

Association between Red Blood Cell Distribution Width-to-Albumin Ratio and All-Cause Mortality in the General Population: A Cohort Study

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Abstract

Background: The red blood cell distribution width (RDW) to albumin ratio (RAR) has emerged as a novel indicator for mortality in patients with various diseases. However, whether RAR is associated with all-cause mortality in the general population remains unknown. This study aims to investigate the relationship between RAR and all-cause mortality and to elucidate their dose-response association. **Methods:** Data were derived from the National Health and Nutrition Examination (NHANES) Survey (1998-2018). The RAR was calculated by dividing RDW (%) by the albumin concentration (g/dL). The primary outcome was all-cause mortality, which was linked to the National Death Index (NDI) database through December 31, 2019. Potential associations between RAR and the risk of all-cause mortality were assessed using Cox proportional hazards regression models. Restricted cubic spline regressions were applied to examine possible nonlinear associations. Subgroup analyses were conducted to evaluate the robustness of these associations. **Results:** A total of 30840 participants aged 18 years old and above, of whom 48.48% were male, were included in the study. The multivariate-adjusted HR (95% CI) for all-cause mortality was 1.00 (reference), 2.03 (1.82 - 2.26), 3.29 (2.96 - 3.66), and 5.04 (4.54 - 5.59) across the RAR quartiles (Q1, Q2, Q3, and Q4, respectively) ($P < 0.05$). The cubic spline regression identified a nonlinear, positive association between RAR and all-cause mortality (P for overall test < 0.0001 , P for nonlinearity < 0.0001). The Kaplan-Meier survival curves show significantly

lower cumulative survivals with higher RAR quartiles (log-rank test, $P < 0.0001$). Subgroup analyses identified significant associations between high RAR and increased all-cause mortality risk in the general population. **Conclusions:** In this cohort study, RAR is independently associated with all-cause mortality in the US general population, with a nonlinear positive dose-response relationship. These findings suggest that RAR may be a simple, reliable, and inexpensive indicator for identifying individuals at high risk of mortality in clinical practice.

Keywords

Red Blood Cell Distribution Width, Albumin, RAR, All-Cause Mortality, Cohort Study

1. Introduction

Early identification of individuals at high risk of mortality remains a critical challenge in public health and clinical practice. Accurate risk stratification enables the implementation of targeted interventions, optimizes the allocation of healthcare resources, and ultimately improves patient outcomes. Although numerous prognostic factors have been identified, there remains an urgent need for simple, reliable, and cost-effective biomarkers that can be readily integrated into routine clinical practice. In recent years, hematological and biochemical parameters obtained from routine laboratory tests, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and prognostic nutritional index (PNI), have garnered increasing attention as potential prognostic biomarkers in the general population due to their wide availability and low cost [1]-[3].

Red blood cell distribution width (RDW) is an indicator in routine laboratory testing that reflects the heterogeneity of red blood cell volume. Traditionally used for the differential diagnosis of anemias, RDW is now recognized as a biomarker of systemic inflammation, oxidative stress, and impaired erythropoiesis. Numerous studies have demonstrated that elevated RDW levels are independently associated with an increased risk of mortality in patients with cardiovascular diseases, cancers, sepsis, and chronic kidney disease (CKD) [4]. Serum albumin is the most abundant circulating protein in blood, which plays a pivotal role in maintaining colloid osmotic pressure, transporting various substances, and regulating immune responses. Low serum albumin levels are an important biomarker of nutritional status, inflammatory response, and hepatic synthetic function [5] [6]. Multiple studies have reported that serum albumin concentration is negatively correlated with the incidence of functional impairment, diseases, and mortality [7]-[9].

Given the complementary biological significance of red blood cell distribution width (RDW) and albumin, a novel integrated biomarker—the red blood cell distribution width to albumin ratio (RAR)—has been proposed, which integrates

information on inflammation, oxidative stress, and nutritional status. Compared with individual indicators, RAR may provide a more comprehensive assessment of health status and exhibit superior prognostic performance. Recently, RAR has been demonstrated to be a potential risk biomarker for adverse outcomes in various diseases, including acute myocardial infarction (AMI), atrial fibrillation (AF), diabetes mellitus (DM), heart failure (HF), chronic kidney disease (CKD), and stroke [10]–[15]. However, the association between RAR and mortality in the general population remains unclear to date.

Therefore, we hypothesized that elevated RAR is related to increased risk of all-cause mortality in the general population. This study aimed to investigate the potential association between RAR and all-cause mortality risk using data from the National Health and Nutrition Examination Survey (NHANES).

2. Methods

2.1. Study Participants

This population-based cohort study was conducted using data from the NHANES, a nationally representative cross-sectional survey administered by the Centers for Disease Control and Prevention (CDC) that evaluates the health and nutritional status of the civilian non-institutionalized population in the United States through a complex, multistage, stratified, clustered probability sampling design, collecting comprehensive demographic, clinical, laboratory, and lifestyle data via household interviews, physical examinations, and standardized laboratory tests in continuous 2-year cycles since 1999, with all de-identified data publicly accessible on the CDC website. We included participants from ten consecutive NHANES cycles spanning 1999 to 2018, yielding an initial eligible population of 102,345 individuals; participants were excluded sequentially if they were under 18 years of age ($n = 43,182$), had missing data on red blood cell distribution width (RDW) ($n = 10,144$) or serum albumin levels ($n = 11,433$), or lacked available survival status and follow-up time information ($n = 6,746$), resulting in a final analytical cohort of 30,840 participants (**Figure 1**). All participants provided written informed consent, and the NHANES study protocol was approved by the National Center for Health Statistics Research Ethics Review Board, with this investigation conducted in full compliance with the Declaration of Helsinki.

2.2. Measurement of RAR

The serum albumin concentration was determined using the bromocresol purple method. The RDW (percentage) was measured by a Coulter analyzer in the mobile examination centers using peripheral blood. The RAR was calculated by dividing RDW (%) by the albumin concentration (g/dL).

2.3. Outcomes

In this study, the primary outcome was all-cause mortality. The dates of death were linked to the National Death Index records through December 31, 2019.

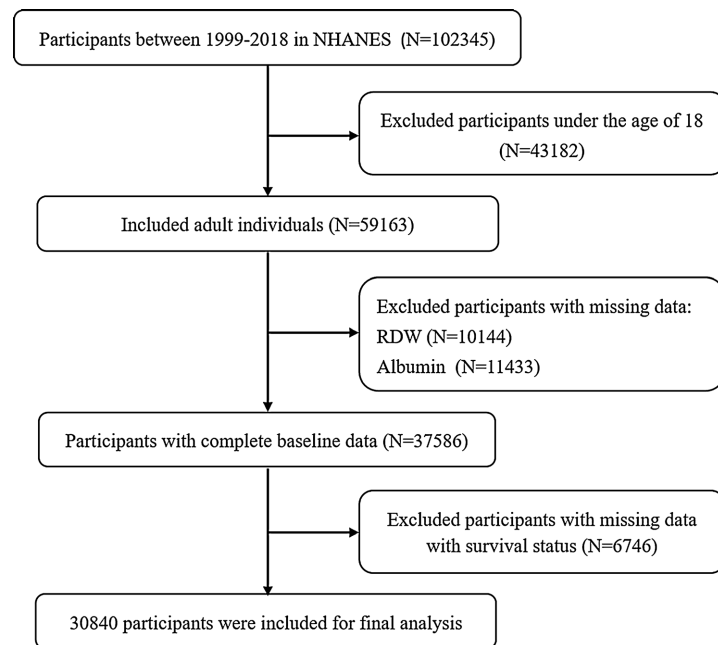


Figure 1. Flowchart of study population in NHANES.

2.4. Covariates

In this study, covariates included demographic characteristics, lifestyle factors, economic factors, and clinical information. The demographic characteristics included age, sex, race and ethnicity, education, and marital status. Race and ethnicity status was categorized into Black (non-Hispanic Black), Hispanic (Mexican American and other Hispanic), White (non-Hispanic White), and other (Asian, multiple races). Educational levels were divided into college or above, high school or equivalent, and less than high school. Participants reported their education qualifications as college graduate or above, some college or associate of arts degree, high school graduate or General Educational Development or equivalent, 9th through 11th grade (including 12th grade with no diploma), less than 9th grade, and unknown or missing (excluded from our analyses). Lifestyle factors included body mass index (BMI; calculated as weight in kilograms divided by height in meters squared). The BMI was used to divide participants into underweight (BMI < 18.5), normal weight (18.5 ≤ BMI < 24.9), overweight (25.0 ≤ BMI < 29.9), and obese (BMI ≥ 30.0) groups. The economic factor included the poverty income ratio (PIR), which is a ratio of family income to poverty threshold and reflects relative household economic status. PIR was grouped according to the quartiles. Information on demographic characteristics, lifestyle factors, and economic factors was collected through a self-report questionnaire. Clinical information, including the presence of hypertension, diabetes, heart disease, stroke, and cancer, was ascertained by self-reports by participants or proxies.

2.5. Statistical Analysis

Baseline characteristics for continuous variables are presented as means ± standard

deviations (SDs) or medians (interquartile ranges, IQRs), as appropriate. The Kruskal-Wallis or Wilcoxon rank-sum test was used to compare continuous variables based on data normality. Categorical variables were compared using the chi-squared or Cochran-Mantel-Haenszel test. Trend *P*-values were calculated using the Cochran-Armitage trend test. Participants were divided into four groups according to RAR quartiles. Potential associations between RAR and the risk of all-cause mortality were assessed using Cox proportional hazards regression models. Restricted cubic spline (RCS) regressions were applied to examine possible nonlinear associations. We conducted a Kaplan-Meier survival analysis to plot the associations of different RAR groups with all-cause mortality. Subgroup analyses were conducted by stratifying for age, sex, race and ethnicity, BMI, education, Marital status, PIR, hypertension, diabetes, dyslipidemia, heart disease, stroke, and cancer. Dummy variables for multi-category variables (RAR quartiles, education, race and ethnicity, PIR) were included in the models. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and GraphPad Prism version 7.04 (GraphPad Software Inc., San Diego, CA, USA). Two-tailed *P*-values were calculated, and statistical significance was defined as $P < 0.05$.

3. Results

3.1. Baseline Characteristics of the Study Population

Table 1 shows the baseline characteristics of the 30840 participants categorized by RAR quartiles. The mean age was 47.71 years, and 48.48% of the participants were males. Participants in the higher RAR quartile were more likely to have diabetes, heart disease, and higher BMI and RDW, and lower albumin than those in the lower RAR quartile (all the *P* values < 0.05). Individuals in higher RAR quartiles had a lower proportion of white people and a higher proportion of people from other racial/ethnic groups, as well as a higher proportion with higher education levels and a lower proportion with lower education levels (all *P* values < 0.05).

Table 1. Baseline characteristics of the study population.

Characteristics	RAR Quartiles				<i>P</i> -Value
	Q1 (n = 7584)	Q2 (n = 8213)	Q3 (n = 7330)	Q4 (n = 7713)	
Age (year)	47.40 ± 19.52	47.79 ± 19.44	47.93 ± 19.40	47.73 ± 19.42	0.3902
Age Category (n, %)					0.4578
<45	3602 (47.49)	3834 (46.68)	3379 (46.10)	3609 (46.79)	
45 - 64	2214 (29.19)	2399 (29.21)	2206 (30.10)	2286 (29.64)	
≥65	1768 (23.31)	1980 (24.11)	1745 (23.81)	1818 (23.57)	
Sex (n, %)					0.8040
Female	3672 (48.42)	3958 (48.19)	3639 (49.65)	3682 (47.74)	

Continued

Male	3912 (51.58)	4255 (51.81)	3691 (50.35)	4031 (52.26)	
BMI (kg/m ²)	26.16 ± 4.92	27.90 ± 5.58	29.47 ± 6.66	31.58 ± 8.32	<0.0001
BMI Category (<i>n</i> , %)					<0.0001
Underweight (<18.5)	220 (2.90)	146 (1.78)	105 (1.43)	80 (1.04)	
Normal (18.5 - 24.9)	3152 (41.56)	2453 (29.87)	1789 (24.41)	1462 (18.96)	
Overweight (25.0 - 29.9)	2711 (35.75)	3089 (37.61)	2445 (33.36)	2329 (30.20)	
Obese (≥30.0)	1501 (19.79)	2525 (30.74)	2991 (40.80)	3842 (49.81)	
Race and Ethnicity (<i>n</i> , %)					<0.0001
Black	1598 (21.07)	1708 (20.80)	1600 (21.83)	1656 (21.47)	
Hispanic	2006 (26.45)	2211 (26.92)	1966 (26.82)	2044 (26.50)	
White	3338 (44.01)	3589 (43.70)	3040 (41.47)	3167 (41.06)	
Other	642 (8.47)	705 (8.58)	724 (9.88)	846 (10.97)	
Education (<i>n</i> , %)					0.0195
< High School	2525 (33.34)	2690 (32.81)	2367 (32.35)	2410 (31.32)	
High School or Equivalent	1615 (21.33)	1749 (21.33)	1546 (21.13)	1713 (22.26)	
≥College or Above	3433 (45.33)	3759 (45.85)	3404 (46.52)	3572 (46.42)	
Marital Status (<i>n</i> , %)					0.7117
Non-Single	4185 (57.34)	4575 (58.05)	4037 (57.70)	4273 (57.78)	
Single	3114 (42.66)	3306 (41.95)	2960 (42.30)	3122 (42.22)	
PIR	2.06 (1.07, 4.00)	2.05 (1.08, 3.93)	2.06 (1.09, 3.94)	2.09 (1.08, 4.04)	0.7203
PIR Category (<i>n</i> , %)					0.6534
<1.33	2964 (39.08)	3268 (39.79)	2935 (40.04)	3077 (39.89)	
1.33 - 3.22	2331 (30.74)	2497 (30.40)	2207 (30.11)	2291 (29.70)	
≥3.22	2289 (30.18)	2448 (29.81)	2188 (29.85)	2345 (30.40)	
RDW (%)	12.2 (11.9, 12.5)	12.7 (12.4, 13.1)	13.2 (12.7, 13.6)	14.1 (13.5, 15.1)	<0.0001
Albumin (g/dL)	4.6 (4.5, 4.7)	4.3 (4.2, 4.5)	4.1 (4.0, 4.3)	3.9 (3.7, 4.1)	<0.0001
RAR	2.67 (2.58, 2.75)	2.93 (2.87, 3.00)	3.18 (3.12, 3.26)	3.63 (3.46, 3.93)	<0.0001
Chronic Disease (<i>n</i> , %)					
Hypertension	1786 (23.55)	1892 (23.04)	1683 (22.96)	1715 (22.24)	0.0611
Diabetes	894 (11.79)	1310 (15.95)	1403 (19.14)	1989 (25.79)	<0.0001
Dyslipidemia	4178 (55.09)	4830 (58.81)	4257 (58.08)	4247 (55.06)	0.6635
Heart Disease	368 (4.85)	411 (5.00)	385 (5.25)	429 (5.56)	0.0350
Stroke	180 (2.37)	197 (2.40)	188 (2.56)	188 (2.44)	0.6536
Cancer	369 (4.87)	415 (5.05)	399 (5.44)	407 (5.28)	0.1534

BMI: body mass index; PIR: poverty income ratio; RDW: red blood cell distribution width; RAR: red blood cell distribution width to albumin ratio.

3.2. Association between RAR and All-Cause Mortality

Table 2 presents the Cox proportional hazards regression analysis results on the association between the RAR and all-cause mortality. Four Cox models were employed to assess the association of RAR with the risk of all-cause mortality. In Model 4, after adjusting for age, sex, race and ethnicity, BMI, PIR, education, marital status, hypertension, diabetes, dyslipidemia, heart disease, stroke, and cancer, the multivariate-adjusted HRs with 95% CIs for all-cause mortality were 1.00 (reference), 2.03 (1.82 - 2.26), 3.29 (2.96 - 3.66) and 5.04 (4.54 - 5.59), across the RAR quartiles (Q1, Q2, Q3, and Q4, respectively) ($P < 0.05$).

Table 2. Hazard ratios of all-cause mortality according to continuous levels of the ratio of red blood distribution width to albumin.

Population	No. of Events	HR (95% CI)			
		Model 1	Model 2	Model 3	Model 4
RAR	4359	2.10 (2.02, 2.18)	2.11 (2.03, 2.19)	2.18 (2.09, 2.26)	2.14 (2.06, 2.23)
RAR Quartiles					
Q1	601	1.00	1.00	1.00	1.00
Q2	1054	2.03 (1.84, 2.24)	2.03 (1.84, 2.24)	2.08 (1.87, 2.32)	2.03 (1.82, 2.26)
Q3	1160	3.05 (2.77, 3.37)	3.05 (2.77, 3.37)	3.39 (3.05, 3.77)	3.29 (2.96, 3.66)
Q4	1544	4.57 (4.16, 5.02)	4.57 (4.16, 5.02)	5.31 (4.79, 5.89)	5.04 (4.54, 5.59)

Model 1: un-adjusted; Model 2: adjusted for age, sex, race and ethnicity; Model 3: adjusted for age, sex, race and ethnicity, BMI, PIR, education, marital status; Model 4: adjusted for age, sex, race and ethnicity, BMI, PIR, education, marital status, hypertension, diabetes, dyslipidemia, heart disease, stroke, and cancer. RAR: red blood cell distribution width to albumin ratio; HR: hazard ratio.

3.3. RCS Analysis and Kaplan-Meier Survival Analysis

We used cubic spline regression to evaluate the dose-response association between RAR and all-cause mortality. Our study identified a nonlinear, positive association between RAR and all-cause mortality (**Figure 2**) (P for overall test < 0.0001 , P for nonlinearity < 0.0001).

Figure 3 shows the Kaplan-Meier survival curves of patients, stratified by the quartiles of RAR. The figure shows significantly lower cumulative survivals with higher RAR quartiles (log-rank test, $P < 0.0001$).

3.4. Subgroup Analyses

To further elucidate the association between RAR and all-cause mortality risk, we performed subgroup analyses stratified by age, sex, race and ethnicity, BMI, education, marital status, PIR, and chronic diseases. The results are shown in **Figure 4**. Notably, the analysis identified significant associations between high RAR and increased all-cause mortality risk in the general population, independent of demographic characteristics, lifestyle factors, economic factors, and clinical information. The findings indicate that the RAR effectively predicts all-cause mortality in the general population.

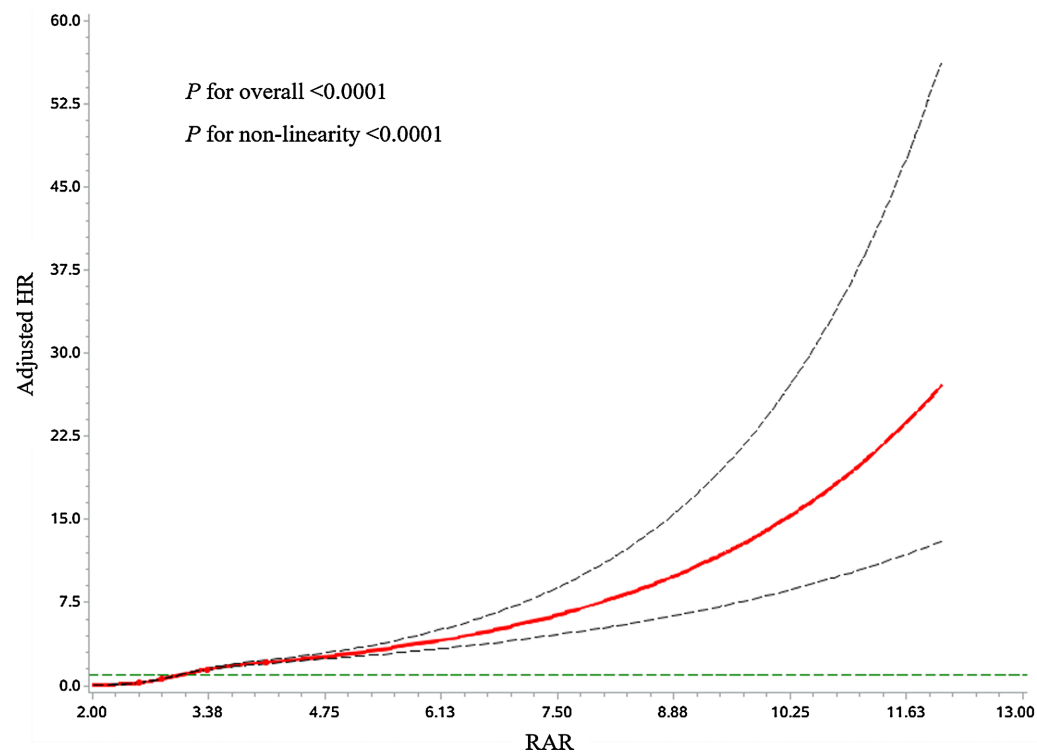


Figure 2. The dose-response relationship between baseline RAR and the risk of all-cause mortality.

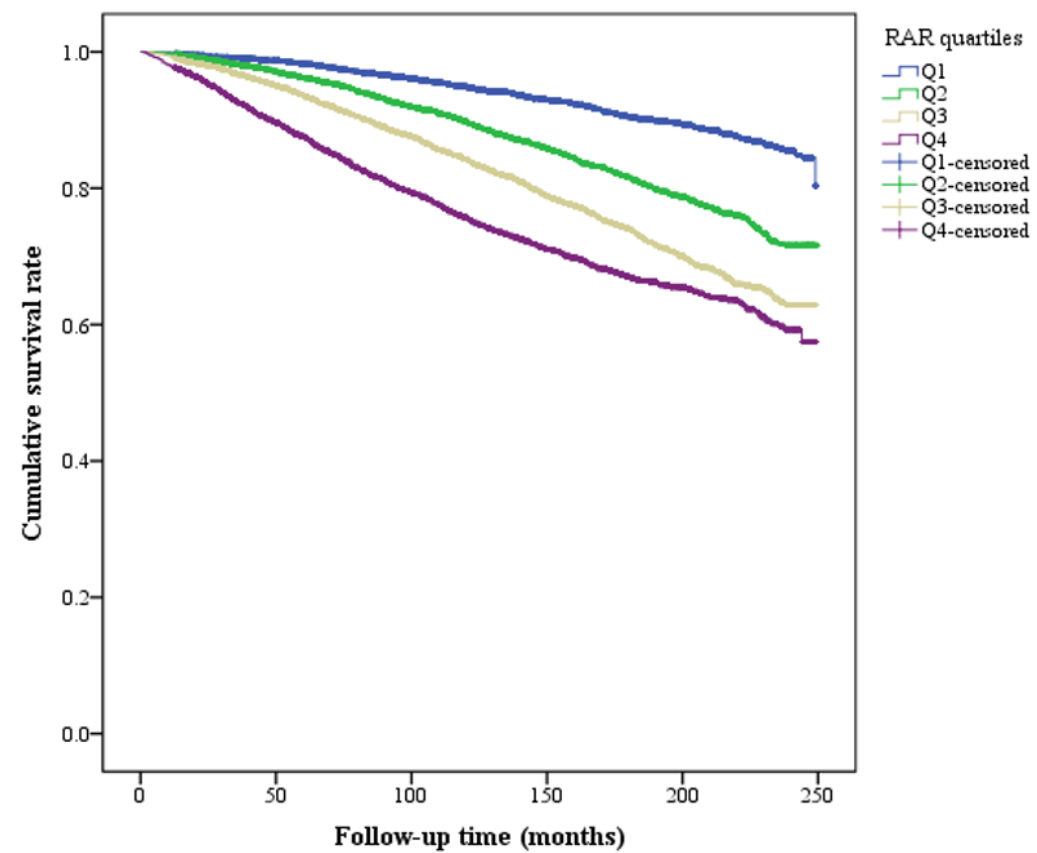


Figure 3. The Kaplan-Meier curve analysis of all-cause mortality by RAR quartile in NHANES.

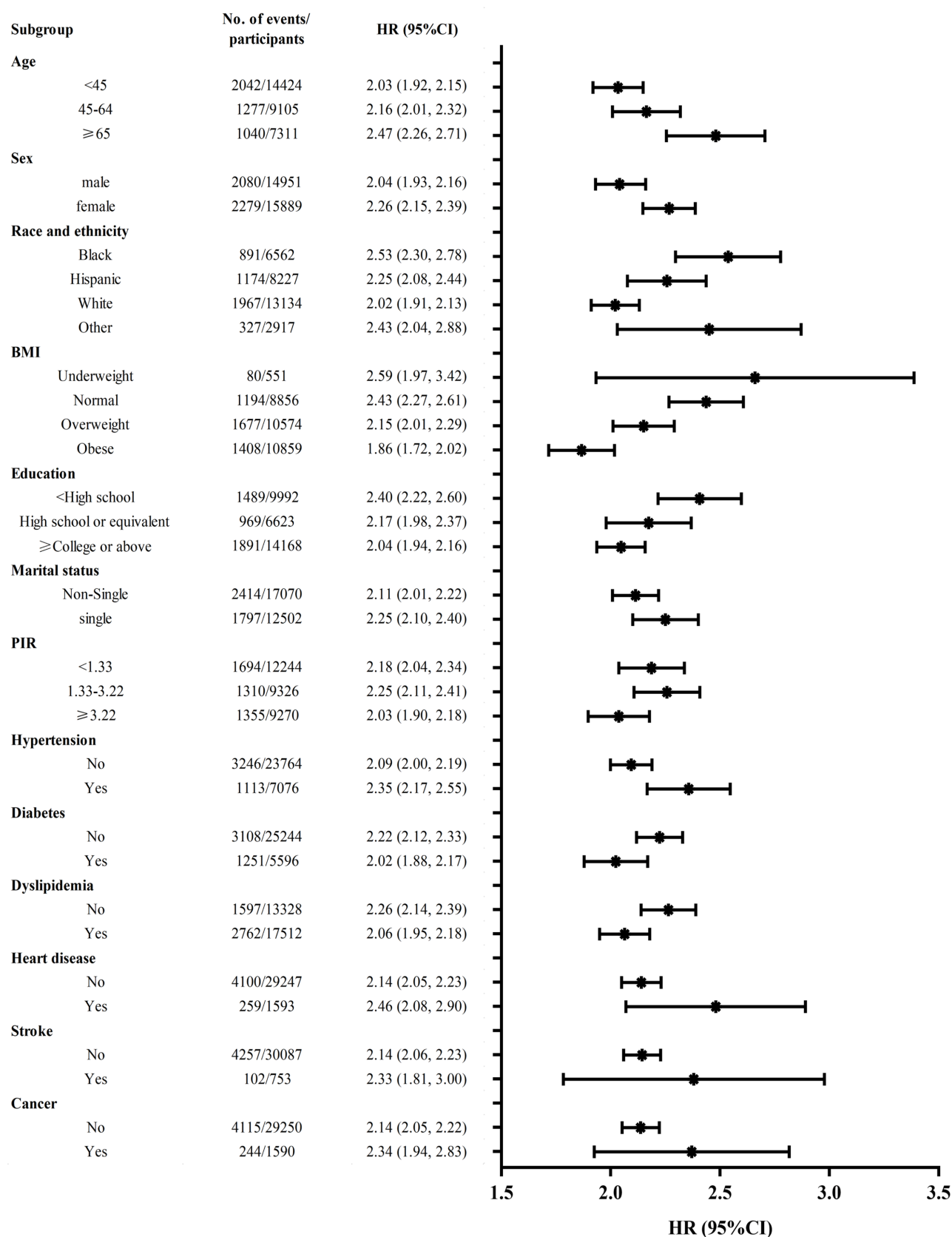


Figure 4. Associations between the ratio of red blood distribution width to albumin and all-cause mortality among subgroups.

4. Discussion

In this study, we identified a significant, independent, and nonlinear positive association between RAR and all-cause mortality. After adjustment for potential confounders, participants in the highest RAR quartile exhibited a more than 5-fold increased risk of all-cause mortality compared with those in the lowest quartile. RCS analysis further confirmed this nonlinear dose-response relationship, with mortality risk accelerating progressively as RAR levels rose. These associations remained consistent across multiple subgroups, demonstrating the robustness of our findings. The findings of this study could provide important evidence on the utility of RAR as a simple and cost-effective prognostic marker for population-level risk stratification.

Our findings align with and extend the growing body of evidence supporting the prognostic significance of RAR in specific disease populations. Elevated RAR has been consistently shown to predict adverse outcomes in patients with cardiovascular disease, including coronary artery disease, acute myocardial infarction, heart failure, and ischemic stroke [16]-[19]. A recent systematic review and dose-response meta-analysis of 16 studies involving 30,933 patients with cardiovascular disease found that each 1 unit increase in RAR corresponded to a 27% higher risk of all-cause mortality [20]. Beyond cardiovascular disease, RAR has emerged as a strong independent predictor of mortality in patients with diabetes mellitus [21], chronic kidney disease [22], various malignancies [23], and critical illness [24]. However, the vast majority of prior research has focused on individuals with established diseases, and data on the association between RAR and mortality in unselected community-dwelling populations remain scarce. Our study, with a large sample size, longer follow-up period, and nationally representative design, provides far more robust evidence and is the first to fully characterize the nonlinear dose-response relationship between RAR and mortality in the general population.

At present, the precise biological mechanisms underlying the association between the red blood cell distribution width to albumin ratio (RAR) and mortality have not been fully elucidated. Existing studies hypothesize that this association may be mediated primarily through multiple pathways, including chronic inflammation, oxidative stress, and nutritional status. Elevation of the RAR index typically results from increased red blood cell distribution width (RDW) and/or decreased serum albumin levels. Among these, RDW serves as an indicator reflecting the heterogeneity of red blood cell volume. Its elevation can be mediated by pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin (IL)-6, and IL-1 β [4] [25], which lead to impaired erythropoiesis and abnormal red blood cell survival. Meanwhile, hyperglycemia can further impair red blood cell function by affecting hemodynamic parameters such as blood viscosity and promoting inflammatory responses. Serum albumin is an important biomarker for assessing nutritional status and inflammatory responses in the body [26] [27]. Previous studies have confirmed that both elevated RDW alone and decreased albumin alone are significantly associated with an increased risk of developing various

chronic diseases (including cardiovascular diseases, diabetes, and chronic kidney disease) and elevated all-cause mortality in the general population [28]–[33]. Specifically, RDW has been identified as a novel prognostic marker for chronic inflammation. Therefore, RAR, as the combined index of RDW and albumin, can more comprehensively integrate and reflect an individual's long-term inflammatory status, nutritional imbalance, and other underlying metabolic abnormalities, which provides a theoretical basis for its application as a derived biomarker in routine laboratory tests for clinical prognostic assessment.

Strengths and Limitations:

Our study has several strengths. First, the large sample size and nationally representative design ensure that our findings are generalizable to the entire civilian non-institutionalized adult population of the United States. Second, mortality data were obtained from the National Death Index (NDI), the gold standard for mortality ascertainment in the US, which minimizes misclassification of outcomes. Finally, RAR is a simple, inexpensive, and widely available biomarker that can be easily calculated from routine complete blood count and basic chemistry panels, making it highly feasible for implementation in both primary care and population health settings.

Several limitations of the study should be acknowledged. First, this is an observational study, and we cannot establish a causal relationship between RAR and all-cause mortality. Second, RAR was measured only once at baseline, and we did not have information on changes in RAR levels during follow-up. Third, some covariates, including clinical information, were based on self-report, which may be subject to recall bias. Fourth, although we adjusted for a wide range of confounders, residual confounding from unmeasured factors such as physical activity level, dietary patterns, and medication use cannot be completely excluded. Finally, our study was conducted exclusively in the US population, and the results may not be directly generalizable to other countries or ethnic groups.

5. Conclusion

This cohort study demonstrated that RAR is independently associated with all-cause mortality in the US general population, with a nonlinear positive dose-response relationship. Additionally, since RAR is assessed via routine laboratory tests, it serves as a promising indicator that is simple, reliable, and inexpensively accessible for identifying individuals in clinical practice at high risk of mortality. Future prospective studies are needed to validate these findings and investigate the potential mechanisms between RAR and all-cause mortality risk.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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