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Neutrophil to albumin ratio predicts cardiovascular and all cause mortality in CVD patients with abnormal glucose metabolism

Jiaxin Li, Mingyue Yang, Xue Zhang, Rui Huang, Ying Zhang & Kuanlu Fan✉

This study examined the relationship between the neutrophil-to-albumin ratio (NPAR) and both all-cause and cardiovascular mortality in U.S. patients with cardiovascular disease (CVD) and abnormal glucose metabolism, using NHANES data from 1999 to 2018. Restricted cubic spline analysis identified a significant nonlinear association between NPAR and mortality ($p < 0.001$). Cox regression results showed that patients in the highest NPAR group (T3, ≥ 15.8) had higher risks of all-cause (HR 1.75, 95% CI 1.50–2.04) and cardiovascular mortality (HR 2.03, 95% CI 1.53–2.68) compared to the lowest group (T1, < 13.5), both with $p < 0.0001$. Kaplan–Meier survival curves confirmed greater mortality in the T3 group. Mediation analysis found that renal function, measured by eGFR, accounted for 14.49% of the effect on all-cause mortality and 13.38% on cardiovascular mortality. Among the 3163 participants, 1342 experienced all-cause deaths and 462 cardiovascular deaths. This study demonstrated a significant correlation of high NPAR and increased mortality in patients with abnormal glucose metabolism and CVD, suggesting that NPAR may represent a reliable predictor of mortality risk in this population, and emphasizing the importance of both inflammation and renal function monitoring.

Keywords Neutrophil-percentage-to-albumin ratio, NHANES, Mortality, Cardiovascular, Mediation analysis

With an aging global population, the incidence and mortality rates of cardiovascular disease (CVD) have risen significantly worldwide[1]. CVD not only significantly affects the quality of life of patients, but also puts enormous economic pressure on the global health system. Numerous studies demonstrate that increased human lifespan has contributed to CVD becoming one of the leading causes of mortality globally, particularly among middle-aged and older individuals[2]. Recent epidemiological data exhibit a significant increase in both crude and CVD-specific mortality across numerous countries, posing a growing public health challenge[1].

Glucose metabolism abnormalities are common among individuals with CVD and are strongly correlated with negative clinical outcomes[3,4] . Identifying remaining risk factors is critical for effectively reducing mortality risk, especially for those with diabetes and prediabetes.

Research has demonstrated that traditional inflammatory markers, such as CRP and leukocyte counts, are closely associated with the risk of cardiovascular events[5,6]. However, NPAR, a novel composite marker incorporating neutrophil and albumin ratios, may offer supplementary information for cardiovascular risk assessment[7]. Neutrophils contribute to regulating responses to acute injury, autoimmune processes, and chronic inflammation[8]; whereas, albumin levels typically demonstrate an inverse relationship with oxidative stress and inflammation[9]. Recent studies indicate that NPAR is strongly correlated with NAFLD[10], depression[11], and chronic kidney disease[12] and it is also significantly correlated with the prevalence of cardiovascular disease (CVD)[13]. Additionally, emerging evidence suggests that NPAR has increasingly utilized in assessing disease risk and prognosis[14].

Novel methodologies that has found its application in clinical trials is mediation analysis[15]; it allows the breaking down of total effects into direct effects and mediated effects, allowing researchers to assess the effectiveness of the interventions from a broader perspective. In relation to cardiovascular diseases, renal function (e.g., eGFR)[16] is considered a highly important prognostic factor and is assumed to act as a mediator in the link between NPAR and cardiovascular disease mortality. While prior work has examined the prognostic value of NPAR in broader diabetic or hypertensive populations[17,18], our study is to focus specifically on individuals with coexisting CVD and abnormal glucose metabolism (AGM)—a particularly high-risk subgroup. Moreover, we

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incorporated mediation analysis to investigate the mechanistic role of eGFR in this relationship, offering novel insight into how inflammation-related renal dysfunction may contribute to mortality.

Therefore, this study aims to evaluate the association between NPAR and both all-cause and cardiovascular mortality in U.S. adults with CVD and AGM, using data from NHANES 1999–2018.

Methods

The design and population of the study

The National Health and Nutrition Examination Survey (NHANES) is a crucial program designed to evaluate the health and nutritional well-being of adults and children in the United States. Overseen by the Centers for Disease Control and Prevention (CDC), NHANES operates under a protocol reviewed and approved by the NCHS Research Ethics Review Board, guaranteeing participant rights through informed consent. Data from this study are available to the public on the official NHANES website (https://www.cdc.gov/nchs/nhanes/index.html), and this study utilized NHANES data between 1999 and 2018. Diabetes was identified utilizing the ADA's diagnostic criteria, which include self-reported diagnosis, current use of insulin or oral hypoglycemic medication, a fasting blood glucose FBG level of 126 mg/dL or higher, or a glycated hemoglobin HbA1c level of 6.5% or higher[17]. Prediabetes was determined based on self-reported prediabetes, an FBG level between 100 mg/dL and 125 mg/dL, or an HbA1c level between 5.7% and 6.4%[17]. CVD diagnosis was determined through self-reported physician diagnoses collected during standardized individual interviews utilizing a medical status questionnaire. Participants were asked, "Have you been informed by a medical professional on your having congestive heart failure, coronary heart disease, angina, myocardial infarction, or stroke?" confirmative responses to any of these questions indicated a CVD diagnosis. A total of 4,295 adults aged 20 to 85 years were included based on the following inclusion criteria: a confirmed diagnosis of cardiovascular disease (CVD) and either diabetes or prediabetes. Participants were excluded if they had missing NPAR data (n = 326), were pregnant (n = 1), had a history of cancer (n = 801), or lacked sufficient follow-up data (n = 4). After applying these exclusion criteria, the final analysis included 3,163 eligible participants (Fig. 1).

Assessment of covariates

Data on relevant population and health information were collected, including factors such as age, sex, race/ethnicity, education background, household income, smoking habit, and medical history. Body mass index (BMI) was computed by dividing weight in kilograms by the square of height in meters. Race/ethnicity was categorized as White, Black, Mexican American, or other. Education level was categorized as less than high school completion, high school graduate or equivalent, or completion of post-secondary education. Smoking habit was recorded as never smoker, former smoker, or current smoker. Drinking behavior was classified into five categories: heavy drinkers (defined as consuming 3 or more drinks on a daily basis for women and 4 or more drinks on a daily basis for men, or binge drinking five times or more per month); moderate drinkers (defined as consuming 2 or more drinks on a daily basis for women and 3 or more drinks on a daily basis for men, or binge drinking two times or more per month); mild drinkers (those not meeting the criteria for heavy or moderate drinking); and non-drinkers or individuals with a history of alcohol abuse. Clinical indicators included blood glucose, glycosylated hemoglobin (HbA1c), triglycerides (TG), total cholesterol (TC), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), serum creatinine (Scr), estimated glomerular filtration rate (eGFR), lactate dehydrogenase (LDH), uric acid (UA), albumin (Alb), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBil), and gamma-glutamyltransferase (GGT), all of which were measured in the "NHANES laboratory."

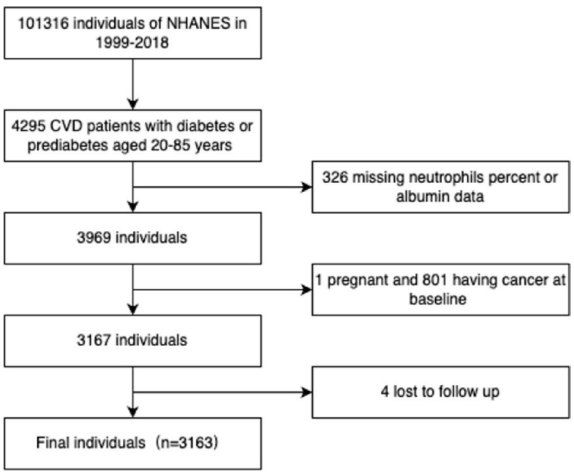

Fig. 1. Study population selection: inclusion and exclusion criteria.

Assessment of NPAR

Blood samples were collected, processed, and sent to NHANES for analysis. An extensive explanation of the procedures that were adopted in the laboratory is located at the NHANES site. The complete blood count was conducted utilizing the Beckman-Coulter method. Then, the NPAR was calculated from the same blood sample as the ratio of neutrophil percentage to albumin: (neutrophil percentage (%) ÷ albumin (g/dL))[18]. For NPAR tertile analysis, participants were grouped and categorized in three NPAR tertiles (T1, T2, T3), wherein T1 being the reference group.

Ascertainment of mortality

Mortality information had been sourced through linking the cohort database to national mortality indices. Crude mortality rate comprised any documented cause of death, while CVD mortality was categorized according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Edition (ICD-10)[19]. The specific codes employed for this classification ranged from I00 to I09, I11, I13, I20 to I51, and I60 to I69. To maintain the accuracy of mortality data, a probabilistic matching algorithm was employed to associate the data with participant IDs.

Statistical analysis

R software (version 4.4.1; https://www.r-project.org) facilitated all statistical analyses. Considering the complex sampling design of the National Health and Nutrition Examination Survey, analyses accounted for sample weights, clustering, and stratification, crucial for accurate interpretation of NHANES data. Participants were categorized into three cohorts based on NPAR tertiles (T1–T3). Continuous variables are reported as means ± standard deviations (SD), while categorical variables are presented as counts and percentages. Baseline characteristics were compared across NPAR tertile cohorts through one-way analysis of variance for continuous variables and Pearson's chi-square test for categorical variables. Missing covariate data were handled with multiple imputation approach utilizing the "mi" R package. Crude and CVD mortality rates were determined for each NPAR tertile group throughout follow-up. To evaluate the independent prognostic significance of NPAR, multivariate Cox proportional hazards regression models were developed with three levels of covariate adjustment. Model 1 was unadjusted; Model 2 was adjusted for age, race, and sex; and Model 3 further accounted for body mass index, smoking habit, alcohol consumption, educational attainment, hypertension, and household income-to-poverty ratio. These variables were selected based on prior literature and clinical guidelines, given their strong associations with systemic inflammation, renal function, and cardiovascular outcomes in patients with cardiometabolic diseases[17,22]. This progressive modeling approach aimed to control for potential confounders while preserving model stability and statistical power. The correlation of NPAR and mortality was explored utilizing Cox proportional hazards models incorporating restricted cubic splines and penalized spline methods for smooth curve fitting. Cumulative survival differences across NPAR cohorts were compared utilizing weighted Kaplan–Meier curves and the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the correlation of NPAR levels and both crude and CVD mortality risk were calculated utilizing multivariate Cox proportional hazards regression models.

To explore the mediating role of renal function (eGFR) in the relationship between NPAR and mortality, the distribution-of-the-product (DTP) method was employed to analyze the mediating effect. Statistical significance of the mediating effect was assessed utilizing 95% confidence intervals (CIs), calculated with the R mediation software package. The mediating effect was considered statistically significant if the CI did not contain zero. All statistical analyses were performed utilizing R version 4.4.1 software, and two-sided p-values less than 0.05 were considered statistically significant.

Results

Baseline characteristics of study participants

Table 1 presents the baseline characteristics of the study participants (n = 3163), stratified by NPAR tertiles. The mean age of the participants was 65.04 years, with 56.18% being male. The mean NPAR among participants was 14.73 ± 2.93. The laboratory characteristics at baseline, stratified by NPAR tertiles, are demonstrated in Table 2. Participants with higher NPAR were more to be older, obese, and have a higher representation of males compared to those in the lowest tertile. In addition, family income-poverty ratio, marital status, and race were significantly correlated with the NPAR index. Among patients with abnormal glucose metabolism, a significant difference in the distribution was observed across the NPAR cohorts (p-value < 0.0001), with a higher proportion of diabetic patients present in the group with the higher NPAR index. Significant differences in biochemical indices were also observed among the three cohorts presented in Table 2, with participants in the highest tertile exhibiting higher levels of HbA1c, BUN, Scr, and UA, and lower levels of eGFR, LDL, TC, TG, Albumin, and AST compared to those in the first tertile.

Crude and CVD mortality with tertiles of NPAR levels and survival analyses

Table 3 details crude and CVD mortality (1342 and 462 mortalities, respectively) during follow-up. Three Cox regression models analyzed the independent relationship between NPAR levels and mortality risk. After adjusting for age, sex, race, BMI, smoking, alcohol consumption, education, hypertension, and the household income-to-poverty ratio (model 3), the risk ratio for crude mortality rate comparing high and low NPAR tertiles was 1.75(95%CI 1.50–2.04). Likewise, the risk ratio for CVD mortality was 2.03(95% CI 1.53–2.68). This positive association with mortality remained statistically significant for both outcomes (trend p-value < 0.0001).

Nonlinear association of NPAR with all- cause mortality and CVD-cause mortality

Prior multivariate analyses indicated a nonlinear relationship between baseline NPAR and both crude and cardiovascular disease mortality. To clarify this relationship, we employed restricted cubic spline ("RCS") fitting,

Characteristics	Tertiles of NPAR				
	overall	T1(< 13.5)	T2(13.5–15.8)	T3(≥ 15.8)	P-value
Age	65.04 ± 0.27	63.28 ± 0.44	65.21 ± 0.49	66.67 ± 0.41	< 0.0001
PIR	2.48 ± 0.04	2.59 ± 0.07	2.46 ± 0.06	2.37 ± 0.06	0.03
Bmi	31.63 ± 0.20	30.58 ± 0.20	31.59 ± 0.31	32.75 ± 0.34	< 0.0001
Sex					0.01
Male	1816(56.18)	632(60.23)	614(56.81)	570(51.39)	
Female	1347(43.82)	423(39.77)	439(43.19)	485(48.61)	
Marital					0.04
Never married	203(5.77)	73(5.57)	66(6.84)	64(4.87)	
Married or cohabitation	1747(60.22)	605(63.58)	598(59.89)	544(57.11)	
Widowed or separated	1213(34.01)	377(30.85)	389(33.26)	447(38.02)	
BMI					0.59
< 24	417(12.07)	148(12.16)	127(11.08)	142(13.00)	
≥ 24	2746(87.93)	907(87.84)	926(88.92)	913(87.00)	
Eth					0.01
Mexican American	416(4.90)	130(4.34)	138(4.55)	148(5.83)	
Non-hispanic white	1540(71.24)	449(68.01)	534(72.62)	557(73.14)	
Non-hispanic black	751(13.29)	320(16.72)	228(12.09)	203(11.00)	
Other Race	456(10.57)	156(10.92)	153(10.74)	147(10.03)	
Edu					0.53
Less than 12th grade	1196(28.01)	392(27.88)	405(27.57)	399(28.58)	
High school or equivalent	782(27.91)	254(26.32)	252(27.49)	276(29.96)	
College graduate or above	1185(44.08)	409(45.80)	396(44.94)	380(41.46)	
Alcohol					0.87
Never	507(14.03)	153(12.94)	180(15.42)	174(13.74)	
Former	1053(30.24)	350(30.78)	333(28.94)	370(31.02)	
Mild	1031(36.87)	351(36.56)	343(36.45)	337(37.63)	
Moderate	243(8.30)	86(9.33)	82(8.37)	75(7.19)	
Heavy	329(10.55)	115(10.40)	115(10.82)	99(10.42)	
Smoke					0.35
Never	1273(39.16)	456(41.44)	426(39.52)	391(36.46)	
Ever	1287(40.19)	404(40.09)	429(38.97)	454(41.54)	
Current	603(20.65)	195(18.47)	198(21.51)	210(22.00)	
Hypertension					0.2
No	610(21.99)	221(24.80)	198(21.23)	191(19.88)	
Yes	2553(78.01)	834(75.20)	855(78.77)	864(80.12)	
preDM					< 0.0001
PreDM	1418(49.18)	546(57.77)	485(49.86)	387(39.68)	
DM	1745(50.82)	509(42.23)	568(50.14)	668(60.32)	

Table 1. Baseline characteristics of the study population. *NPAR* Neutrophil percentage-to-albumin ratio, *PIR* Poverty Income Ratio, *BMI* Body Mass Index, *eth* Ethnicity, *edu* Education.

generating the adjusted smoothed curves depicted in Fig. 2. Figure 2A presents the nonlinear relationship between NPAR and crude mortality rate, and Fig. 2B displays the corresponding association for CVD mortality. The risk of crude mortality rate increased sharply as NPAR values approached 12.45923, while the risk of CVD mortality demonstrated a significant increase beginning at an NPAR of 11.00435. Above these thresholds, further increases in NPAR were correlated with much greater risks of both crude and CVD mortality. Subgroup analyses, stratifying CVD patients by diabetes mellitus ("DM") and prediabetes mellitus ("PreDM") status, confirmed a significant nonlinear correlation of NPAR and both crude and CVD mortality in those with CVD and diabetes(Fig. 3). This relationship was particularly significant among the diabetic patients ($P < 0.001$), where higher NPAR values corresponded with a significantly increased risk of both outcomes. A similar, albeit weaker, yet still statistically significant ($P < 0.001$) nonlinear relationship was observed between NPAR and mortality among the prediabetic cohort.

Survival analysis

The NPAR level analysis included 3163 adults (mean (standard error) age 65.04 ± 0.27years; 1347 females (weighted 43.82%) and 1816 males (weighted 56.18%)). The median follow-up time was 76 months (interquartile range = 85 months), 1,342 crude mortalities and 462 cardiovascular mortalities were observed. Figure 4 displays Kaplan–

Characteristics	Tertiles of NPAR				P value
	total	T1	T2	T3	
HbA1c, %	6.43(0.03)	6.26(0.04)	6.45(0.06)	6.58(0.06)	< 0.0001
eGFR, mL/min/1.73m2	73.66(0.52)	77.18(0.73)	74.85(0.90)	68.84(0.98)	< 0.0001
LDL-cholesterol, mmol/L	2.63(0.03)	2.72(0.04)	2.70(0.05)	2.47(0.04)	< 0.0001
HDL-cholesterol, mmol/L	1.25(0.01)	1.26(0.02)	1.22(0.02)	1.26(0.02)	0.11
TC, mmol/L	4.74(0.03)	4.85(0.05)	4.84(0.06)	4.51(0.05)	< 0.0001
TG, mmol/L	1.97(0.03)	2.03(0.06)	2.06(0.06)	1.81(0.05)	< 0.001
Scr, umol/L	94.78(1.17)	88.76(1.01)	92.78(1.95)	102.97(2.39)	< 0.0001
LDH, IU/L	144.53(0.95)	143.54(1.19)	143.97(1.72)	146.13(1.65)	0.41
Uric acid, umol/L	359.45(2.42)	355.89(3.26)	354.92(4.15)	367.72(4.63)	0.05
Albumin, g/L	4.12(0.01)	4.29(0.01)	4.17(0.01)	3.90(0.01)	< 0.0001
BUN, mmol/L	6.31(0.06)	5.81(0.08)	6.17(0.10)	6.96(0.13)	< 0.0001
AST, IU/L	25.54(0.41)	26.66(0.46)	25.68(0.66)	24.26(0.85)	0.03
ALT, IU/L	24.66(0.59)	25.69(0.52)	25.46(1.06)	22.78(1.37)	0.14
TBil, umol/L	11.30(0.12)	11.33(0.17)	11.44(0.24)	11.14(0.19)	0.5
GGT, IU/L	35.45(1.10)	36.49(1.96)	35.96(2.20)	33.88(1.45)	0.46

Table 2. Baseline laboratory data of the study population. Data are presented as mean (SD) or n (%). HbA1c, glycated hemoglobin; eGFR, Estimated Glomerular Filtration Rate; LDL-cholesterol, Low-Density Lipoprotein Cholesterol; HDL-cholesterol, High-Density Lipoprotein Cholesterol; TC, Total Cholesterol; TG, Triglycerides; Scr, Serum Creatinine; LDH, Lactate Dehydrogenase; Uric acid, Uric Acid; Albumin, Serum Albumin; BUN, Blood Urea Nitrogen; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; TBil, Total Bilirubin; GGT, Gamma-Glutamyl Transferase.

Neutrophil percentage to albumin ratio	Number of death	Model 1		Model 2		Model 3	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Crude mortality rate							
T1 (< 13.5)	365	Ref	–	Ref	–	Ref	–
T2 (13.5–15.8)	427	1.23(1.05,1.45)	0.01	1.13(0.96,1.33)	0.13	1.09(0.93,1.27)	0.30
T3 (≥ 15.8)	550	2.03(1.76,2.35)	< 0.0001	1.82(1.56,2.12)	< 0.0001	1.75(1.50,2.04)	< 0.0001
P for trend			< 0.0001		< 0.0001		< 0.0001
CVD-cause mortality							
T1 (< 13.5)	114	Ref	–	Ref	–	Ref	–
T2 (13.5–15.8)	157	1.28(0.96,1.69)	0.09	1.14(0.87,1.49)	0.33	1.13(0.87,1.46)	0.37
T3 (≥ 15.8)	191	2.30(1.79,2.95)	< 0.0001	2.03(1.57,2.62)	< 0.0001	2.03(1.53,2.68)	< 0.0001
P for trend			< 0.0001		< 0.0001		< 0.0001

Table 3. Cox regression of the correlation of neutrophil percentage to albumin ratio and crude mortality rate and CVD-cause mortality among CVD patients with diabetes or pre-diabetes. CVD- cause mortality: cardiovascular disease—cause mortality; HR: Hazard ratio; CI: Confidence interval; T1: tertiles 1; T2: tertiles 2; T3: tertiles 3. Model 1: Non-adjusted. Model 2: Adjusted for age, race and gender. Model 3: Adjusted for age, gender, race, BMI, tobacco use, alcohol use, education, hypertension, family income-poverty ratio.

Meier survival curves from the start of follow-up. Unadjusted log-rank tests indicated significantly higher crude mortality rate (Fig. 4A) and cardiovascular mortality (Fig. 4B) in the T3 group compared with the T1 and T2 cohorts ($P < 0.001$).

Role of eGFR in the associations of NPAR with crude mortality rate and CVD mortality

Mediation analysis indicated that eGFR levels significantly mediated the relationship between NPAR and mortality (Fig. 5). After adjusting for age, sex, race, household income-to-poverty ratio, marital status, education, BMI, alcohol consumption, smoking habit, and hypertension, eGFR mediated 14.49% (Table 4) of the total effect of NPAR on crude mortality rate ($P < 0.001$). Similarly, eGFR mediated 13. 38% ($P < 0.001$) of the total effect of NPAR on cardiovascular mortality (Table 5).

Discussion

This study evaluated the correlation of NPAR and crude and cardiovascular mortality in patients with CVD and abnormal glucose metabolism. Abnormal glucose metabolism, including diabetes and prediabetes, is generally correlated with an increased risk of mortality in CVD patients. This increased risk is closely related to the

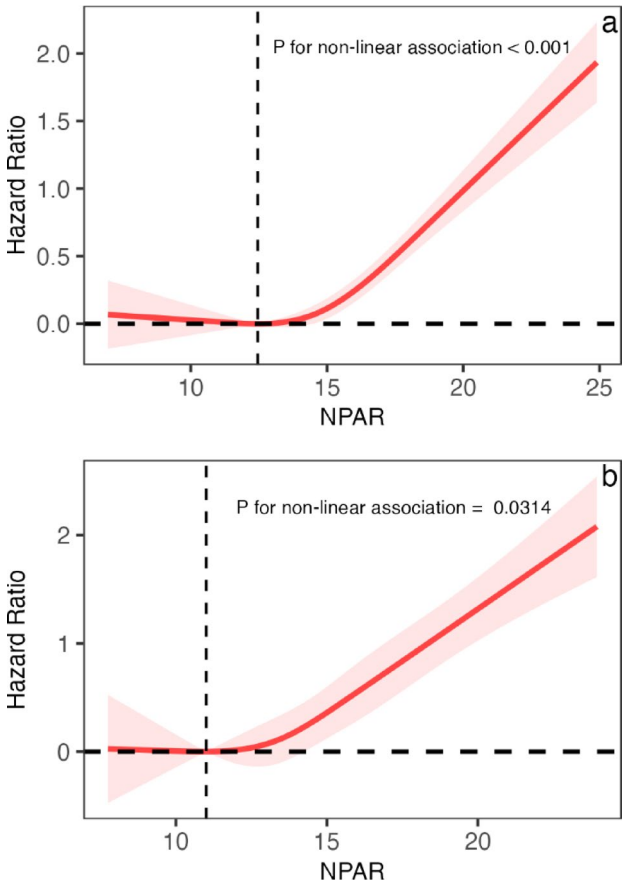

Fig. 2. Dose–response relationships of NPAR level with the probability of crude mortality rate (**A**) and CVD mortality (**B**) in CVD patients with Impaired glucose metabolism or A nonlinear correlation of NPAR level with both crude and CVD-cause mortality was identified ($P < 0.001$). Solid and dashed lines represent the estimated values and their corresponding 95% confidence intervals, respectively. Covariates included age, sex, ethnicity, education level, poverty income, and number of people with diabetes or pre-diabetes. Additional adjustments included poverty income ratio, marital status, smoking habit, and body mass index.

combined effects of systemic inflammation and metabolic dysfunction[21]. Analysis of health screening data from 3,163 participants in the NHANES database between 1998 and 2018 indicated a significant, nonlinear correlation of high NPAR levels and both crude and cardiovascular mortality. Patients with abnormal glucose metabolism, particularly those with diabetes and prediabetes, demonstrate a greater probability of developing renal impairment due to the combined influence of chronic inflammation and metabolic dysfunction, which thereby elevates their risk of mortality. This further strengthens NPAR's potential as a robust, independent predictor of adverse survival outcomes. Mediation analysis indicated that eGFR is a significant mediator in the relationship between NPAR and mortality. This suggests that NPAR may be a crucial prognostic indicator for CVD patients with abnormal glucose metabolism, facilitating the identification of high-risk patients and informing the development of personalized intervention strategies.

Studies have also evaluated the relationship between NPAR and mortality in diverse populations. For instance, a significant positive correlation between NPAR and crude mortality rate has been observed in heart failure patients[20]. Among individuals with chronic obstructive pulmonary disease (COPD), NPAR predicted an increased risk of mortality and proved superior to other hematologic inflammatory biomarkers in forecasting 5-year crude mortality rate[10]. In addition, an analysis of 8,990 U.S. adults with hypertension demonstrated a significant correlation of high NPAR levels and increased risks of crude and CVD mortality, independent of potential confounders[21]. These results consistently highlight a strong correlation of NPAR and mortality risk, presumably as NPAR reflects underlying systemic inflammation and immune activity. While the predictive utility of NPAR has been extensively confirmed across various cohorts, analyses in CVD populations represented by abnormal glucose metabolism are scarce. By closely analyzing this high-risk group, this study offers novel insights into the prognostic significance of NPAR in patients with both abnormal glucose metabolism and CVD, thus filling a critical gap in the existing literature.

The association between NPAR and cardiovascular mortality may be explained by the synergistic pathophysiological roles of its components—neutrophils and serum albumin—both of which reflect underlying inflammatory and nutritional states that are critical in cardiovascular disease (CVD) progression. While neutrophils mainly reflect the pro-inflammatory component of NPAR, the albumin level contributes another

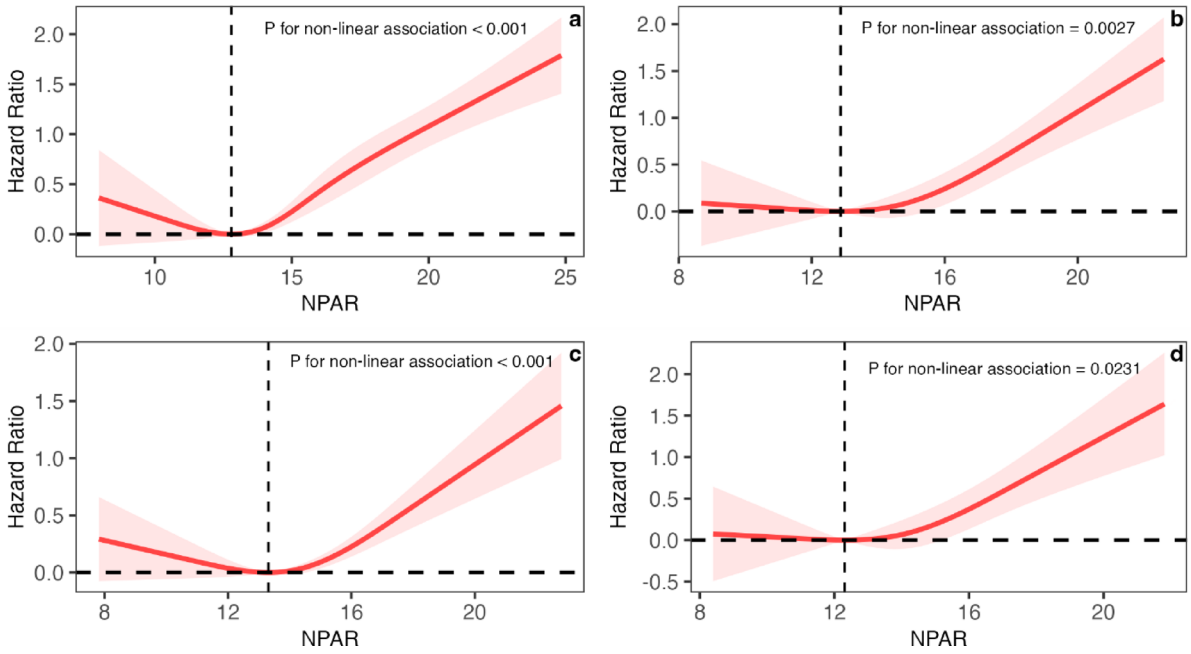

Fig. 3. Dose–response relationships of NPAR level with the probability of crude mortality rate (**A**) and CVD mortality (**B**) in CVD patients with diabetes and crude mortality rate (**C**) and CVD mortality (**D**) in CVD patients with pre-DM. A nonlinear correlation of NPAR level with both crude and CVD-cause mortality was identified (P < 0.001). Solid and dashed lines represent the estimated values and their corresponding 95% confidence intervals, respectively. Covariates included age, sex, ethnicity, education level, poverty income, and number of people with diabetes or pre-diabetes. Additional adjustments included poverty income ratio, marital status, smoking habit, and body mass index.

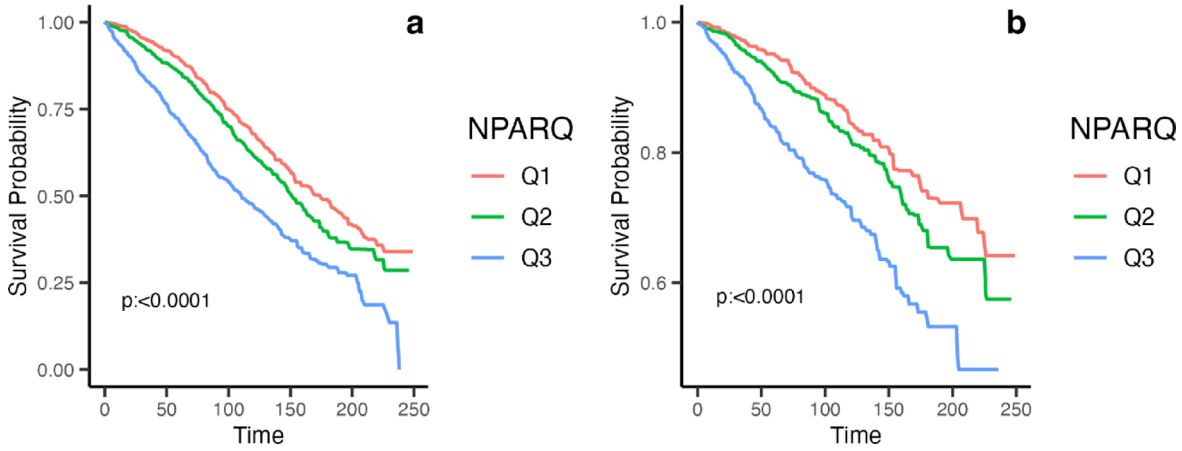

Fig. 4. Kaplan–Meier curves for survival probability, with follow-up in years. (**A**) Crude mortality rate; (**B**) CVD-cause mortality.

crucial dimension—nutritional and antioxidative status[23,24]. Neutrophils, as key effectors of innate immunity, participate in the initiation and amplification of systemic inflammation[25]. Elevated neutrophil counts have been implicated in the activation of endothelial cells, release of reactive oxygen species (ROS), and the promotion of pro-thrombotic states, which contribute to atherosclerotic plaque formation and instability[26,27]. In diabetic or prediabetic populations, chronic hyperglycemia may further potentiate neutrophil adhesion and dysfunction, compounding vascular injury[28].In parallel, serum albumin is widely recognized as both a nutritional and anti-inflammatory biomarker. Beyond its function in maintaining oncotic pressure, albumin binds and neutralizes free radicals and pro-inflammatory molecules, exhibiting antioxidant and protective vascular effects. Hypoalbuminemia is independently associated with oxidative stress, endothelial dysfunction, increased vascular permeability, and cardiac cachexia in patients with CVD[28]. Additionally, low albumin levels have been linked to impaired drug binding, delayed wound healing, and immune dysregulation, all of which may worsen long-term

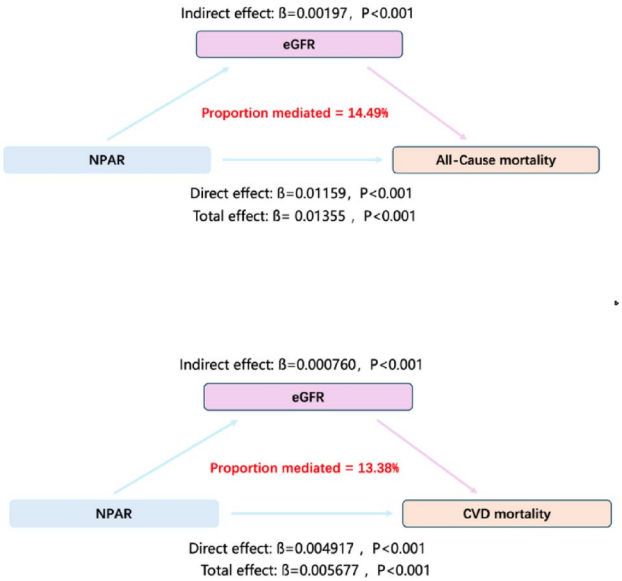

Fig. 5. The mediating effect of eGFR on the relationship between NPAR and all-cause mortality (**A**) and cardiovascular mortality (**B**). ACME (Averaged Causal Mediation Effects); ADE (Average Direct Effect); Prop. Mediated (Proportion Mediated). eGFR, Estimated Glomerular Filtration Rat. Adjusted: age, sex, race, poverty-income ratio, marital, educational level, bmi, alcohol intake, smoke, Hypertension.

	Non-adjusted		Adjusted	
Effect	Estimate	P-value	Estimate	P-value
Total effect	0.01345	< 0.001	0.01355	< 0.001
ACME	0.00439	< 0.001	0.00197	< 0.001
ADE	0.00907	< 0.001	0.01159	< 0.001
Prop. mediated	0.32606	< 0.001	0.14499	< 0.001

Table 4. Results of mediation effect model on NPAR, eGFR and crude mortality rate. ACME (Averaged Causal Mediation Effects); ADE (Average Direct Effect); Prop. Mediated (Proportion Mediated). Model adjusted for age, sex, race, poverty-income ratio, marital, educational level, bmi, alcohol intake, smoke, Hypertension.

	Non-adjusted		Adjusted	
Effect	Estimate	P-value	Estimate	P-value
Total effect	0.004614	< 0.001	0.005677	< 0.001
ACME	0.001413	< 0.001	0.000760	< 0.001
ADE	0.003200	< 0.001	0.004917	< 0.001
Prop. mediated	0.306372	< 0.001	0.133863	< 0.001

Table 5. Results of mediation effect model on NPAR, eGFR and CVD-cause mortality. ACME (Averaged Causal Mediation Effects); ADE (Average Direct Effect); Prop. Mediated (Proportion Mediated). Model adjusted for age, sex, race, poverty-income ratio, marital, educational level, bmi, alcohol intake, smoke, Hypertension.

outcomes in high-risk populations[29–31]. Therefore, a higher NPAR—reflecting both heightened neutrophilic inflammation and reduced albumin-mediated antioxidant capacity—may serve as a composite indicator of immune-metabolic dysregulation, associated with poor cardiovascular prognosis. Several cohort studies have validated this hypothesis, showing consistent associations between elevated NPAR and increased all-cause and CVD mortality in patients with chronic comorbidities, including diabetes[17], chronic kidney disease[12], and heart failure[20].

Our findings not only reinforce these observations but also add mechanistic support by incorporating eGFR as a mediator, suggesting a possible inflammation-mediated renal dysfunction pathway through which

NPAR exerts its deleterious effects on survival. Despite these prior findings[17], few studies have investigated the intermediate biological pathways through which NPAR affects mortality, particularly in high-risk cardiometabolic populations. Our mediation analysis indicated that NPAR levels were correlated with increased crude and cardiovascular mortality through a reduction in eGFR, especially among individuals with CVD and abnormal glucose metabolism, suggesting potential mechanisms. Individuals with abnormal glucose metabolism, particularly those with diabetes and prediabetes, frequently present with chronic inflammation and renal impairment, increasing their susceptibility to renal function decline and higher mortality risk. Extensive research demonstrates the prevalence of low-grade chronic inflammation in CVD and other chronic conditions, including chronic kidney disease (CKD). Inflammation plays a crucial role in CKD progression, with neutrophils possibly exacerbating renal impairment by increasing the inflammatory response[32]. Simultaneously, hypoalbuminemia is a known risk factor for CKD progression, potentially contributing to further renal function decline through the combined effects of malnutrition and systemic inflammation[33]. In individuals with CVD and abnormal glucose metabolism, high NPAR levels signal a serious inflammatory state and compromised renal function. Declining eGFR not only magnifies the effect of NPAR on mortality risk but also strengthens this relationship through feedback mechanisms. Our mediation analysis demonstrated that eGFR explained 14.49% of the mediating effect of NPAR on crude mortality rate and 13.38% on cardiovascular mortality. This strong mediating influence was particularly evident in patients with diabetes and prediabetes, emphasizing the critical importance of renal function management in these vulnerable populations. Therefore, managing renal function, particularly by slowing or reversing eGFR decline, may be a vital strategy for reducing mortality risk in individuals with CVD and abnormal glucose metabolism. Further research should explore whether interventions targeting renal function can effectively lessen the effect of NPAR on mortality.

The primary strength of this study is reflected by its extensive sample size and protracted follow-up period, contributing to reliable results and a robust statistical analysis. Multiple statistical methods controlled for confounding factors, strengthening the study's conclusions. Moreover, this study represents the first systematic evaluation of the long-term relationship between NPAR and crude and cardiovascular mortality in patients with abnormal glucose metabolism and CVD. The sample weighting procedure enhances the generalizability of the findings to a broader U.S. population. Nevertheless, this study is subject to limitations. As a single-center observational study, it cannot determine causality. While multivariate adjustment lessened the effect of confounding factors, residual confounders may remain. Finally, this study analyzed only the prognostic value of baseline NPAR, highlighting the need for additional research to study whether changes in NPAR during follow-up similarly forecast mortality.

Conclusion

In conclusion, the extensive sample size and protracted follow-up period of this study indicated a nonlinear correlation of NPAR and both crude and cardiovascular mortality in patients with abnormal glucose metabolism and CVD. The study also verified the mediating role of eGFR in the relationship between NPAR and mortality. These results suggest that NPAR represents a reliable predictor of mortality risk in patients with abnormal glucose metabolism and CVD. By observing early changes in renal function, clinicians can better evaluate patient risk and apply specific interventions to enhance prognosis.

Data availability

This study utilized data from a publicly available database, which can be accessed at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx. For further research inquiries or access to additional data, requests can be made directly to the authors.

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Author contributions

JX. L.: Data curation, formal analysis, investigation, methodology, software, visualization, and writing; KL. F.: Data curation, formal analysis, investigation, methodology, software, visualization, and writing, Supervision, conceptualization, review & editing; MY. Y: Review, supervision & validation; X. Z.: Resources, project administration, and review & editing; R. H.: Review, supervision & validation; Y. Z.: Review, supervision & validation.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB) Approval.

Additional information

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