLR	1.21 (1.14, 1.29)	1.19 (1.12, 1.26)	1.17 (1.09, 1.24)
SII per 100-unit increase	1.05 (1.04, 1.06)	1.05 (1.03, 1.06)	1.05 (1.03, 1.07)

Model 1: Unadjusted. Model 2: Adjusted for age, sex, and race. Model 3: Adjusted for age, sex, race, BMI, tobacco use, alcohol use, education, FPIR, hypertension, red blood cells, platelets, GGT, uric acid, TC, HDL, eGFR, TBil, LDH, and BUN.
RAR – red cell distribution width-to-albumin ratio, NLR – neutrophil-to-lymphocyte ratio, SII – systemic immune-inflammation index, BMI – body mass index, FPIR – family poverty income ratio, GGT – γ-glutamyl transferase, TC – total cholesterol, HDL-C – high-density lipoprotein, eGFR – estimated glomerular filtration rate, TBil – total bilirubin, LDH – lactate dehydrogenase, BUN – blood urea nitrogen, HR – hazard ratio, CI – confidence interval, SD – standard deviation.

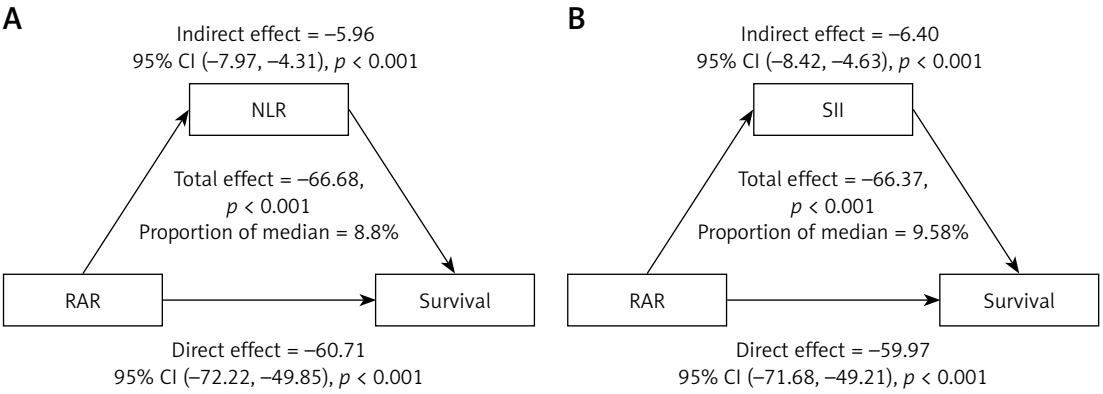

Figure 6. Analysis of associations of RAR with all-cause mortality mediated by NLR (**A**), SII (**B**)

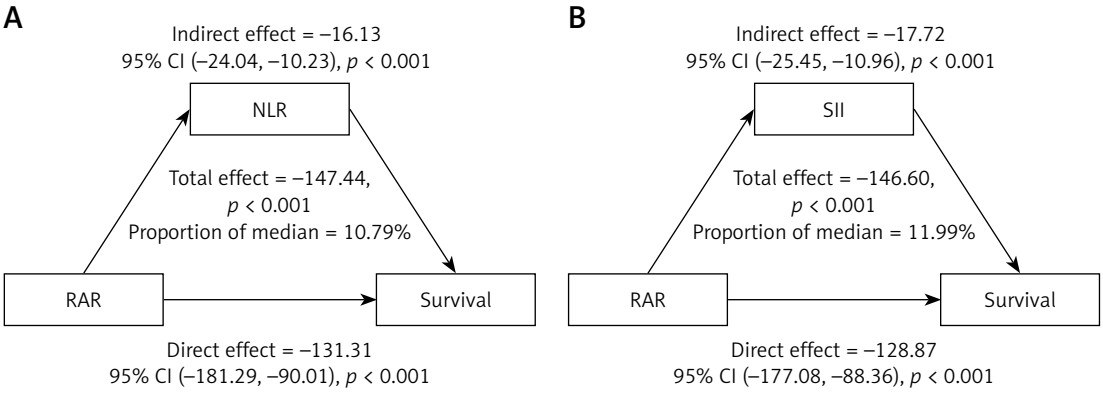

Figure 7. Analysis of associations of RAR with cardiovascular mortality mediated by NLR (**A**), SII (**B**)

differ significantly among RAR groups in our study, previous studies indicate that oxidized LDL and dysfunctional HDL – rather than their total levels – are key factors influencing atherosclerosis and oxidative stress [38, 39], which may explain our findings. Future studies should further explore the role and clinical significance of ox-LDL and dysfunctional HDL in this population.

Although the underlying biological mechanisms linking elevated RAR to increased mortality remain to be fully clarified, possible explanations include the roles of chronic inflammation and nutritional status. RAR is calculated from RDW and ALB, two parameters that are extensively studied as indicators of inflammation and nutritional health. Elevated RDW has been linked to chronic inflammation [40, 41], while low ALB is associated not only with malnutrition but also with inflammation and impaired hepatic synthesis [42–45]. In our study, RAR was positively correlated with systemic inflammatory markers including NLR and SII, suggesting that inflammation might partially mediate the observed association.

In particular, accumulating evidence indicates that systemic inflammation is not only involved in the formation and progression of atherosclerotic lesions, but also plays a central role in the rupture of vulnerable plaques – the key trigger for acute cardiovascular events [46–48]. Accordingly, anti-inflammatory intervention has attracted extensive attention in recent years. Large randomized controlled trials (RCTs) of colchicine (e.g., COLCOT [49] and LoDoCo2 [50]) have demonstrated reduced major adverse cardiovascular events in patients with coronary artery disease, whereas studies such as COPS [51] did not identify clear benefits and raised concerns about safety, leading to an ongoing debate regarding its clinical role [52]. Additionally, ongoing clinical trials are investigating novel anti-inflammatory agents, such as interleukin-1β inhibitors (e.g., canakinumab [53]), which may provide further insight into the potential benefit of inflammation modulation for cardiovascular prevention, particularly in high-risk diabetic populations. These recent advances highlight the importance of targeting systemic inflammation in the management of plaque instability and prevention of adverse outcomes. Meanwhile, recent studies also emphasize that, for high cardiovascular risk patients, early combination lipid-lowering therapy can not only more effectively control lipid levels, but also improve plaque stability and modulate inflammation, thereby further reducing the risk of adverse cardiovascular event [54, 55].

Chronic low-grade inflammation plays a well-recognized role in the development and progression of CVD and metabolic disorders such as DM [7, 56–58]. Neutrophils and lymphocytes, reflected in the NLR, are critical in these inflammatory responses and have been linked to vascular injury and metabolic dysfunction [59–64]. Taken together, these findings suggest that the RAR may integrate information about both inflammatory burden and nutritional status, which could help explain its association with adverse outcomes. However, given the observational design, these hypotheses require further validation in mechanistic studies.

In summary, patients with abnormal glucose metabolism and CVD often exhibit obesity, insulin resistance, lipid metabolism disorders, and endothelial dysfunction. These factors interact to trigger heightened inflammatory responses. Chronic inflammation and oxidative stress can impair erythropoiesis, reduce erythrocyte survival, and increase the RDW. Concurrently, malnutrition and chronic inflammation may reduce ALB levels, ultimately promoting plaque instability, thrombosis, microcirculatory disorders, and other adverse events. Therefore, we believe that chronic low-grade inflammation may be one of the mechanisms by which elevated RAR leads to poor prognosis and increased mortality. This study hypothesized that inflammation is a key mediator in the relationship between RAR and mortality among CVD patients who have DM or pre-DM. The NLR and SII mediated 10.79% and 11.99%, respectively, of the association between RAR and cardiovascular mortality. These findings highlight the role of systemic inflammation as a mediating pathway in the relationship between RAR and mortality.

This study has several key strengths. First, we used data from NHANES, a large and representative cohort study. More importantly, this is the first study to demonstrate that inflammatory pathways significantly mediate the association between RAR and mortality in CVD patients with DM or pre-DM, providing novel mechanistic insights. Additionally, RAR represents a readily available and cost-effective marker for risk stratification in clinical practice.

Our study has some limitations. As a retrospective study, the relationship between RAR and mortality reflects associations rather than causality. Additionally, this analysis focused solely on baseline RAR levels, and the prognostic value of RAR changes during follow-up remains to be investigated. Furthermore, the NHANES database currently lacks data on ox-LDL and dysfunctional HDL, which limits further mechanistic exploration. Future research should incorporate these biomarkers to clarify their roles in the relationship between RAR and cardiovascular outcomes. In addition, although NHANES is designed to be

nationally representative of the U.S. population, our findings may not fully represent populations in other countries or regions. Therefore, the generalizability of our findings to non-US populations may be limited.

In conclusion, higher RAR levels were independently associated with increased risks of both ACM and CVM in patients with CVD and DM or pre-DM, based on NHANES data. Systemic inflammation was identified as an important mediator in these relationships. These findings highlight the prognostic value of RAR for risk stratification in CVD patients with DM or pre-DM and support further research on its clinical utility.

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Shuangya Yang and Ning Gu contributed equally to this work.

Data availability

The NHANES data used for this analysis can be found at https://www.cdc.gov/nchs/nhanes.

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Ethical approval

The NHANES protocol was authorized by the National Center for Health Statistics and the Ethics Review Board, with all participants signing informed consent.

Conflict of interest

The authors declare no conflict of interest.

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