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Neutrophil percentage to albumin ratio predicts cardiovascular and all-cause mortality in diabetes and pre diabetes patients

Hua Ji, Yongqi Wang, Xinyi Cao, Yichang Liu, Murong Xu, Xiaotong Zhao✉ & Mingwei Chen✉

The association between Neutrophil-Percentage-to-Albumin Ratio (NPAR) and mortality in cardiovascular disease (CVD) patients with diabetes or pre-diabetes is not well understood. This study investigates the relationship between baseline NPAR levels and all-cause and cardiovascular mortality among American adults with CVD and diabetes or pre-diabetes. This study enrolled 6,080 patients with diabetes or prediabetes from the National Health and Nutrition Examination Survey (2001–2018). Mortality outcomes were determined by linkage to the National Death Index (NDI) records through December 31, 2019. Multivariate Cox proportional hazards models were used to explore associations between NPAR and mortality. Non-linear correlations were assessed with restricted cubic splines, and segmented Cox proportional hazards models were used to evaluate threshold effects. Receiver operating characteristic (ROC) curves were used to evaluate NPAR's predictive ability for all-cause mortality. Weighted Kaplan–Meier curves with log-rank tests assessed cumulative survival differences across NPAR levels. In this cohort study, with a total follow-up of 53,217 person-years, 1,378 deaths from all causes and 476 deaths from CVD were recorded. Restricted cubic spline analysis revealed a J-shaped association between NPAR and both all-cause and cardiovascular mortality. Threshold effect analysis identified inflection points for NPAR in relation to all-cause mortality at 15.1 and cardiovascular mortality at 14.2. When baseline NPAR exceeded these inflection points, a positive correlation was observed with all-cause mortality (HR: 1.55, 95% CI: 1.08–2.16) and cardiovascular mortality (HR: 1.25, 95% CI: 1.09–1.86). ROC curves for 3-year, 5-year, and 10-year survival rates for all-cause mortality had areas under the curve (AUC) of 0.83, 0.83, and 0.81, respectively. For cardiovascular mortality, the AUC values were 0.86, 0.87, and 0.84. Increased NPAR is significantly associated with increased all-cause and cardiovascular mortality in individuals with diabetes or prediabetes, suggesting its potential role as a prognostic marker.

Keywords Neutrophil-Percentage-to-Albumin ratio, Diabetes, Prediabetes, Mortality, Cardiovascular disease, NHANES

Diabetes and its complications are among the leading causes of global death and disability, posing a major public health challenge. In 2021, approximately 537 million people worldwide were living with diabetes, a number projected to rise significantly due to aging populations and poor dietary choices[1]. Diabetes is also the eighth leading cause of death globally, contributing to healthcare costs of $966 billion and placing a significant financial burden on healthcare systems[2–5].Cardiovascular disease (CVD) is a leading cause of mortality in diabetic patients, with chronic inflammation playing a pivotal role in the pathogenesis of both conditions[6,7]. Recent studies have identified several inflammatory biomarkers, such as C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), which have shown predictive and prognostic value for CVD[8–10]. However, these markers often require specialized assays or may not fully capture the complex interplay between inflammation and nutritional status in diabetic patients.

The neutrophil percentage to albumin ratio (NPAR), calculated as neutrophil percentage divided by albumin level, is a novel biomarker that integrates systemic inflammation (reflected by neutrophil percentage) and nutritional status (indicated by albumin levels). Neutrophils are key players in inflammatory processes, which contribute to coronary artery disease[11], while low albumin levels are associated with worse cardiovascular

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outcomes and higher mortality[12]. Compared to other inflammatory markers, NPAR is cost-effective, easily accessible, and provides a more comprehensive evaluation of both inflammatory and nutritional status, which are critical in diabetic patients[13].Previous studies have demonstrated the prognostic value of NPAR in various conditions, including cardiogenic shock, myocardial infarction, COPD, cancer, and acute kidney injury[14–17]. In the context of diabetes and CVD, NPAR has been associated with adverse outcomes, but its prognostic value across different metabolic states (e.g., diabetes, prediabetes) remains unclear. This gap in the literature highlights the need for further investigation to determine whether NPAR can serve as a reliable biomarker for predicting all-cause and CVD mortality in diabetic and prediabetic patients.

The objective of our study was to explore the prognostic value of NPAR for the risk of all-cause mortality and CVD mortality in patients with diabetes or prediabetes.

Methods

Study population and design

The NHANES is a comprehensive national survey aimed at evaluating the health and nutritional status of adults and children in the U.S. This survey employs a sophisticated stratified multistage sampling design and includes interviews, physical exams, and laboratory tests. The research protocol has received approval from the National Center for Health Statistics (NCHS) Research Ethics Review Board, and all participants have given informed consent. Moreover, the datasets generated and analyzed in the current study are readily available on the official NHANES website (https://www.cdc.gov/nchs/nhanes/index.html). This study analyzes NHANES data collected from 2001 to 2018, involving 91,351 participants. We excluded individuals under the age of 20 ($n = 41550$) and those who did not meet the 2021 American Diabetes Association's criteria for diabetes or prediabetes ($n = 29936$). Definitions for diabetes include self-reported diabetes, use of insulin or hypoglycemic medications, an HbA1c of 6.5% or higher, fasting blood glucose of 7.0 mmol/L or higher, or a 2-hour postprandial glucose of 11.1 mmol/L or higher. Prediabetes is defined by an HbA1c of 5.7–6.4%, fasting blood glucose of 5.6 to 6.9 mmol/L, or 2-hour postprandial glucose of 7.8 to 11.0 mmol/L[18]. Additional exclusions were made for missing NPAR data ($n = 1119$).Finally, after excluding participants with missing mortality data or any key variable values ($n = 13066$), a total of 6080 partici pants were included in this study (Fig. 1).

Assessment of covariates

Data on a variety of demographic and health characteristics were collected from NHANES household interviews, such as age, sex, race/ethnicity, education, family income, smoking habits, disease conditions, and medication usage. Body mass index (BMI) was determined using the formula: weight in kilograms divided by the square of height in meters. Race/ethnicity was categorized into White, Black, Mexican, or Other, and education was classified into three levels: below high school, high school or equivalent, and Some College or above. Household income and poverty rate(PIR) was segmented by poverty ratios into three groups: 0–1.3, 1.3–3.5, and above 3.5. Drinking status was assessed by the participants' answer to the single choice of questionnaire, "Have you consumed a minimum of 12 alcoholic drinks per year?" The smoking status was determined based on the criterion of smoking at least 100 cigarettes during a person's lifetime. hypertension was determined based on self-reported diagnoses provided by medical professionals.Key clinical measures such as fasting glucose, HbA1c, albumin, triglycerides (TG), total cholesterol (TC), LDL cholesterol (LDL-C), and HDL cholesterol (HDL-C) were assessed in NHANES laboratory evaluations.

Measurement of indicators of NPAR

Hematologic parameters were measured following the NHANES CBC Profile using the Beckman Coulter Automated Hematology Analyzer DxH 900 (Beckman-Coulter, Brea, CA, USA), which performs red and white cell counts, hemoglobin, hematocrit, and redblood cell indices. The Coulter VCS system is used for the WBC differential. The Beckman Coulter Analyzer system counts and sizes cells using an automatic dilution and mixing system for sample processing, and a single beam photometer for hemoglobinometry. NPAR was calculated using the same blood sample and the following formula: Neutrophil percentage (in total WBC count) (%) 100/Albumin(g/dL).

Ascertainment of mortality

To track mortality status within the follow-up cohort, we utilized the NHANES public-use linked mortality file as of December 31, 2019. This mortality file is linked to the National Death Index (NDI) through a probability matching algorithm conducted by the National Center for Health Statistics (NCHS). For identifying cause-specific mortality, we applied the International Statistical Classification of Diseases, 10th Revision (ICD-10). The NCHS uses specific ICD-10 codes to categorize deaths, designating codes for heart diseases (054–064), malignant neoplasms (019–043), and other causes (010) pertinent to our study[19].

Statistical analysis

Statistical analyses were conducted using R software (version 4.2.1; available at https://www.r-project.org). To accommodate the complex sampling design of NHANES, all analyses incorporated sample weights, clustering, and stratification, as these are necessary steps to accurately analyze data from NHANES.Study participants were classified into four groups according to quartiles (Q1-Q4) of the NPAR. Continuous variables were summarized as mean and standard deviation (SD), while categorical variables were presented as frequency and percentage. The comparison of baseline characteristics across NPAR quartile groups was performed using one-way ANOVA for continuous variables and Pearson chi-square test for categorical variables. The incidence rates of all-cause mortality and CVD mortality for each NPAR quartile group were computed during the total follow-up period. To evaluate the independent predictive value of the NPAR, we developed multivariate Cox proportional hazards

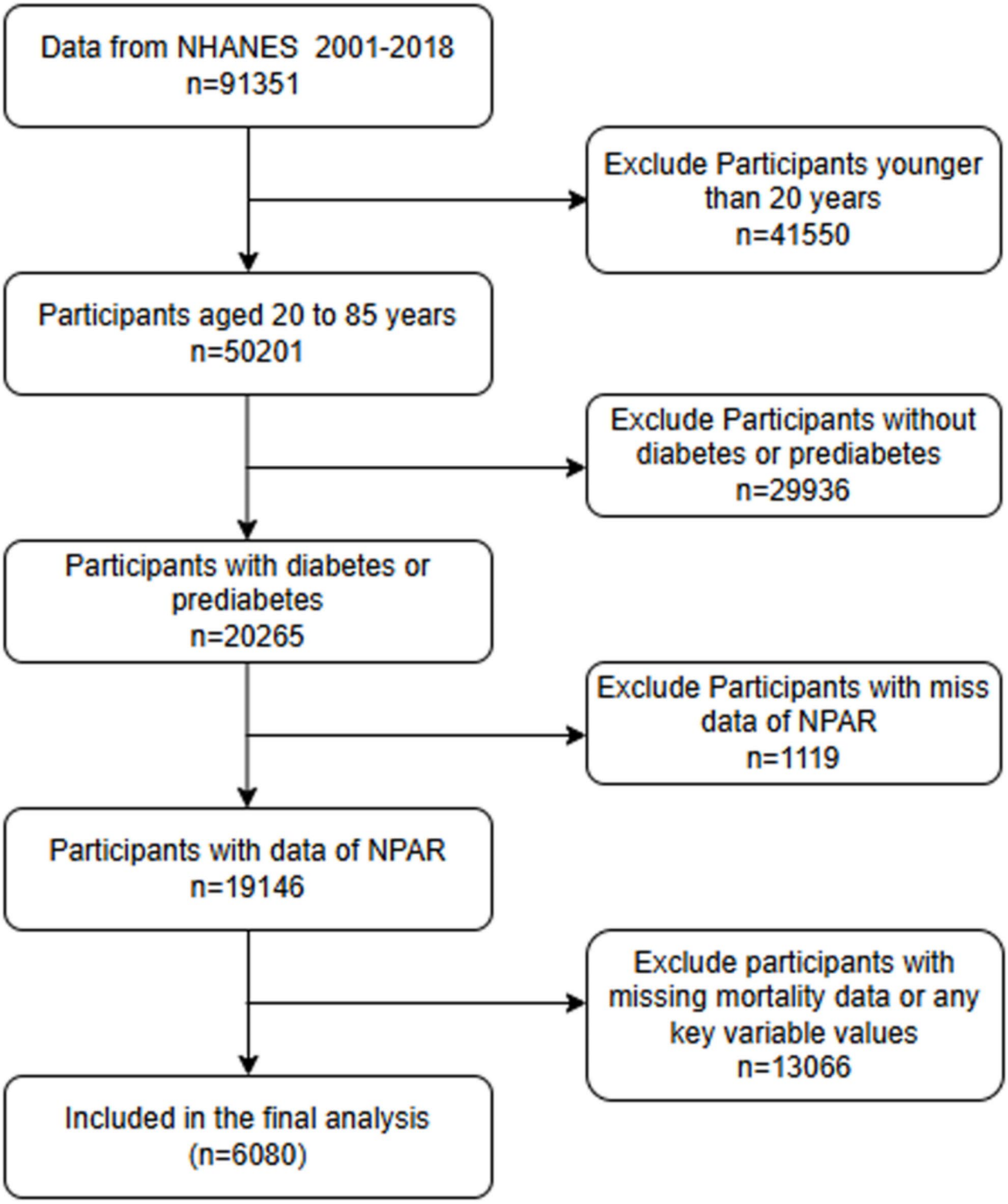

Fig. 1. Flow chart of the study participants.

regression models, which included three models to control for confounding factors. Model 1 was unadjusted, Model 2 was adjusted for Age, Gender, Race, Marital status, Smoke, Alcohol and BMI, and Model 3 was adjusted for Age, Gender, Race, Maritalstatus, Smoke, and Hypertension(We tested the proportional hazards assumption using Schoenfeld residuals, which indicated violations. To address this, we applied stratified modeling, which resolved the issue and allowed for different baseline hazards across groups. The final model showed no significant violations, with a global p-value of 0.5303).To explore the relationship between NPAR and mortality, we employed a restricted cubic spline within a Cox proportional hazards regression model. Additionally, we

utilized a penalized spline approach for smooth curve fitting, which helps prevent overfitting while allowing the model to capture complex nonlinear patterns in the data. This methodology enables us to accurately determine the variations in the relationship between NPAR and mortality risk, thereby providing more reliable results for interpretation.

If the relationship is nonlinear, we estimate the threshold value by testing all possible values and selecting the one with the highest likelihood. Then, we apply a two-piecewise Cox proportional hazards model on both sides of the threshold to examine the association between NPAR and the risk of all-cause mortality and CVD mortality.To account for the potential risk of Type I errors arising from multiple comparisons, we applied the False Discovery Rate (FDR) control method. Specifically, FDR was used to adjust the p-values for all statistical tests, including subgroup analyses and ROC curve evaluations. Additionally, we utilized a two-piecewise Cox proportional risk model on either side of the inflection point to assess the association between NPAR and the risk of all-cause mortality and CVD mortality. Stratified analyses were performed based on gender, age (less than 55 years or 55 years and older), BMI (less than 28.00 or 28.00 and above), and race (White, Black, Mexican, or Other). ROC curves were used to assess the predictive value of NPAR for all-cause and cardiovascular mortality, with AUC reported for 3-year, 5-year, and 10-year survival predictions. Weighted Kaplan-Meier (KM) survival curves were generated for different NPAR quartile groups, and log-rank tests were used to determine significant differences in cumulative survival among the groups.A p-value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics of study participants

Table 1 displays the baseline characteristics of the cohort study participants ($n = 6080$), organized by quartiles of the NPAR.The average age of the study participants was 58.54 years, with males comprising 54.01% of the group. The mean NPAR among the participants was 14.08 ± 2.80. Baseline laboratory characteristics, according to the quartiles of NPAR, are detailed in Table 2.

Participants with a higher NPAR tended to be older, White, and obese compared to those in the lowest quartile. Significant differences in biochemical indicators were noted across the groups, with those in the highest quartile exhibiting markedly elevated levels of HbA1c, blood urea nitrogen (BUN), creatinine (Cr), fasting insulin (FINS), fasting plasma glucose (FPG), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and platelet count compared to those in the lowest quartile. Conversely, levels of total bilirubin (TBIL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (ALB), and high-density lipoprotein cholesterol (HDL-C) were lower in the highest quartile than in the first quartile.

The data are presented as the mean (SD) or n (%). All estimates were obtained from complex survey designs, analysis of variance or $\chi 2$ tests where appropriate.

Associations of the NPAR with mortality

Participants were divided into four groups based on NPAR quartiles (Q1-Q4). Kaplan-Meier survival analysis showed significant differences in survival across the quartiles ($p < 0.001$). Participants in the highest quartile (Q4) exhibited significantly lower survival rates compared to those in the lowest quartile (Q1) for both all-cause and cardiovascular mortality (Fig. 2).

Table 3 presents the outcomes of 1,378 cases of all-cause mortality and 476 cases of cardiovascular disease-related mortality observed during the follow-up period. We employed three Cox regression models to examine the independent relationship between levels of NPAR and the risk of mortality.In Model 3, after adjustments for age, gender, race, BMI, smoking, alcohol use, hypertension, and marital status. The hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality across quartiles of NPAR were 1.00 (reference), 1.09 (0.92, 1.31), 1.19 (1.01, 1.41), and 1.80 (1.52, 2.11) respectively, demonstrating statistical significance ($P < 0.001$). For cardiovascular mortality, the HRs were 1.00 (reference), 1.01(0.72,1.39), 1.33(0.99,1.79), and 1.93(1.46,2.56) ($P < 0.001$).The results from the Cox regression analysis highlight a significant association between higher NPAR levels and increased cardiovascular mortality risk (HR of 1.93 in Q4 vs. Q1 for cardiovascular mortality). Participants in the highest NPAR quartile experienced a 1.93-fold increase in cardiovascular mortality risk and a 1.80-fold increase in all-cause mortality risk compared to those in the lowest quartile.

The predictive capability of NPAR was further confirmed by the ROC curves (Fig. 3), demonstrating high AUC values for the prediction of all-cause and cardiovascular mortality across different time points. The AUC for 3-year survival prediction was 0.83 (sensitivity: 0.795, specificity: 0.728), 5-year survival was 0.83, (sensitivity: 0.772, specificity: 0749), and 10-year survival reached 0.81, (sensitivity: 0.796, specificity: 0.703) For cardiovascular mortality, the AUCs were 0.86（sensitivity：0.830，specificity：0.734） at 3 years, 0.87（sensitivity：0.831，specificity：0.745） at 5 years, and 0.84（sensitivity：0.827，specificity：0.746） at 10 years, illustrating NPAR's stability and high predictive accuracy in both short-term and long-term forecasts.

The detection of nonlinear relationships

Previous multivariate analyses revealed a nonlinear association between baseline NPAR levels and risks of all-cause mortality and CVD mortality. Consequently, we applied Cox proportional hazards regression models with restricted cubic splines and smooth curve fitting using a penalized spline approach to further explore this relationship. The resulting adjusted smoothed plots demonstrated J-shaped correlations between NPAR and both all-cause mortality(Fig. 4A) and CVD mortality(Fig. 4B).We assessed the association between baseline NPAR and mortality outcomes employing standard Cox proportional hazards models alongside two-piecewise Cox proportional hazards models. Through the latter, we delineated distinct inflection points at NPAR indices of 15.1 for all-cause mortality and 14.2 for CVD mortality, with log-likelihood ratio tests yielding P values less than 0.05 for both(Table 4).

Characteristics	NPAR, Neutrophil-to-Albumin Ratio				*P* value
	Q1(<12.23)	Q2(12.23–14.01)	Q3(14.01–15.74)	Q4(>15.74)	
N%	1520(25.00)	1533(25.21)	1508(24.81)	1519(29.98)	
Age, year, mean(SD)	56.17(1.51)	57.79(1.41)	59.72(1.49)	60.51(1.58)	<0.001
Gender, n(%)					<0.001
Male	821(54.01)	817(53.30)	762(50.53)	694(45.69)	
Female	699(45.99)	716(46.70)	746(49.47)	825(54.31)	
BMI, kg/m^2, mean(SD)	29.44(6.24)	30.57(6.57)	31.35(7.11)	32.77(8.93)	<0.001
Race, n(%)					<0.001
Black	532(35.00)	345(22.50)	305(20.23)	301(19.82)	
Mexican	239(15.72)	296(19.30)	278(18.43)	234(15.40)	
White	452(29.74)	639(41.69)	707(46.89)	796(52.40)	
Other	297(19.54)	253(16.51)	218(14.45)	188(12.38)	
Education, n(%)					0.18
Less than high school	443(29.14)	449(29.29)	472(31.30)	489(32.20)	
High school grad or equivalent	365(24.02)	399(26.02)	352(23.24)	380(25.01)	
Some College or above	712(46.84)	685(44.69)	684(45.36)	650(42.79)	
Marital status, n(%)					0.01
Married/living with partner	934(61.45)	989(64.52)	942(62.47)	863(56.81)	
Never married	209(13.75)	146(9.52)	135(8.95)	155(10.21)	
Separated/ Divorced/Widowed	377(24.80)	398(25.96)	431(28.58)	501(32.98)	
Alcohol status, n(%)					0.243
Current	1027(67.56)	1010(68.88)	1016(67.38)	979(64.45)	
Former	255(16.78)	250(16.31)	264(17.50)	276(18.17)	
Never	238(15.68)	273(16.81)	228(15.12)	264(17.38)	
Smoke status, n(%)					<0.001
Former	443(29.14)	450(29.35)	477(31.63)	518(34.10)	
Never	820(53.95)	807(52.64)	737(48.87)	652(42.93)	
Now	257(16.91)	276(18.01)	294(19.50)	349(22.97)	
PIR, n(%)					0.16
<1.3	478(31.44)	488(31.83)	463(30.70)	519(34.17)	
1.3–3.5	613(40.33)	596(38.88)	620(41.11)	617(40.62)	
>3.5	429(28.23)	449(29.29)	425(28.19)	383(25.21)	
Hypertension, n(%)					<0.001
No	787(51.78)	733(47.81)	672(44.56)	620(40.82)	
Yes	733(48.22)	800(52.19)	836(55.44)	899(59.18)	
CVD, n (%)					<0.001
No	1336(87.89)	1299(84.74)	1256(83.29)	1178(77.55)	
Yes	184(12.11)	234(15.26)	252(16.71)	341(22.45)	
Diabetes					<0.001
DM, n (%)	442(29.08)	508(33.14)	594(39.39)	680(44.77)	
PreDM, n (%)	1078(70.92)	1025(66.86)	914(60.61)	839(55.23)	

Table 1. Baseline characteristics according to the NPAR quartiles. BMI: Body mass index; PIR: Poverty income ratio; DM: Diabetes Mellitus; PreDM: pre-diabetes; PIR: Poverty-to-incomeratio.

After adjusting for Age, Gender, Race, Marital status, Smoke, Alcohol, BMI, and Hypertension, Baseline NPAR levels were found to be significantly and positively correlated with increased risks of both all-cause and CVD mortality when exceeding thresholds of 15.1. (HR: 1.55, 95% CI: 1.08–2.16) and 14.2 (HR: 1.25, 95% CI: 1.09–1.86), respectively. The Kaplan-Meier curve (Fig. 5) supports the findings, showing that individuals with higher NPAR levels exhibit a significantly lower survival rate over 20 years of follow-up compared to those with lower NPAR levels in the diabetes or prediabetes populations (log-rank P for trend < 0.001).

Subgroup analyses

To further elucidate the relationship between NPAR and the risks of all-cause and cardiovascular mortality, we performed subgroup analyses (Tables 5 and 6). The results demonstrated that higher NPAR levels (≥ 15.1 for all-cause mortality and ≥ 14.2 for CVD mortality) were significantly associated with increased risks, with hazard ratios (HRs) consistently above 1 across all subgroups, including gender, age, BMI, and race. No significant interactions were observed between NPAR and the stratified variables (gender, age, BMI, and race;

	NPAR, Neutrophil-to-Albumin Ratio				*P* value
	Q1(<12.23)	Q2(12.23–14.01)	Q3(14.01–15.74)	Q4(>15.74)	
HbA1c,%,mean(SD)	6.27(1.24)	6.31(1.25)	6.42(1.38)	6.52(1.46)	<0.001
HDL-cholesterol, mmol/L, mean (SD)	1.37(0.40)	1.34(0.37)	1.32(0.38)	1.31(0.38)	<0.05
LDL-cholesterol, mmol/L, mean (SD)	2.79(0.95)	2.96(0.98)	3.06(0.93)	3.13(0.96)	<0.001
TC, mmol/L, mean (SD)	4.89(1.09)	5.01(1.11)	5.13(1.08)	5.19(1.11)	<0.001
TG, mmol/L, mean (SD)	1.49(0.81)	1.57(0.82)	1.55(0.79)	1.49(0.77)	0.058
BUN, mmol/L, mean (SD	4.97(2.01)	5.14(2.04)	5.32(2.29)	5.76(3.39)	<0.001
Cr, umol/L, mean (SD)	81.68(3.71)	81.13(2.93)	82.74(4.23)	92.24(4.34)	<0.001
Uric acid, umol/L, mean (SD)	342.8(8.55)	343.8(8.50)	342.2(8.32)	346.0(8.47)	0.65
ALB, g/dL, mean (SD)	4.308(0.29)	4.245(0.26)	4.154(0.26)	3.914(0.32)	<0.001
ALT(IU/L)	27.92(1.75)	27.41(1.79)	27.21(1.84)	23.27(1.86)	<0.001
AST(IU/L)	27.63(1.37)	26.62(1.37)	27.17(2.51)	24.54(2.48)	0.01
TBILumol/L, mean (SD)	12.36(4.71)	12.36(4.83)	12.09(4.87)	11.55(4.85)	<0.001
FPG, mmol/L, mean (SD)	6.260(2.21)	6.497(2.32)	6.741(2.61)	6.939(2.77)	<0.001
FINS, pmol/L, mean(SD)	90.78(9.64)	98.56(10.60)	101.8(11.33)	112.4(9.41)	<0.001
Neutrophil.percentage (%)	46.11(6.33)	55.84(3.94)	61.61(4.18)	68.63(6.01)	<0.001
Platelet count, (1000 cells/uL)	241.7(6.35)	245.9(6.86)	247.6(7.02)	259.9(8.59)	<0.001

Table 2. Baseline levels of laboratory characteristics according to NPAR. The data are presented as the mean (SD) or n (%). HbA1c: Glycated Haemoglobin; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; TC: Total Cholesterol; TG: Triglycerides; BUN: Blood Urea Nitrogen; Scr: Serum Creatinine; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; TBIL: Total Bilirubin; FPG: Fasting Plasma Glucose; FINS: Fasting Insulin.

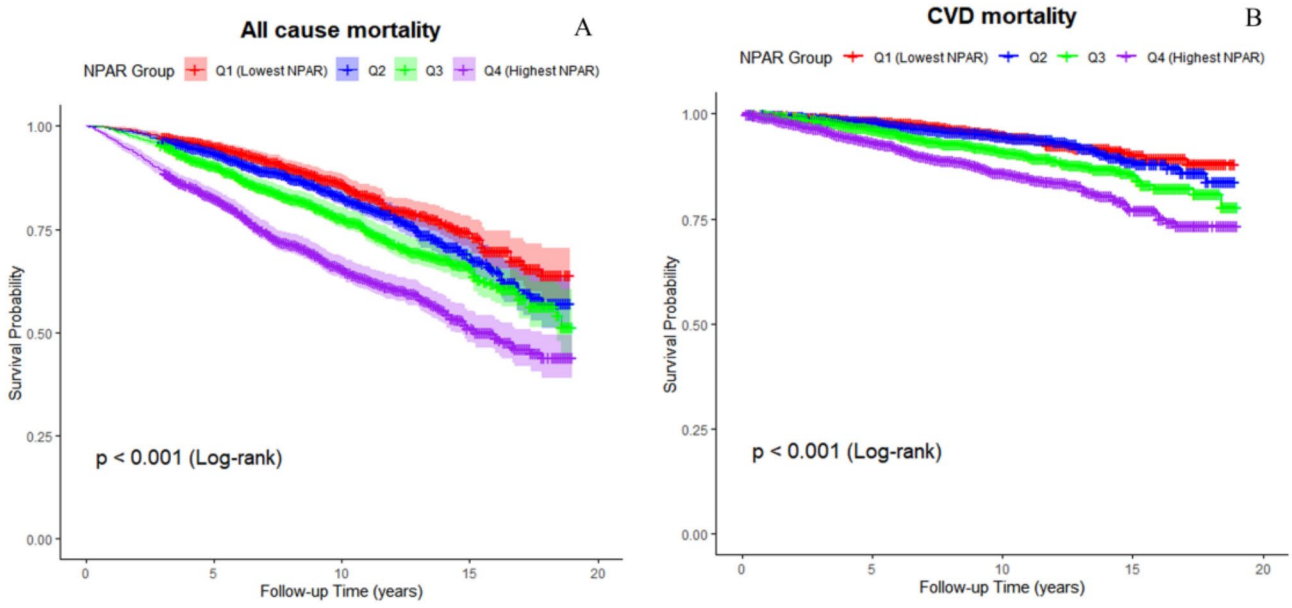

Fig. 2. Kaplan-Meier survival analysis curves for all-cause and CVD-cause mortality. (**A**) Kaplan–Meier analysis for all-cause mortality; (**B**) Kaplan–Meier analysis for CVD-cause mortality. statistical analysis is conducted using the log-rank test.

p interaction > 0.05), indicating a consistent effect of NPAR on mortality risk across different demographic and clinical subgroups.

Discussion

To our knowledge, this is the first prospective cohort study to explore the association between the Neutrophil-to-Albumin Ratio (NPAR) and all-cause and cardiovascular mortality in individuals with diabetes or prediabetes. We identified a J-shaped relationship, with inflection points at NPAR levels of 15.1 and 14.2 for all-cause and cardiovascular mortality, respectively. Above these thresholds, each unit increase in NPAR was associated with a

	NPAR, Neutrophil-to-Albumin Ratio				
	Q1(<12.23)	Q2(12.23–14.01)	Q3(14.01–15.74)	Q4(>15.74)	P trend
All-cause mortality					
Number of deaths	223	276	348	531	
Model 1,h(95%CI) P-value	1	1.24(1.03, 1.47)0.25	1.57(1.33,1.86) < 0.001	2.56(2.19,2.95) < 0.001	<0.001
Model 2,h(95%CI) P-value	1	1.12(0.94, 1.34)0.34	1.24(1.04,1.47)0.03	1.95(1.66, 2.29)<0.001	<0.001
Model 3,h(95%CI) P-value	1	1.09(0.92, 1.31)0.35	1.19(1.01, 1.41)0.04	1.80(1.52, 2.11)<0.001	<0.001
CVD mortality					
Number of deaths	72	82	129	193	
Model 1,h(95%CI) P-value	1	1.13(0.82, 1.55)0.43	1.81(1.35, 2.41)0.03	2.87(2.19,3.77)<0.001	<0.001
Model 2,h(95%CI) P-value	1	1.01(0.73,1.39)0.95	1.35(1.01,1.81)0.03	2.03(1.54, 2.69)<0.001	<0.001
Model 3,h(95%CI) P-value	1	1.01(0.72,1.39)0.96	1.33(0.99,1.79)0.04	1.93(1.46,2.56)<0.001	<0.001

Table 3. HRs (95% CIs) for mortality according to the NPAR quartiles. Model1: Non-adjusted. Model2: Adjusted for Age, Gender, Race, BMI. Model3: Adjusted for Age, Gender, Race, Marital status, Smoke, Alcohol, BMI, and Hypertension. HR: Hazard ratio; CI: Confidence interval.

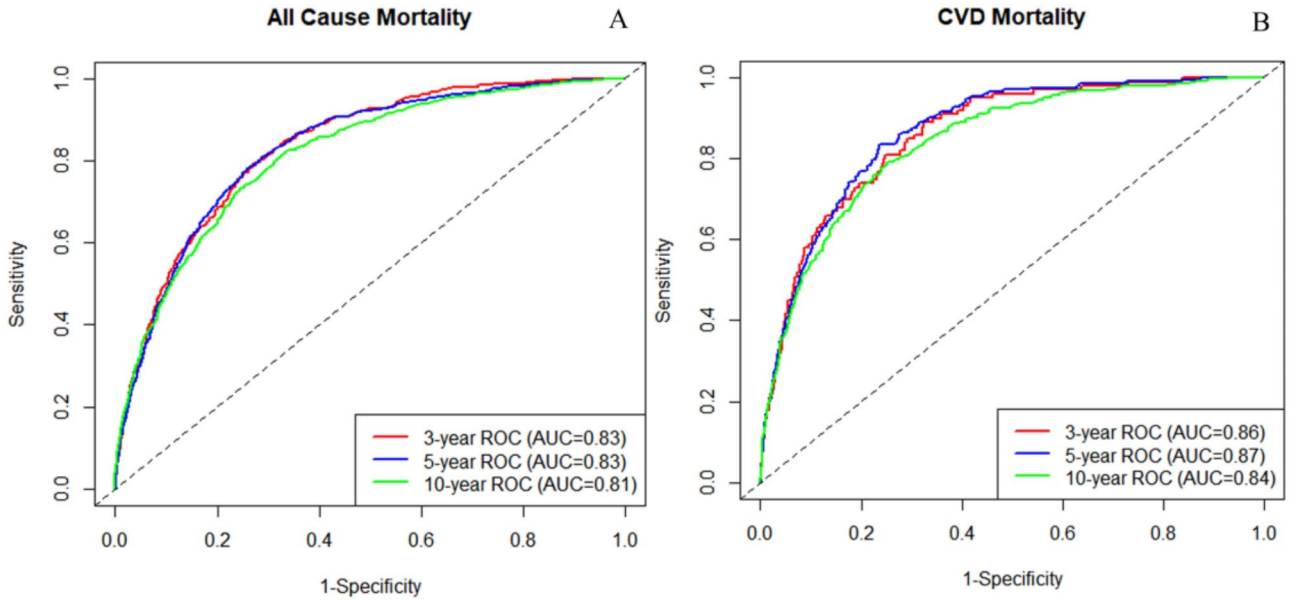

Fig. 3. The ROC value of NPAR in predicting outcomes in in the diabetes or prediabetes populations. The ROC curve analysis of NPAR for all-cause mortality is shown in Figure (**A**) The AUC values of Model 3 for predicting 3-year, 5-year, and 10-year outcomes were 0.83, 0.83, and 0.81, respectively. The ROC curve analysis of NPAR for cardiovascular disease (CVD) mortality is shown in Figure (**B**) The AUC values of Model 3 for predicting 3-year, 5-year, and 10-year outcomes were 0.86, 0.87, and 0.84, respectively. Adjusted for Age, Gender, Race, Marital status, Smoke, Alcohol, BMI, and Hypertension,

55% higher risk of all-cause mortality and a 25% increased risk of cardiovascular mortality. ROC curve analysis demonstrated NPAR's strong predictive ability, with AUC values ranging from 0.81 to 0.87 for 3-, 5-, and 10-year mortality predictions. Kaplan-Meier curves further confirmed that higher NPAR levels were associated with significantly lower survival rates over a 20-year follow-up. These findings highlight NPAR as a promising prognostic marker for risk stratification in this population.

NPAR, a biomarker derived from peripheral blood neutrophil and albumin levels, is characterized by its cost-effectiveness and accessibility. NPAR is a relatively novel inflammatory marker, and accumulating evidence has demonstrated its clinical prognostic value in various diseases. To further elucidate these findings, it is important to note that the use of constrained cubic splines allows for flexible modeling of these nonlinear relationships. This approach reveals a J-shaped association between baseline NPAR and both all-cause mortality and cardiovascular mortality (Fig. 4), identifying critical inflection points at 15.1 and 14.2, respectively, for each outcome. Specifically, each unit increase in NPAR was associated with a 56% increase in all-cause mortality risk and a 25% increase in cardiovascular mortality risk.Studies have shown that elevated NPAR is associated with increased risk of all-cause mortality in critically ill patients with severe sepsis or septic shock[20]. Another study on critically ill patients with coronary artery disease (CAD) indicated that NPAR is an independent risk factor for

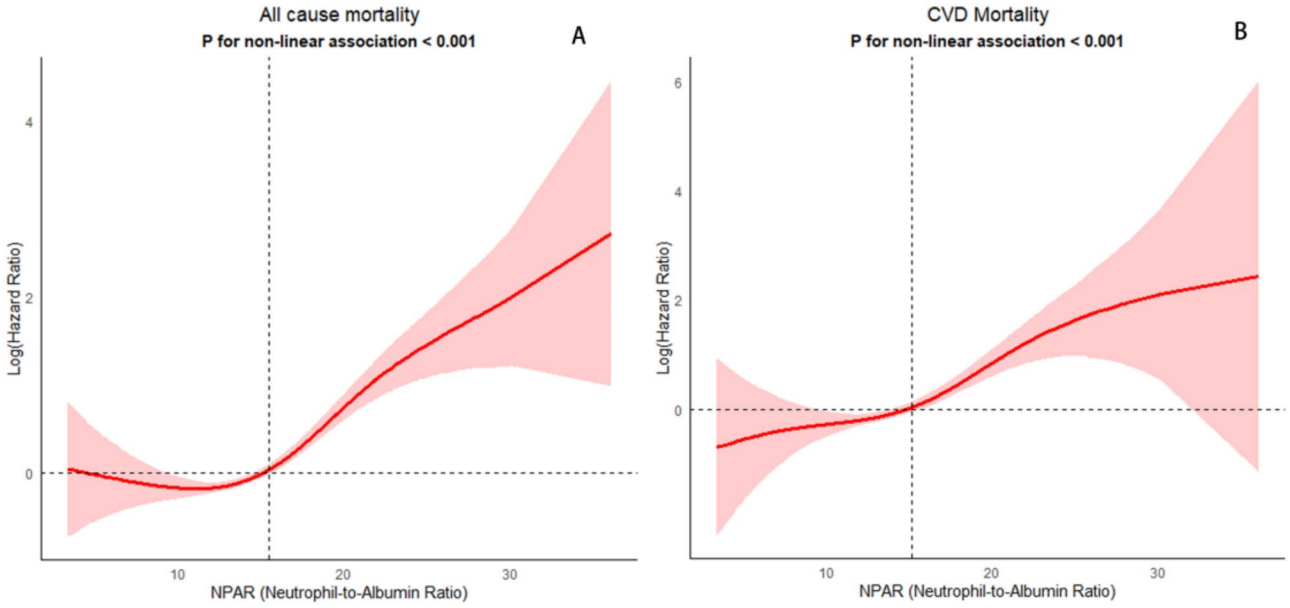

Fig. 4. Association between NRAP and all-cause (A) and CVD mortality (B) in CVD patients with diabetes or pre-diabetes. Each hazard ratio was computed with a NRAP level of A 15.1 and B 14.2 as the reference. Adjusted for Age, Gender, Race, BMI, Marital status, Smoke, Alcohol, and Hypertension. The solid line and red area represent the estimated values and their corresponding 95% CIs, respectively (NRAP: Neutrophil-to-Albumin Ratio; CVD: cardiovascular disease).

	Adjusted HR (95% CI),	*P*-value
All-cause mortality		
Total	1.32 (1.09–1.84)	< 0.001
Fitting by two-piecewise Cox proportional risk		
Inflection point	15.1	
NPAR < 15.1	1	
NPAR ≥ 15.1	1.55 (1.08–2.16)	< 0.001
P for Log-likelihood ratio		0.04
CVD-cause mortality	Adjusted HR (95% CI),	P-value
Total	1.14 (1.11–1.58)	< 0.01
Fitting by two-piecewise Cox proportional risk		
Inflection point	14.2	
NPAR < 14.2	1	
NPAR ≥ 14.2	1.25(1.09–1.86)	< 0.001
P for Log-likelihood ratio		0.03

Table 4. Threshold effect analysis of NPAR on all-cause and CVD mortality in diabetes or pre-diabetes patients. Cox proportional hazards models were used to estimate HR and 95% CI. Adjusted for Age, Gender, Race, Maritalstatus, Smoke, Alcohol, BMI, and Hypertension. NPAR: Neutrophil-to-Albumin Ratio; CVD: cardiovascular disease; HR: Hazard ratio; CI: Confidence interval.

in-hospital mortality in this patient group[13]. In a retrospective study by Xu et al. involving critically ill patients with atrial fibrillation, NPAR was found to be a good predictor of 90-day all-cause mortality[21]. Additionally, He et al.[22]reported that higher NPAR is positively associated with an increased risk of diabetic retinopathy (DR) and is an independent risk factor for DR in patients with diabetes. These studies indirectly support our findings. Furthermore, other research has revealed a positive correlation between NPAR and adult depression, highlighting the link between inflammation and mental health[23].

Chronic inflammation is increasingly recognized as a central mechanism linking diabetes and cardiovascular disease, originating from inflammation pathways activated in obesity and type 2 diabetes, which are also involved in the pathogenesis of atherosclerotic cardiovascular disease (ASCVD)[24];Inflammation can lead to various diabetic complications, such as diabetic nephropathy[25]and vascular complications[26].Diabetes also alters pro-inflammatory and anti-inflammatory signaling pathways, enhancing leukocyte activation and accumulation

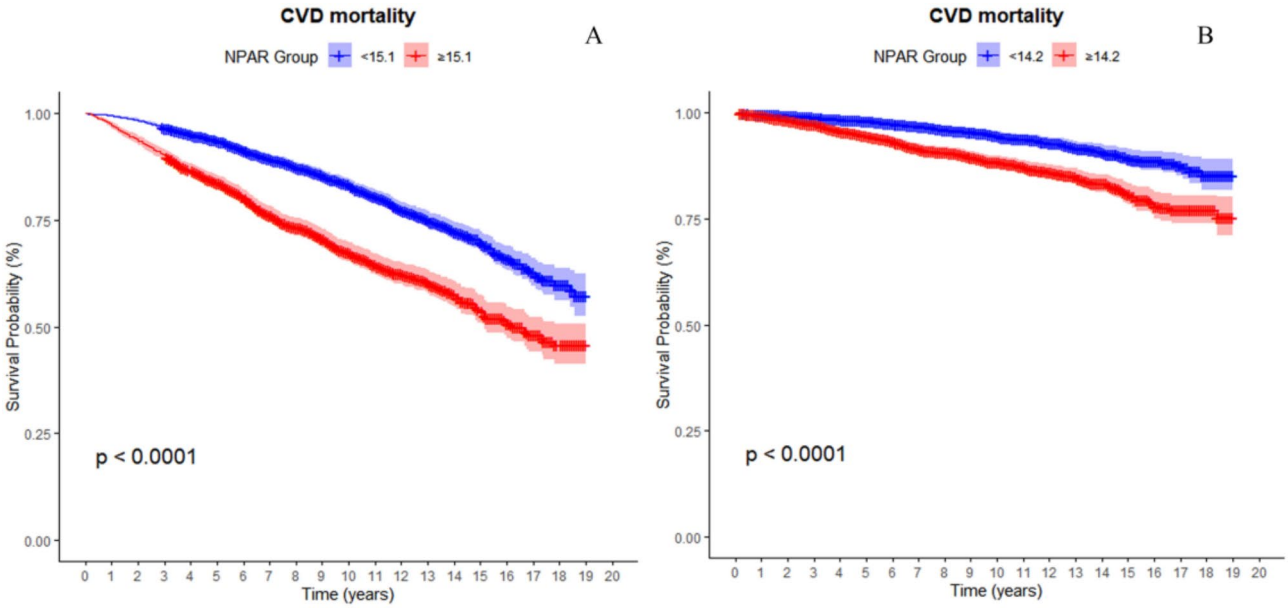

Fig. 5. Kaplan-Meier survival curves were generated for (**A**) all-cause mortality and (**B**) cardiovascular mortality, with participants stratified into two groups based on NPAR thresholds. For all-cause mortality, the thresholds were < 15.1 and ≥ 15.1, while for cardiovascular mortality, the thresholds were < 14.2 and ≥ 14.2. Statistical analysis was conducted using the log-rank test to compare survival differences between the groups.

	All-cause mortality		
	HR(95% CI) P-value		
NPAR	<15.1	≥ 15.1	p for interaction
Overall	1	1.78(1.61, 1.99)< 0.001	
Gender			0.29
Female		1.65(1.37, 1.99)< 0.001	
Male		1.82(1.60–2.07)< 0.001	
Age, years		2.06 (1.64–2.59)	0.94
< 55		1.66(1.21–2.07)< 0.001	
≥ 55		1.77(1.58–1.98)< 0.001	
BMI, kg/m2, n(%)			0.37
<28		1.68(1.46–1.94)< 0.001	
≥ 28		1.85 (1.57–2.17) < 0.001	
Race			0.58
Black		1.57 (1.23–2.02) < 0.001	
Mexican		1.75(1.53–2.01)< 0.001	
White		1.91(1.48–2.35)< 0.001	
Other		1.88(1.23–2.44)< 0.001	

Table 5. Stratified analyses of the associations between NPAR and all mortality. NPAR: Neutrophil-to-Albumin Ratio; BMI: Body mass index; CVD: cardiovascular disease; HR: Hazard ratio; CI: Confidence interval.

in vascular tissues, and causing endothelial injury through oxidative stress[27,28].Neutrophils play a crucial role in innate inflammation and have been shown to be strongly associated with multiple cardiovascular disease (CVD) patterns, including heart failure, peripheral artery disease, ischemic heart disease, myocardial infarction, and more, in a UK-based large dataset cohort study[11,29,30].Additionally, another cohort study based on the UK Biobank further demonstrated that neutrophils were most consistently associated with both fatal and non-fatal CVD events[31].The potential mechanism may involve increased neutrophils exacerbating chronic inflammation[32], with the pro-inflammatory response inducing severe oxidative stress and endothelial dysfunction, leading to atherosclerosis, instability of existing plaques, and an increased risk of cardiovascular disease.Albumin has long been considered an indicator of nutritional status, and there is substantial evidence indicating that serum albumin exhibits anti-inflammatory, antioxidant, anticoagulant, and antiplatelet aggregation activities which

	CVD mortality		
	HR(95% CI) P-value		
NPAR	<14.2	≥ 14.2	p for interaction
Overall	1	1.86(1.53, 2.23)< 0.001	
Gender			0.12
Female		1.53(1.12, 2.08) < 0.001	
Male		2.01 (1.64, 2.68) < 0.001	
Age, years			0.22
< 55		1.63(1.35–1.83)< 0.001	
≥ 55		1.79(1.46–2.19)< 0.001	
BMI, kg/m2, n(%)			0.35
<28		1.66 (1.25–2.01) < 0.001	
≥ 28		2.01(1.54–2.36)< 0.001	
Race			0.36
Black		2.16 (1.44–2.91) < 0.001	
Mexican		1.82(1.42–2.07)< 0.001	
White		1.88(1.04–2.32)< 0.001	
Other		1.31(0.65–1.74)< 0.001	

Table 6. Stratified analyses of the associations between NPAR and CVD mortality. NPAR: Neutrophil-to-Albumin Ratio; BMI: Body mass index; CVD: cardiovascular disease; HR: Hazard ratio; CI: Confidence interval.

may be involved in various cardiovascular diseases[[34,, 34].A cohort study in the United States found that[35], among elderly individuals without heart failure, baseline hypoalbuminemia was associated with an increased risk of heart failure events over a 10-year follow-up period.Additionally, hypoalbuminemia was an independent predictor of new-onset heart failure and in-hospital mortality in patients with acute coronary syndrome (ACS)[36].In our study, compared to participants in the lowest quartile (Q1), those in the highest NPAR quartile (Q4) exhibited significantly higher BMI, elevated neutrophil levels, and lower albumin levels, consistent with previous findings. Additionally, TBIL, which has antioxidant properties, was also decreased. These findings suggest an imbalance between pro-inflammatory and anti-inflammatory states, as well as the presence of chronic inflammation, which may contribute to the development and progression of CVD. NPAR was positively correlated with HbA1c, FPG, TC, and LDL-C, and negatively correlated with HDL-C. These results indicate that the association between NPAR and poor prognosis may be attributable to the presence of traditional cardiovascular risk factors, as previously reported[13].These findings highlight the potential of NPAR as a marker for cardiovascular risk stratification in patients with diabetes or prediabetes.

The Kaplan-Meier survival analysis revealed significant differences in survival rates across NPAR quartiles (log-rank $P < 0.001$), with the highest quartile (Q4) exhibiting markedly lower survival rates compared to the lowest quartile (Q1) for both all-cause and cardiovascular mortality (Fig. 2). These findings were further supported by weighted Kaplan-Meier curves (Fig. 5), which demonstrated significantly reduced survival rates over a 20-year follow-up period in individuals with higher NPAR levels (log-rank P for trend < 0.001). The log-rank test p-values (< 0.001) confirm the statistical significance of these differences, highlighting the strong association between elevated NPAR levels and increased mortality risk. Stratified analysis demonstrated that hazard ratios (HRs) for NPAR were consistently above 1 across all subgroups (including gender, age, BMI, and race), with no significant interactions, suggesting a consistent effect of NPAR on mortality risk across different demographic and clinical contexts. Liu et al.[37] also reported a significant association between elevated NPAR and increased all-cause mortality risk in the general population, emphasizing its high predictive value and supporting our findings.

This study has several limitations. As a single-center observational study, causality cannot be established, and residual confounding may persist despite multivariable adjustments. We only evaluated baseline NPAR, leaving its dynamic changes unexplored. Additionally, low serum albumin, a component of NPAR, is often associated with conditions like malnutrition or chronic inflammation, which may have overestimated the association between NPAR and mortality and limited the generalizability of our findings. Future studies should investigate longitudinal NPAR changes, validate its utility in diverse cohorts, and explore whether interventions targeting NPAR can improve outcomes. Despite these limitations, our findings highlight NPAR as a cost-effective biomarker for risk stratification in individuals with diabetes or prediabetes.

Conclusion

Our findings demonstrate that the Neutrophil-to-Albumin Ratio (NPAR) is a robust predictor of all-cause and cardiovascular disease (CVD) mortality in individuals with diabetes or prediabetes, with a nonlinear association observed between NPAR levels and mortality risk. These results suggest that NPAR could serve as a simple and cost-effective prognostic marker for risk stratification, enabling early identification of high-risk patients for

targeted interventions. Future studies should explore NPAR-guided therapeutic strategies and validate its utility in diverse cohorts and clinical settings.

Data availability

Availability of Data and MaterialsThe data used in this study were obtained from the National Health and Nutrition Examination Survey (NHANES) database, a publicly available resource provided by the Centers for Disease Control and Prevention (CDC). The NHANES data can be accessed at https://www.cdc.gov/nchs/nhanes/index.htm. The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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Author contributions
H. Ji designed the study and performed the statistical analysis, contributing significantly to the data visualization aspects. X. Cao supported the data management and was pivotal in creating the statistical graphs and charts. Y. Liu contributed to the study design and was involved in refining the graphical representations of the methodology. M. Xu assisted in the literature review and played a key role in the visualization of data trends and findings. Y. Wang provided critical assistance in statistical analysis during the revision process, ensuring the accuracy and robustness of the results. X. Zhao, as a corresponding author, coordinated the research efforts and oversaw the integration of text and graphical content in the manuscript. M. Chen, also a corresponding author, guided the overall presentation of graphical data, ensuring the visualizations accurately represented the study's findings, and prepared the final version for publication. All authors reviewed and approved the final manuscript.

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Declarations

Consent for publication
All authors have declared their consent for this publication.

Competing interests
The authors declare no competing interests.

Ethical approval
The National Center for Health Statistics and Ethics Review Board approved the protocol for NHANES, and all participants provided written informed consent. The authors have disclosed no conflicts of interest.

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