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The systemic immune-inflammation index and systemic inflammation response index are useful for predicting mortality in patients with diabetic nephropathy

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Abstract

Background This study investigated the correlation between the systemic immune-inflammation index (SII) and the systemic inflammation response index (SIRI) and all-cause, cardiovascular, and kidney disease mortality in patients with diabetic nephropathy (DN). It aimed to provide a new predictive assessment tool for the clinic and a scientific basis for managing inflammation in DN.

Methods The data utilized in this study were obtained from the National Health and Nutrition Examination Survey (NHANES) database, spanning 1999 to 2018. A total of 2641 patients diagnosed with DN were included in the analysis. The association between SII and SIRI levels and mortality in patients with DN was investigated using multivariate Cox proportional risk regression models. These relationships were further validated by Kaplan-Meier survival curves and restricted cubic spline (RCS) modeling, and subgroup analyses were performed to explore the heterogeneity among different characteristic subgroups.

Results The multivariate Cox regression analysis indicated that SII and SIRI levels were independently associated with all-cause mortality and cardiovascular mortality in patients with DN. SIRI levels were found to be an independently associated factor with kidney disease mortality in patients with DN. Patients in the highest quartile of SII and SIRI exhibited a 1.49-fold and 1.62-fold increased risk of all-cause mortality, respectively, compared to patients in the lowest quartile. The risk of cardiovascular mortality was 1.31 and 1.73 times higher than that in patients in the lowest quartile, respectively. The risk of kidney disease mortality in patients in the highest quartile of SIRI was 2.74 times higher than that in patients in the lowest quartile. Kaplan-Meier survival curve and RCS analyses further confirmed the positive association between SII and SIRI and mortality and a significant nonlinear relationship between SII and all-cause mortality. The SII and SIRI indices offer incremental value in model predictive power for mortality in patients with DN. Subgroup analyses demonstrated that the correlation between SII and SIRI and mortality risk was stable but heterogeneous across different subgroups.

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Conclusion SII and SIRI can be utilized as biomarkers for forecasting the likelihood of all-cause and cardiovascular mortality in patients with DN.

Keywords Systemic immune-inflammation index, Systemic inflammation response index, Diabetic nephropathy, All-cause mortality, Cardiovascular mortality, Kidney disease mortality

Background

Diabetes mellitus (DM), a global chronic metabolic disease, represents a significant challenge to global public health, with its prevalence increasing year on year [1]. DM not only affects the quality of life of patients but also significantly increases the risk of cardiovascular disease, nephropathy, and other complications, which has a profound impact on the prognosis of patients [2]. Diabetic nephropathy (DN) is one of the most prevalent microvascular complications of DM. It is characterized by glomerulosclerosis and tubulointerstitial fibrosis, which ultimately result in chronic renal failure [3, 4]. DN is the primary cause of end-stage renal disease (ESRD), a condition that significantly increases the medical burden and risk of mortality for patients [5]. The pathogenesis of DN is intricate and involves many factors, including glucose metabolism disorders, inflammation, oxidative stress, and other mechanisms [6–8].

In recent years, there has been a growing recognition of the role of the inflammatory response in the pathogenesis of diabetes and its associated complications. The inflammatory response is not only implicated in the pathogenesis of DN but is also closely related to other complications, including cardiovascular disease [9]. As our comprehension of the part played by the inflammatory response in diabetes and its complications has grown, the search for biomarkers that can reflect the body's inflammatory state and predict the prognosis of DN has become a prominent area of research. The systemic immune-inflammation index (SII) and the systemic inflammation response index (SIRI), as emerging biomarkers, are capable of providing a more comprehensive reflection of the inflammatory state and immune response of the body by integrating neutrophils, lymphocytes, monocytes, and platelets [10–12].

It has been demonstrated that SII and SIRI are significantly correlated with the prognosis of a range of tumors, cardiovascular diseases, and infectious diseases [13–17]. Nevertheless, only a limited number of studies have been conducted on SII and SIRI in patients with DN, particularly about their association with the risk of all-cause mortality, cardiovascular mortality, and kidney disease mortality. In light of the evidence above, this study aimed to examine the relationship between SII and SIRI and the mortality risk in patients with DN. This was done to provide a new predictive assessment tool for clinical use and a scientific basis for managing inflammation in DN.

To achieve the aims of this study, data from the National Health and Nutrition Examination Survey (NHANES) database were employed, spanning the period from 1999 to 2018. The database offers a comprehensive repository of demographic, clinical, and biochemical data, providing a valuable resource for investigating DN and its associated risk factors. Following the implementation of rigorous cleaning and screening procedures, 2,641 eligible patients with DN were identified for analysis. The objective of this study was to comprehensively assess the relationship between SII and SIRI and mortality in patients with DN.

Methods

Study population

The data utilized in this study were obtained from the NHANES database, spanning 1999 to 2018. This database contains the results of cross-sectional surveys conducted every two years by the Centers for Disease Control and Prevention (CDC). The research protocol of the NHANES project adhered to the guidelines set forth by the Ethics Review Committee of the National Center for Health Statistics (NCHS), and all participants were required to sign an informed consent form. In the course of data analysis, NIH policy regulations were adhered to. Given the anonymity and non-direct contact nature of the data, it was used directly in the study without requiring additional ethical review. The study used the standards outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement to ensure the highest study design and reporting quality.

At the study's outset, a sample population was selected from ten consecutive survey cycles, comprising 101,316 participants. To guarantee the precision and relevance of the study outcomes, we rigorously implemented data cleaning and exclusion criteria to remove ineligible participants, including those under the age of 20, non-diabetic patients, pregnant women, individuals with missing data (specifically missing data on demographic characteristics, chronic disease status, routine blood, and some biochemical data, diagnostic indicators of DN, and survival follow-up), and patients with non-DN. Following the implementation of the aforementioned rigorous screening process, 2,641 eligible participants were identified for analysis in this study (Fig. 1).

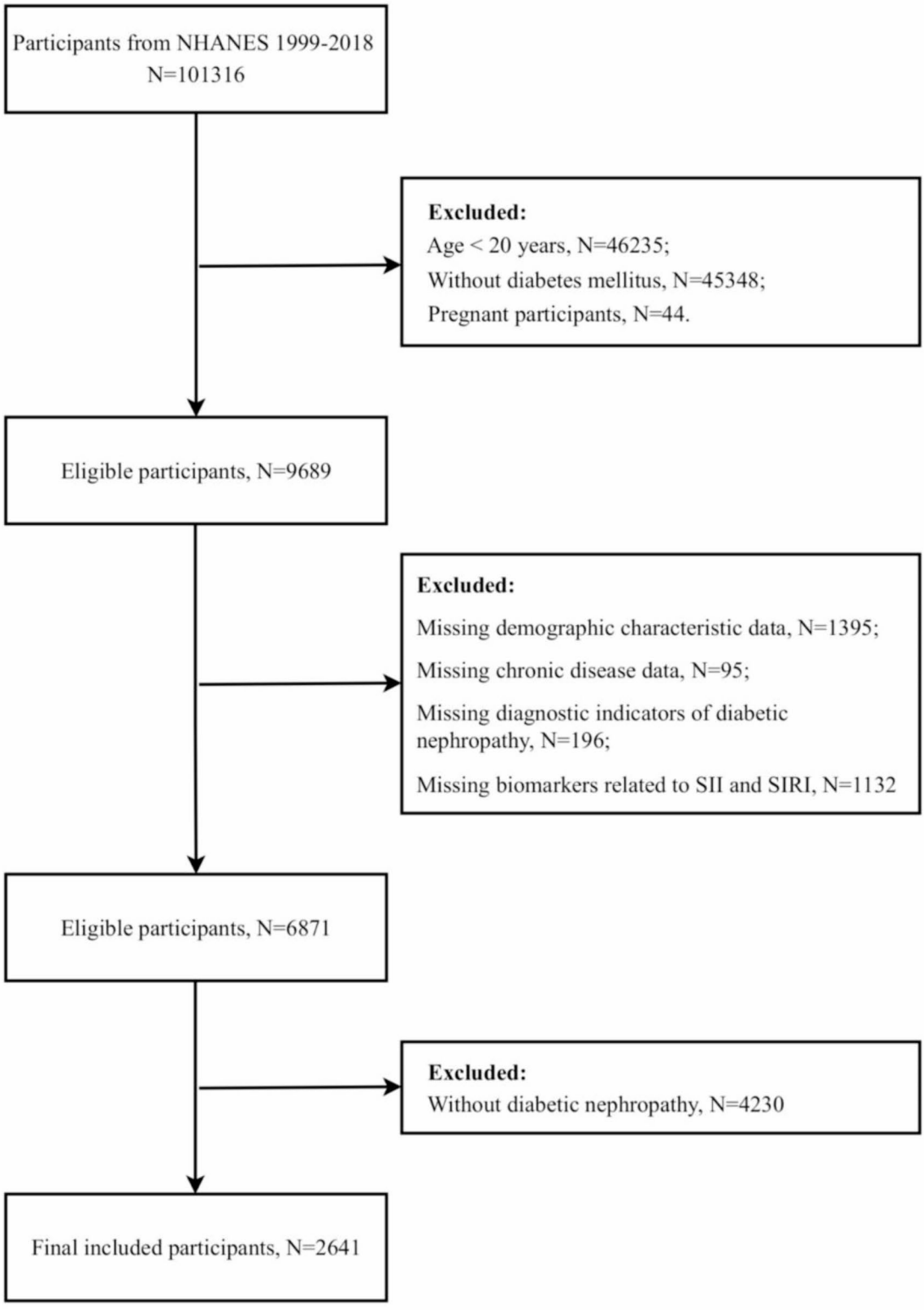

Fig. 1 Participant screening flowchart. Abbreviations: SII: Systemic immune inflammation index; SIRI: Systemic inflammation response index

Definition of disease

In this study, DM was defined according to one of the following criteria: (1) a definitive diagnosis by a qualified healthcare professional; (2) fasting plasma glucose (FPG) levels at or above the established threshold of 126 mg/dL; (3) glycosylated hemoglobin (HbA1c) levels of not less than 6.5%; (4) the individual's current use of diabetic medication or insulin therapy. To accurately assess renal function, we employed the urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) as the core indicators. The eGFR was calculated precisely according to the recommended formula by the Collaborative Group on Epidemiology of Chronic Kidney Disease (CKD-EPI) [18]. The diagnosis of DN was based on internationally recognized criteria, namely a UACR value of at least 30 mg/g or an eGFR value of less than 60 mL/min/1.73 m^2 [19]. Patients were classified into five stages of CKD based on disease severity, according to the Kidney Disease Quality Outcome Initiative (K/DOQI) CKD classification. Stage 1: eGFR≥90 mL/min/1.73m^2; Stage 2: eGFR 60–89 mL/min/1.73m^2; Stage 3: eGFR 30–59 mL/min/1.73m^2; Stage 4: eGFR 15–29 mL/min/1.73m^2; Stage 5: eGFR<15 mL/min/1.73m^2.

Definition of SII and SIRI

A complete blood count (CBC) was conducted for each participant using a Beckman Coulter DxH 800 analyzer at the NHANES Mobile Examination Center (MEC). Accordingly, SII and SIRI were calculated using the following formula: SII is calculated as the platelet count multiplied by the neutrophil count divided by the lymphocyte count [10]. Similarly, SIRI is calculated as the neutrophil count multiplied by the monocyte count divided by the lymphocyte count [12].

Mortality assessment

The primary outcomes of this study were all-cause mortality and cardiovascular mortality in patients with DN. All-cause mortality was defined as deaths from heart disease, malignant neoplasms, and all other causes. The determination of disease-specific mortality was conducted by the International Statistical Classification of Diseases, 10th edition (ICD-10). Cardiovascular mortality was defined as deaths due to heart disease (ICD-10 codes 100–109, 111, 113, 120–151) and cerebrovascular disease (ICD-10 codes 160–169). Kidney disease mortality was defined as deaths resulting from kidney disease, as classified by the ICD-10 codes N00-N07, N17-N19, and N25-N27. The mortality data for the follow-up population were obtained from the NHANES Public Use-Related Mortality File (as of December 31, 2019). This file is correlated to the NCHS and the National Death Index (NDI) through a probabilistic matching algorithm. The follow-up period was calculated from the initial interview to the date of the patient's death or December 31, 2019 [20].

Assessment of covariates

In examining the correlation between SII and SIRI levels and mortality in patients with DN, we developed multivariable-adjusted models to isolate the influence of confounding variables on this relationship. The following covariates were included in this study: gender, age, race, education, marital status, family economic status (as measured by the Poverty Income Ratio), alcohol intake, smoking behavior, physical activity level, and history of a range of important chronic diseases, including hypertension, coronary heart disease, stroke, and cancer. For racial categorization, participants were subdivided into the following categories: Mexican American, non-Hispanic white, non-Hispanic black, and other racial group. The sample was divided into three categories based on the years of education completed: less than 9th grade, 9th through 12th grade, and more than 12th grade. For this study, marital status was simplified into two categories: cohabitation and solitude. This was done to explore the role of family structure factors. To categorize family economic status, income was carefully divided into three intervals based on the Poverty-to-Income Ratio (PIR) criterion, as officially defined by the U.S. government. The intervals were defined as follows: low (PIR≤1.3), medium (PIR>1.3 to ≤3.5), and high (PIR>3.5). For this study, smoking and drinking habits were assessed using standardized methods. Smoking status was defined by the number of cigarettes smoked by the participant, with a minimum of 100 required for classification as a current smoker. Alcohol consumption was assessed by asking the participant whether they had consumed at least 12 alcoholic beverages of any type in the past year. Physical activity was classified into three categories: vigorous, moderate, and inactive. Chronic medical history was collected for hypertension (whether the participant had ever been told they had high blood pressure or were currently taking prescription medication for high blood pressure), coronary heart disease (whether a doctor had ever told the participant that they had coronary heart disease, angina, or a heart attack), stroke (whether a doctor had ever told the participant that they had a stroke), and cancer (whether a doctor had ever told the participant that they had cancer).

Statistical analysis

In the case of continuous variables, the Shapiro-Wilk test was employed to verify the normality of the data. The test results selected the mean±standard deviation or median (25th and 75th percentile) to characterize the variables. One-way analysis of variance (ANOVA) or Kruskal-Wallis nonparametric tests were employed to

ascertain differences between groups about the distribution characteristics of the variables in question. For categorical variables, the data were presented in the form of frequencies and percentages, and the chi-square test was employed to analyze the differences between groups.

To investigate the correlation between SII and SIRI levels and mortality in patients with DN, we developed multivariate Cox proportional risk regression models to assess the impact of each index and its quartiles on the risk of death in patients with DN. This was achieved by estimating the hazard ratio (HR) and its 95% confidence interval (CI). Three multivariable-adjusted models were constructed stepwise to eliminate the potential confounding effects of other variables. Model 1 served as the baseline model without any adjustments. Model 2 incorporated essential demographic characteristics, including age, gender, and race. Model 3 introduced additional adjustment variables to enhance the model's explanatory power and predictive accuracy. These include variables about education, marital status, family PIR, smoking and drinking habits, physical activity level, and history of chronic diseases such as hypertension, coronary heart disease, stroke, and cancer. These variables were included based on Model 2.

The cumulative incidence of mortality between SII and SIRI quartile strata was evaluated using the Kaplan-Meier method and the Log-rank test. A restricted cubic spline (RCS) model was employed to elucidate a potential nonlinear dose-response relationship between SII and SIRI and mortality in patients with DN. In this model, SII and SIRI were considered as continuous variables. Based on their distributional properties, the 5th, 35th, 65th, and 95th percentiles were selected as crucial points for analysis. The likelihood ratio test was employed to ascertain the critical point between the index and the risk of death from DN.

A baseline model was constructed in this study to ascertain the incremental value of SII and SIRI in predictive performance. The model incorporated gender, age, race, smoking habits, drinking behavior, physical activity level, and hypertension status. The incremental predictive power of SII and SIRI was evaluated using the C statistic, net reclassification improvement (NRI), and integrated discriminant improvement (IDI).

Furthermore, we conducted subgroup analyses to investigate the heterogeneity of the association between inflammatory indices and the risk of death from DN among subgroups with different characteristics. This was done by stratifying participants based on variables such as gender, race, level of education, marital status, family PIR, smoking habits, drinking habits, level of physical activity, and prevalence of hypertension, coronary heart disease, stroke, and cancer. Through interaction analyses, we evaluated the stability and consistency of the index-mortality risk association within each subgroup.

All statistical analyses employed the two-sided test, and a p-value of less than 0.05 was considered statistically significant. All data analysis was conducted using R 4.4.0 software (provided by the R Foundation at http://www.R-project.org) in conjunction with SPSS version 23.0 (IBM Corporation, Armonk, New York, USA). Graphic presentations were generated using GraphPad Prism version 9.0 (GraphPad Software, Inc., USA).

Results

Baseline characteristics of patients with DN

This study included 2,641 patients with DN, who were categorized into a survivor group ($n=1,546$) and a non-survivor group ($n=1,095$) based on their survival status. Baseline characterization revealed significant differences between the two groups concerning several demographic and clinical variables. In particular, the non-survivor group comprised more males (56.89%). The mean age was significantly higher in the non-survivor group (73.00 years) than in the survivor group (63.00 years). The racial distribution revealed that most individuals in the non-survivor group were Non-Hispanic Black participants (53.24%). Additionally, significant differences were observed in educational level and marital status, with a higher proportion of individuals with less education and those living alone in the non-survivor group. The non-survivor group exhibited a lower mean family income. The prevalence of smoking was higher in the non-survivor group (59.18%). The incidence of CHD, stroke, and cancer was higher in the non-survivor group. Regarding the clinical parameters, the mean BMI, HbA1c, and eGFR were lower in the non-survivor group. In contrast, the mean creatinine and urine ACR were higher ($P<0.05$). It is noteworthy that the SII and the SIRI were significantly higher in the non-survivor group ($P<0.001$), indicating an association between inflammation and mortality in this cohort (Table 1).

Baseline characteristics of participants based on SII quartiles

The patients were divided into quartiles based on their SII levels. The analysis revealed a significant correlation between SII levels and several factors, including gender, race, smoking habits, cancer prevalence, and multiple biomarkers ($P<0.05$). As SII levels increased, the proportion of males decreased, the proportion of Non-Hispanic Black participants increased significantly, the proportion of smokers increased, and the prevalence of cancer increased. The elevated SII levels were accompanied by increased FPG and triglyceride (TG) levels, as well as significant increases in neutrophil, monocyte, and platelet counts and significant decreases in lymphocyte

Table 1 Baseline characteristics of participants with diabetic nephropathy

Variables	Total (*n* = 2641)	Survivors (*n* = 1546)	Non-survivors (*n* = 1095)	*P*
Gender, n (%)				0.031
Male	1437 (54.41)	814 (52.65)	623 (56.89)	
Female	1204 (45.59)	732 (47.35)	472 (43.11)	
Age (years)	67.00 (58.00, 76.00)	63.00 (52.25, 72.00)	73.00 (65.00, 80.00)	< 0.001
Race, n (%)				< 0.001
Mexican American	512 (19.39)	341 (22.06)	171 (15.62)	
Non-Hispanic White	388 (14.69)	290 (18.76)	98 (8.95)	
Non-Hispanic Black	1112 (42.11)	529 (34.22)	583 (53.24)	
Other Race	629 (23.82)	386 (24.97)	243 (22.19)	
Education Level, n (%)				< 0.001
Less than 9th grade	556 (21.05)	277 (17.92)	279 (25.48)	
9–12th grade	1084 (41.05)	611 (39.52)	473 (43.20)	
More than 12th grade	1001 (37.90)	658 (42.56)	343 (31.32)	
Marital Status, n (%)				< 0.001
Cohabitation	1469 (55.62)	914 (59.12)	555 (50.68)	
Solitude	1172 (44.38)	632 (40.88)	540 (49.32)	
Family PIR, n (%)				0.002
Low (≤ 1.3)	988 (37.41)	577 (37.32)	411 (37.53)	
Medium (1.3–3.5)	1125 (42.60)	626 (40.49)	499 (45.57)	
High (> 3.5)	528 (19.99)	343 (22.19)	185 (16.89)	
Smoke, n (%)				< 0.001
Yes	1419 (53.73)	771 (49.87)	648 (59.18)	
No	1222 (46.27)	775 (50.13)	447 (40.82)	
Alcohol, n (%)				0.265
Yes	1522 (57.63)	877 (56.73)	645 (58.90)	
No	1119 (42.37)	669 (43.27)	450 (41.10)	
Physical Activity, n (%)				< 0.001
Inactive	399 (15.11)	320 (20.70)	79 (7.21)	
Moderate	798 (30.22)	499 (32.28)	299 (27.31)	
Vigorous	1444 (54.68)	727 (47.02)	717 (65.48)	
Hypertension, n (%)				0.099
Yes	1917 (72.61)	1104 (71.41)	813 (74.31)	
No	723 (27.39)	442 (28.59)	281 (25.69)	
Coronary heart disease, n (%)				< 0.001
Yes	380 (14.39)	165 (10.67)	215 (19.63)	
No	2261 (85.61)	1381 (89.33)	880 (80.37)	
Stroke, n (%)				< 0.001
Yes	303 (11.47)	131 (8.47)	172 (15.71)	
No	2338 (88.53)	1415 (91.53)	923 (84.29)	
Cancer, n (%)				< 0.001
Yes	438 (16.58)	197 (12.74)	241 (22.01)	
No	2203 (83.42)	1349 (87.26)	854 (77.99)	
BMI (kg/m^2)	30.74 (26.85, 35.89)	31.68 (27.66, 36.80)	29.57 (25.95, 34.29)	< 0.001
FPG (mg/dL)	136.00 (110.00, 187.00)	137.00 (110.00, 189.75)	135.00 (110.00, 181.00)	0.192
HbA1c (%)	6.90 (6.20, 8.20)	6.90 (6.30, 8.50)	6.80 (6.10, 8.00)	< 0.001
TC (mg/dL)	181.00 (153.00, 218.00)	181.00 (153.00, 217.00)	182.00 (155.00, 218.00)	0.658
TG (mg/dL)	162.00 (108.00, 245.00)	165.00 (110.00, 247.00)	159.00 (105.00, 240.50)	0.102
HDL-c (mg/dL)	45.00 (38.00, 55.00)	45.00 (38.00, 55.00)	45.00 (38.00, 56.00)	0.266
Neutrophils (10^3 cells/μL)	4.50 (3.50, 5.60)	4.40 (3.50, 5.50)	4.50 (3.50, 5.70)	0.105
Lymphocyte (10^3 cells/μL)	2.00 (1.50, 2.60)	2.10 (1.60, 2.60)	1.80 (1.40, 2.40)	< 0.001
Monocyte (10^3 cells/μL)	0.60 (0.50, 0.70)	0.60 (0.40, 0.70)	0.60 (0.50, 0.70)	< 0.001
Platelet (10^3 cells/μL)	233.00 (192.00, 282.00)	236.00 (199.00, 286.00)	229.00 (186.00, 273.50)	< 0.001

Table 1 (continued)

Variables	Total (*n* = 2641)	Survivors (*n* = 1546)	Non-survivors (*n* = 1095)	*P*
Creatinine (mg/dL)	1.08 (0.82, 1.36)	1.00 (0.80, 1.30)	1.16 (0.90, 1.46)	< 0.001
UACR (mg/g)	59.55 (27.55, 175.83)	55.88 (30.03, 150.30)	63.94 (25.91, 219.07)	0.017
eGFR (ml/min/1.73m^2)	62.45 (48.94, 91.46)	71.09 (53.10, 97.73)	55.82 (43.68, 78.55)	< 0.001
SII	519.20 (357.07, 754.09)	495.62 (351.00, 714.91)	552.00 (372.97, 815.08)	< 0.001
SIRI	1.27 (0.83, 1.89)	1.18 (0.78, 1.73)	1.43 (0.93, 2.17)	< 0.001

Data are shown as median (25th, 75th percentiles) or percentages, $p < 0.05$ considered statistically significant

Abbreviations: PIR: Poverty-to-income ratio; BMI: Body mass index; FPG: Fasting plasma-glucose; HbA1c: Hemoglobin A1c; TC: Total cholesterol; TG: Triglyceride; HDL-c: High-density lipoprotein cholesterol; UACR: Urinary albumin/creatinine ratio; eGFR: Estimated glomerular filtration rate; SII: Systemic immune inflammation index; SIRI: Systemic inflammation response index

counts ($P < 0.05$). However, no significant association was observed between SII levels and age, education level, marital status, family PIR, physical activity, hypertension, coronary heart disease, stroke, BMI, HbA1c, total cholesterol (TC), creatinine, UACR, and eGFR ($P > 0.05$). It is noteworthy that all-cause mortality increased significantly with rising SII levels in patients with DN ($P < 0.001$), although cardiovascular mortality and kidney disease mortality were not statistically significant ($P > 0.05$) (Table 2).

Baseline characteristics of participants based on SIRI quartiles

Analyses based on quartiles of the SIRI demonstrated a significant association between SIRI levels and several demographic and clinical variables, including gender, age, race, family income, smoking habits, prevalence of hypertension, coronary heart disease, and cancer. Additionally, several biomarkers were significantly correlated with SIRI levels ($P < 0.05$). As SIRI levels increased, there was a significant increase in the proportion of males, an increase in age, a significant increase in the proportion of Non-Hispanic Black participants, a higher proportion of individuals with moderate family income, an increase in the proportion of smokers, and a significant increase in the prevalence of hypertension, coronary heart disease, and cancer. Decreased levels of HbA1c accompanied elevated SIRI levels, reduced levels of TC, TG, and high-density lipoprotein cholesterol (HDL-c), increased counts of neutrophil monocytes, and decreased counts of lymphocytes. Furthermore, there was a positive correlation between SIRI levels and creatinine levels and a negative correlation between SIRI levels and eGFR. This suggests that SIRI may be a helpful indicator of renal impairment in patients with DN. It is noteworthy that both all-cause mortality and cardiovascular mortality were significantly elevated in patients with DN and increasing SIRI levels ($P < 0.001$), although kidney disease mortality was not statistically significant ($P = 0.204$) (Table 3).

SII and SIRI levels of different CKD stages in patients with DN

As the CKD stage increased, the values of both SII and SIRI demonstrated an upward trajectory. In particular, the value of SII exhibited a gradual increase from 506.03 to 586.27. However, the difference in SII between different CKD stages did not reach the significance level ($P = 0.297$). In contrast, the value of SIRI exhibited a significant increase from 1.07 to 1.76, and its difference was significant ($P < 0.001$) (Fig. 2). These data suggest a potential association between CKD staging and systemic inflammatory indicators, particularly with SIRI.

Relationship between SII, SIRI, and mortality in patients with DN

The multivariate Cox regression analysis results demonstrated that SII and SIRI levels were independently associated with all-cause mortality and cardiovascular mortality in patients with DN. SIRI levels were found to be an independently associated factor with kidney disease mortality in patients with DN. As continuous variables, after adjusting for demographic and clinical variables, the risk ratio of SII to all-cause mortality in patients with DN was 1.01 (95% CI: 1.01–1.01), with a *p*-value of less than 0.001, and to cardiovascular mortality was 1.01 (95% CI: 1. 01-1.01), $P = 0.011$. In contrast, the risk ratio of SIRI to DN patients was 1.16 (95% CI: 1.11–1.21) for all-cause mortality, 1.14 (95% CI: 1.06–1.23) for cardiovascular mortality, and 1.25 (95% CI: 1.04–1.51) for kidney disease mortality, respectively. These findings were statistically significant ($P < 0.05$) (Table 4).

Similarly, quartile analyses revealed an association between SII and SIRI levels and all-cause and cardiovascular mortality in patients with DN. Specifically, after adjusting for demographic and clinical variables, the risk of all-cause mortality in the highest quartile of patients with SII was 1.49 times (95% CI: 1.26–1.77) higher than in the lowest quartile, whereas the risk of all-cause mortality in the highest quartile of patients with SIRI was 1.62 times (95% CI: 1.35–1.95) higher than in the lowest quartile ($P < 0.001$). The risk of cardiovascular mortality in the highest quartile of patients with SII was 1.31

Table 2 Baseline characteristics of participants based on SII quartiles

Variables	SII				*P*
	Quartile 1 (*n* = 659)	Quartile 2 (*n* = 661)	Quartile 3 (*n* = 660)	Quartile 4 (*n* = 661)	
Gender, n (%)					0.002
Male	399 (60.55)	358 (54.16)	341 (51.67)	339 (51.29)	
Female	260 (39.45)	303 (45.84)	319 (48.33)	322 (48.71)	
Age (years)	67.00 (60.00,76.00)	67.00 (57.00,75.00)	68.00 (58.00,77.00)	68.00 (57.00,77.00)	0.175
Race, n (%)					< 0.001
Mexican American	128 (19.42)	137 (20.73)	118 (17.88)	129 (19.52)	
Non-Hispanic White	94 (14.26)	112 (16.94)	99 (15.00)	83 (12.56)	
Non-Hispanic Black	210 (31.87)	256 (38.73)	312 (47.27)	334 (50.53)	
Other Race	227 (34.45)	156 (23.60)	131 (19.85)	115 (17.40)	
Education Level, n (%)					0.098
Less than 9th grade	161 (24.43)	147 (22.24)	130 (19.70)	118 (17.85)	
9–12th grade	258 (39.15)	274 (41.45)	268 (40.61)	284 (42.97)	
More than 12th grade	240 (36.42)	240 (36.31)	262 (39.70)	259 (39.18)	
Marital Status, n (%)					0.321
Cohabitation	363 (55.08)	388 (58.70)	360 (54.55)	358 (54.16)	
Solitude	296 (44.92)	273 (41.30)	300 (45.45)	303 (45.84)	
Family PIR, n (%)					0.143
Low (≤ 1.3)	267 (40.52)	237 (35.85)	232 (35.15)	252 (38.12)	
Medium (1.3–3.5)	275 (41.73)	276 (41.75)	284 (43.03)	290 (43.87)	
High (> 3.5)	117 (17.75)	148 (22.39)	144 (21.82)	119 (18.00)	
Smoke, n (%)					0.007
Yes	332 (50.38)	351 (53.10)	344 (52.12)	392 (59.30)	
No	327 (49.62)	310 (46.90)	316 (47.88)	269 (40.70)	
Alcohol, n (%)					0.549
Yes	392 (59.48)	379 (57.34)	367 (55.61)	384 (58.09)	
No	267 (40.52)	282 (42.66)	293 (44.39)	277 (41.91)	
Physical Activity, n (%)					0.113
Inactive	117 (17.75)	93 (14.07)	104 (15.76)	85 (12.86)	
Moderate	208 (31.56)	200 (30.26)	184 (27.88)	206 (31.16)	
Vigorous	334 (50.68)	368 (55.67)	372 (56.36)	370 (55.98)	
Hypertension, n (%)					0.874
Yes	477 (72.38)	480 (72.73)	473 (71.67)	487 (73.68)	
No	182 (27.62)	180 (27.27)	187 (28.33)	174 (26.32)	
Coronary heart disease, n (%)					0.991
Yes	94 (14.26)	97 (14.67)	93 (14.09)	96 (14.52)	
No	565 (85.74)	564 (85.33)	567 (85.91)	565 (85.48)	
Stroke, n (%)					0.919
Yes	71 (10.77)	76 (11.50)	79 (11.97)	77 (11.65)	
No	588 (89.23)	585 (88.50)	581 (88.03)	584 (88.35)	
Cancer, n (%)					0.004
Yes	92 (13.96)	98 (14.83)	110 (16.67)	138 (20.88)	
No	567 (86.04)	563 (85.17)	550 (83.33)	523 (79.12)	
BMI (kg/m^2)	30.43 (26.98,35.27)	30.54 (26.90,35.72)	31.07 (27.28,36.02)	30.84 (26.33,36.71)	0.580
FPG (mg/dL)	130.00 (105.50,180.00)	137.00 (113.00,197.00)	139.00 (109.00,189.00)	138.00 (113.00,188.00)	0.006
HbA1c (%)	6.90 (6.20,8.40)	6.90 (6.20,8.40)	6.90 (6.20,8.10)	6.80 (6.20,8.10)	0.147
TC (mg/dL)	180.00 (150.00,217.00)	182.00 (156.00,219.00)	181.50 (156.00,220.25)	182.00 (152.00,214.00)	0.589
TG (mg/dL)	159.00 (103.50,244.00)	167.00 (113.00,254.00)	169.00 (114.75,251.00)	154.00 (103.00,229.00)	0.020
HDL-c (mg/dL)	45.00 (37.00,54.00)	45.00 (38.00,55.00)	45.00 (38.00,55.00)	46.00 (38.00,58.00)	0.210
Neutrophils (10^3 cells/μL)	3.20 (2.60,3.90)	4.10 (3.40,4.90)	4.80 (4.00,5.70)	5.90 (4.90,7.30)	< 0.001
Lymphocyte (10^3 cells/μL)	2.40 (1.80,2.95)	2.10 (1.70,2.60)	1.90 (1.50,2.40)	1.60 (1.20,2.00)	< 0.001
Monocyte (10^3 cells/μL)	0.50 (0.40,0.70)	0.60 (0.50,0.70)	0.60 (0.50,0.70)	0.60 (0.50,0.70)	< 0.001

Table 2 (continued)

Variables	SII				*P*
	Quartile 1 (*n* = 659)	Quartile 2 (*n* = 661)	Quartile 3 (*n* = 660)	Quartile 4 (*n* = 661)	
Platelet (10^3 cells/μL)	191.00 (156.00,228.00)	226.00 (192.00,261.00)	247.50 (206.75,291.00)	276.00 (233.00,335.00)	< 0.001
Creatinine (mg/dL)	1.10 (0.85,1.34)	1.06 (0.83,1.33)	1.05 (0.80,1.36)	1.10 (0.83,1.40)	0.633
UACR (mg/g)	60.64 (27.48,175.61)	57.78 (26.43,158.00)	57.96 (25.76,161.06)	62.94 (30.59,203.24)	0.512
eGFR (ml/min/1.73m^2)	62.64 (49.79,92.88)	64.56 (50.36,91.86)	61.23 (48.15,89.48)	61.05 (46.88,91.13)	0.180
All-cause mortality, n (%)					< 0.001
Yes	248 (37.63)	249 (37.67)	278 (42.12)	320 (48.41)	
No	411 (62.37)	412 (62.33)	382 (57.88)	341 (51.59)	
Cardiovascular mortality, n (%)					0.340
Yes	98 (14.87)	87 (13.16)	94 (14.24)	110 (16.64)	
No	561 (85.13)	574 (86.84)	566 (85.76)	551 (83.36)	
Kidney disease mortality, n (%)					0.503
Yes	9 (1.37)	16 (2.42)	14 (2.12)	11 (1.66)	
No	650 (98.63)	645 (97.58)	646 (97.88)	650 (98.34)	

Data are shown as median (25th, 75th percentiles) or percentages, $p < 0.05$ considered statistically significant

Abbreviations: SII: Systemic immune inflammation index; PIR: Poverty-to-income ratio; BMI: Body mass index; FPG: Fasting plasma-glucose; HbA1c: Hemoglobin A1c; TC: Total cholesterol; TG: Triglyceride; HDL-c: High-density lipoprotein cholesterol; UACR: Urinary albumin/creatinine ratio; eGFR: Estimated glomerular filtration rate

times that of the lowest quartile ($P=0.060$). In contrast, the risk of cardiovascular mortality in the highest quartile of patients with SIRI was 1.73 times (95% CI: 1.26–2.38) that of the lowest quartile ($P<0.001$). The risk of kidney disease mortality in patients in the highest quartile of SIRI was 2.74 times higher than that in patients in the lowest quartile ($P=0.037$). These findings indicate a robust correlation between SII and SIRI and the mortality risk in patients with DN (Table 4).

Kaplan-Meier survival curve analysis

This study analyzed the effects of SII and SIRI on all-cause mortality and cardiovascular mortality in patients with DN using Kaplan-Meier survival curves. The results demonstrated a significant correlation between all-cause mortality and increasing levels of SII and SIRI (Log-rank $P<0.001$), particularly in the highest quartile group of SII and SIRI, where the all-cause mortality was markedly elevated compared to other groups (Fig. 3A and B). Furthermore, Fig. 3C and D illustrate the correlation between SII and SIRI and cardiovascular mortality, demonstrating a tendency towards a notable increase in cardiovascular mortality with elevated index levels (SII: Log-rank $P=0.047$, SIRI: Log-rank $P<0.001$). Figure 3E and F illustrate the correlation between SII and SIRI and kidney disease mortality. There was a notable trend of increased kidney disease mortality with elevated SIRI levels (Log-rank $P=0.045$). Conversely, SII levels were not significantly associated with kidney disease mortality (Log-rank $P=0.584$). When all-cause, cardiovascular, and kidney disease mortality were considered together, the Kaplan-Meier survival plot demonstrated that patients with DN in the higher SII and SIRI quartiles exhibited a reduced probability of survival.

RCS analysis

This study further examined the dose-response relationship between SII and SIRI and all-cause mortality, cardiovascular mortality, and kidney disease mortality in patients with DN through RCS plots. After adjusting for multiple confounding variables, including gender, age, race, education, marital status, family PIR, smoking habits, drinking status, physical activity level, hypertension, coronary heart disease, stroke, and cancer, the results demonstrated a significant increasing trend in the all-cause mortality with increasing values of SII ($P<0.001$). Furthermore, the trend exhibited nonlinear characteristics ($P<0.001$). These findings are illustrated in Fig. 4A. Similarly, Fig. 4B demonstrates a positive correlation between SIRI and all-cause mortality (P for overall <0.001), although the nonlinear trend of this relationship was not statistically significant (P for nonlinear $=0.474$). Figure 4C illustrates that an increase in SII was associated with an increase in cardiovascular mortality (P for overall $=0.057$). While this trend did not reach a high level of statistical significance, its nonlinear character was not significant (P for nonlinear $=0.405$). In contrast, a significant positive correlation was observed between SIRI and cardiovascular mortality in Fig. 4D (P for overall $=0.013$), with a linear relationship between the variables (P for nonlinear $=0.785$). Furthermore, through threshold analysis, we identified the inflection point values, which were 519.2 and 1.27 for SII and SIRI, respectively. It was determined that when the inflammation indices exceeded these critical thresholds, the risk of death in inpatients with DN would significantly increase with further elevation of the index levels. Nevertheless, no notable dose-response correlation was identified

Table 3 Baseline characteristics of participants based on SIRI quartiles

Variables	SIRI				*P*
	Quartile 1 (*n* = 657)	Quartile 2 (*n* = 662)	Quartile 3 (*n* = 661)	Quartile 4 (*n* = 661)	
Gender, n (%)					< 0.001
Male	293 (44.60)	338 (51.06)	385 (58.25)	421 (63.69)	
Female	364 (55.40)	324 (48.94)	276 (41.75)	240 (36.31)	
Age (years)	64.00 (54.00,73.00)	67.00 (57.25,75.00)	69.00 (59.00,78.00)	71.00 (62.00,79.00)	< 0.001
Race, n (%)					< 0.001
Mexican American	135 (20.55)	146 (22.05)	132 (19.97)	99 (14.98)	
Non-Hispanic White	104 (15.83)	108 (16.31)	96 (14.52)	80 (12.10)	
Non-Hispanic Black	149 (22.68)	255 (38.52)	312 (47.20)	396 (59.91)	
Other Race	269 (40.94)	153 (23.11)	121 (18.31)	86 (13.01)	
Education Level, n (%)					0.085
Less than 9th grade	143 (21.77)	153 (23.11)	150 (22.69)	110 (16.64)	
9–12th grade	271 (41.25)	262 (39.58)	269 (40.70)	282 (42.66)	
More than 12th grade	243 (36.99)	247 (37.31)	242 (36.61)	269 (40.70)	
Marital Status, n (%)					0.521
Cohabitation	352 (53.58)	364 (54.98)	374 (56.58)	379 (57.34)	
Solitude	305 (46.42)	298 (45.02)	287 (43.42)	282 (42.66)	
Family PIR, n (%)					0.021
Low (≤ 1.3)	277 (42.16)	229 (34.59)	256 (38.73)	226 (34.19)	
Medium (1.3–3.5)	260 (39.57)	302 (45.62)	262 (39.64)	301 (45.54)	
High (> 3.5)	120 (18.26)	131 (19.79)	143 (21.63)	134 (20.27)	
Smoke, n (%)					< 0.001
Yes	293 (44.60)	344 (51.96)	379 (57.34)	403 (60.97)	
No	364 (55.40)	318 (48.04)	282 (42.66)	258 (39.03)	
Alcohol, n (%)					0.069
Yes	352 (53.58)	380 (57.40)	399 (60.36)	391 (59.15)	
No	305 (46.42)	282 (42.60)	262 (39.64)	270 (40.85)	
Physical Activity, n (%)					0.395
Inactive	107 (16.29)	107 (16.16)	93 (14.07)	92 (13.92)	
Moderate	204 (31.05)	208 (31.42)	185 (27.99)	201 (30.41)	
Vigorous	346 (52.66)	347 (52.42)	383 (57.94)	368 (55.67)	
Hypertension, n (%)					0.003
Yes	451 (68.65)	487 (73.68)	468 (70.80)	511 (77.31)	
No	206 (31.35)	174 (26.32)	193 (29.20)	150 (22.69)	
Coronary heart disease, n (%)					< 0.001
Yes	53 (8.07)	84 (12.69)	107 (16.19)	136 (20.57)	
No	604 (91.93)	578 (87.31)	554 (83.81)	525 (79.43)	
Stroke, n (%)					0.134
Yes	68 (10.35)	65 (9.82)	81 (12.25)	89 (13.46)	
No	589 (89.65)	597 (90.18)	580 (87.75)	572 (86.54)	
Cancer, n (%)					< 0.001
Yes	76 (11.57)	94 (14.20)	113 (17.10)	155 (23.45)	
No	581 (88.43)	568 (85.80)	548 (82.90)	506 (76.55)	
BMI (kg/m^2)	30.50 (26.70,35.10)	30.65 (26.98,36.14)	30.89 (27.20,35.92)	30.80 (26.60,36.50)	0.371
FPG (mg/dL)	137.00 (110.00,199.00)	133.50 (105.00,184.00)	136.00 (113.00,181.00)	136.00 (112.00,180.00)	0.365
HbA1c (%)	7.10 (6.30,8.90)	6.90 (6.10,8.10)	6.90 (6.30,8.20)	6.70 (6.20,7.80)	< 0.001
TC (mg/dL)	193.00 (161.00,228.00)	183.00 (156.25,223.00)	178.00 (152.00,212.00)	171.00 (147.00,204.00)	< 0.001
TG (mg/dL)	159.00 (104.00,245.00)	167.50 (111.25,260.00)	168.00 (114.00,242.00)	156.00 (105.00,230.00)	0.036
HDL-c (mg/dL)	47.00 (40.00,56.00)	45.00 (38.00,55.00)	44.00 (37.00,55.00)	44.00 (37.00,55.00)	< 0.001
Neutrophils (10^3 cells/μL)	3.20 (2.60,3.80)	4.10 (3.50,4.80)	4.90 (4.10,5.60)	6.10 (5.00,7.30)	< 0.001
Lymphocyte (10^3 cells/μL)	2.30 (1.80,2.80)	2.10 (1.60,2.70)	1.90 (1.60,2.40)	1.60 (1.20,2.10)	< 0.001
Monocyte (10^3 cells/μL)	0.40 (0.40,0.50)	0.50 (0.43,0.60)	0.60 (0.50,0.70)	0.70 (0.60,0.90)	< 0.001

Table 3 (continued)

Variables	SIRI				*P*
	Quartile 1 (*n* = 657)	Quartile 2 (*n* = 662)	Quartile 3 (*n* = 661)	Quartile 4 (*n* = 661)	
Platelet (10^3 cells/μL)	228.00 (190.00,281.00)	234.00 (193.25,283.00)	233.00 (197.00,279.00)	236.00 (190.00,284.00)	0.812
Creatinine (mg/dL)	1.00 (0.77,1.27)	1.02 (0.80,1.30)	1.10 (0.86,1.40)	1.17 (0.90,1.48)	< 0.001
UACR (mg/g)	55.06 (29.57,152.79)	60.36 (30.40,175.35)	56.90 (26.00,162.15)	67.11 (25.32,204.14)	0.230
eGFR (ml/min/1.73m^2)	72.59 (53.82,99.06)	65.93 (50.74,92.14)	59.63 (47.53,88.50)	56.57 (43.22,80.65)	< 0.001
All-cause mortality, n (%)					< 0.001
Yes	212 (32.27)	250 (37.76)	276 (41.75)	357 (54.01)	
No	445 (67.73)	412 (62.24)	385 (58.25)	304 (45.99)	
Cardiovascular mortality, n (%)					< 0.001
Yes	68 (10.35)	97 (14.65)	99 (14.98)	125 (18.91)	
No	589 (89.65)	565 (85.35)	562 (85.02)	536 (81.09)	
Kidney disease mortality, n (%)					0.204
Yes	7 (1.07)	11 (1.66)	16 (2.42)	16 (2.42)	
No	650 (98.93)	651 (98.34)	645 (97.58)	645 (97.58)	

Data are shown as median (25th, 75th percentiles) or percentages, $p < 0.05$ considered statistically significant

Abbreviations: SIRI: Systemic inflammation response index; PIR: Poverty-to-income ratio; BMI: Body mass index; FPG: Fasting plasma-glucose; HbA1c: Hemoglobin A1c; TC: Total cholesterol; TG: Triglyceride; HDL-c: High-density lipoprotein cholesterol; UACR: Urinary albumin/creatinine ratio; eGFR: Estimated glomerular filtration rate

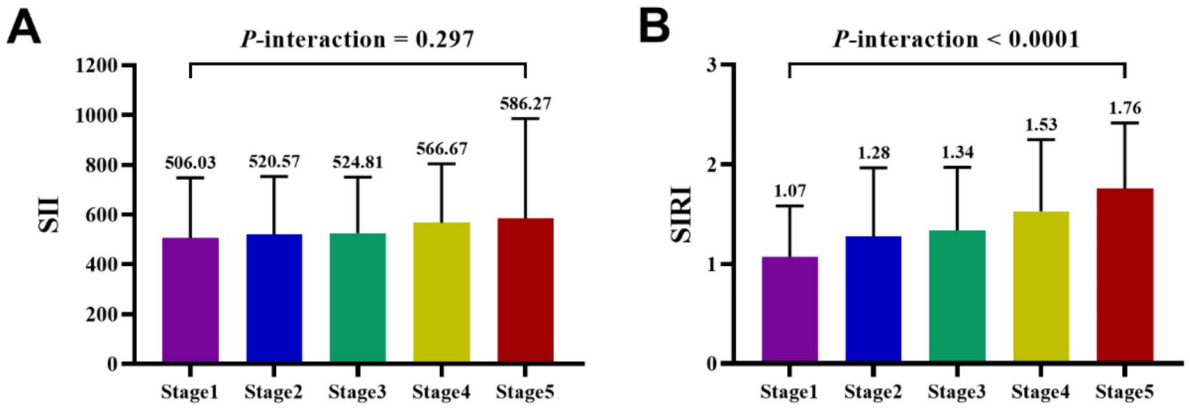

Fig. 2 Levels of SII (**A**) and SIRI (**B**) of different CKD stages in patients with diabetic nephropathy. Abbreviations: SII: Systemic immune inflammation index; SIRI: Systemic inflammation response index; CKD: chronic kidney disease

between SII and SIRI and kidney disease mortality in patients with DN, as illustrated in Fig. 4E and F.

The incremental predictions of SII and SIRI

Table 5 summarizes the incremental predictive value of SII and SIRI for all-cause mortality, cardiovascular mortality, and kidney disease mortality. In particular, incorporating SII markedly enhanced the C-statistics of the baseline model for all-cause mortality and cardiovascular mortality ($P < 0.05$). Similarly, the introduction of SIRI significantly optimized the C-statistics of the baseline model for all-cause mortality, cardiovascular mortality, and kidney disease mortality ($P < 0.05$). Furthermore, when SII and SIRI were integrated into the baseline model, not only did the model's predictive performance improve, but a significant enhancement in risk reclassification for all-cause mortality and cardiovascular mortality was also achieved (Table 5).

Subgroup analysis

Further subgroup analyses of patients with DN revealed an association between the SII and the SIRI with all-cause mortality, cardiovascular mortality, and kidney disease mortality. In the study of all-cause mortality, elevated levels of SII were found to elevate the risk of mortality significantly. This association was observed to be consistent across various demographic subgroups, including gender, marital status, smoking habits, alcohol consumption habits, physical activity level, hypertension, coronary artery disease, stroke, and cancer status (*P* for interaction > 0.05).

Table 4 Relationships between SII, SIRI, and mortality in participants with diabetic nephropathy

Variables	Model 1		Model 2		Model 3	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
All-cause mortality						
SII	1.01 (1.01 ~ 1.01)	**< 0.001**	1.01 (1.01 ~ 1.01)	**< 0.001**	1.01 (1.01 ~ 1.01)	**< 0.001**
Categories						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	0.99 (0.83 ~ 1.18)	0.901	1.04 (0.87 ~ 1.24)	0.702	1.04 (0.87 ~ 1.24)	0.702
Quartile 3	1.12 (0.95 ~ 1.33)	0.183	1.08 (0.91 ~ 1.29)	0.370	1.08 (0.91 ~ 1.29)	0.370
Quartile 4	1.47 (1.24 ~ 1.73)	**< 0.001**	1.49 (1.26 ~ 1.77)	**< 0.001**	1.49 (1.26 ~ 1.77)	**< 0.001**
SIRI	1.20 (1.16 ~ 1.24)	**< 0.001**	1.16 (1.11 ~ 1.21)	**< 0.001**	1.16 (1.11 ~ 1.21)	**< 0.001**
Categories						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.22 (1.02 ~ 1.46)	**0.034**	1.13 (0.93 ~ 1.36)	0.212	1.13 (0.93 ~ 1.36)	0.212
Quartile 3	1.40 (1.17 ~ 1.68)	**< 0.001**	1.12 (0.93 ~ 1.35)	0.251	1.12 (0.93 ~ 1.35)	0.251
Quartile 4	2.15 (1.81 ~ 2.54)	**< 0.001**	1.62 (1.35 ~ 1.95)	**< 0.001**	1.62 (1.35 ~ 1.95)	**< 0.001**
Cardiovascular mortality						
SII	1.01 (1.01 ~ 1.01)	**0.002**	1.01 (1.01 ~ 1.01)	**0.011**	1.01 (1.01 ~ 1.01)	**0.011**
Categories						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	0.87 (0.66 ~ 1.17)	0.363	0.92 (0.69 ~ 1.24)	0.589	0.92 (0.69 ~ 1.24)	0.589
Quartile 3	0.96 (0.72 ~ 1.28)	0.782	0.92 (0.69 ~ 1.24)	0.592	0.92 (0.69 ~ 1.24)	0.592
Quartile 4	1.28 (0.97 ~ 1.67)	0.080	1.31 (0.99 ~ 1.74)	0.060	1.31 (0.99 ~ 1.74)	0.060
SIRI	1.19 (1.12 ~ 1.27)	**< 0.001**	1.14 (1.06 ~ 1.23)	**< 0.001**	1.14 (1.06 ~ 1.23)	**< 0.001**
Categories						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.47 (1.08 ~ 2.01)	**0.014**	1.35 (0.98 ~ 1.86)	0.062	1.35 (0.98 ~ 1.86)	0.062
Quartile 3	1.57 (1.15 ~ 2.14)	**0.004**	1.22 (0.89 ~ 1.69)	0.219	1.22 (0.89 ~ 1.69)	0.219
Quartile 4	2.34 (1.74 ~ 3.15)	**< 0.001**	1.73 (1.26 ~ 2.38)	**< 0.001**	1.73 (1.26 ~ 2.38)	**< 0.001**
Kidney disease mortality						
SII	1.00 (1.00 ~ 1.00)	0.161	1.00 (1.00 ~ 1.00)	0.274	1.00 (1.00 ~ 1.00)	0.181
Categories						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.75 (0.77 ~ 3.96)	0.179	2.02 (0.89 ~ 4.61)	0.093	1.88 (0.82 ~ 4.35)	0.138
Quartile 3	1.56 (0.68 ~ 3.61)	0.295	1.72 (0.73 ~ 4.03)	0.214	1.80 (0.76 ~ 4.26)	0.178
Quartile 4	1.39 (0.58 ~ 3.36)	0.461	1.63 (0.66 ~ 4.00)	0.288	1.61 (0.65 ~ 4.00)	0.304
SIRI	1.24 (1.06 ~ 1.44)	**0.007**	1.23 (1.04 ~ 1.47)	**0.018**	1.25 (1.04 ~ 1.51)	**0.017**
Categories						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.63 (0.63 ~ 4.21)	0.312	1.82 (0.70 ~ 4.76)	0.221	1.61 (0.60 ~ 4.33)	0.344
Quartile 3	2.47 (1.02 ~ 6.01)	**0.046**	2.60 (1.04 ~ 6.52)	**0.042**	2.43 (0.96 ~ 6.13)	0.061
Quartile 4	2.94 (1.21 ~ 7.15)	**0.017**	3.04 (1.19 ~ 7.75)	**0.020**	2.74 (1.06 ~ 7.08)	**0.037**

The bold values indicated statistically significant

Model 1: crude

Model 2: adjusted for Gender, Age, Race

Model 3: adjusted for Gender, Age, Race, Education Level, Marital Status, Family PIR, Smoke, Alcohol, Physical Activity, Hypertension, Coronary heart disease, Stroke, Cancer

Abbreviations: SII: Systemic immune inflammation index; SIRI: Systemic inflammation response index; HR: Hazard ratio; CI: Confidence interval

In the race subgroup, the positive association between SII and all-cause mortality was more pronounced in Mexican American and Non-Hispanic Black participants (*P* for interaction = 0.016). In the subgroup defined by education level, the positive association between SII and all-cause mortality was more pronounced among those with higher education levels (*P* for interaction = 0.024). The positive association between SII and all-cause mortality in the family PIR subgroup was more significant in the lower income group (*P* for interaction = 0.026). The correlation between SIRI and risk of all-cause mortality varied across subgroups. Still, no significant differences were observed in the between-group comparisons of any of the subgroups (*P* for interaction > 0.05). In the analysis

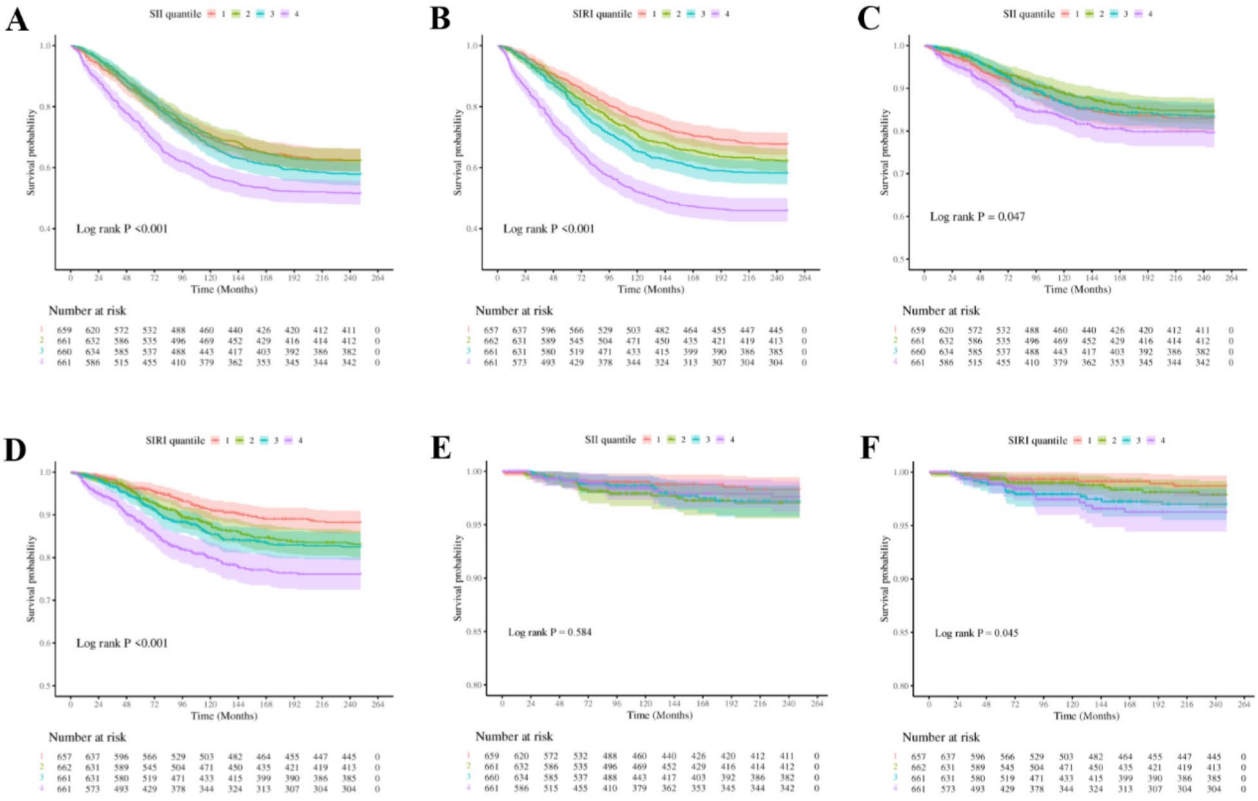

Fig. 3 Kaplan–Meier curves illustrating the effect of the SII and SIRI on mortality outcomes. **A**, **B**: Kaplan–Meier curves for all-cause mortality stratified by the SII and SIRI. **C**, **D**: Kaplan–Meier curves for cardiovascular mortality stratified by the SII and SIRI. **E**, **F**: Kaplan–Meier curves for kidney disease mortality stratified by the SII and SIRI. In the Kaplan-Meier curves, the population is stratified into four groups based on the quartiles of SII and SIRI, and statistical analysis is conducted using the log-rank test. Abbreviations: SII: Systemic immune inflammation index; SIRI: Systemic inflammation response index

of cardiovascular mortality and kidney disease mortality, the correlation between the risk of death for SII and SIRI differed across subgroups. However, none of the comparisons between subgroups reached statistical significance (*P* for interaction > 0.05) (Additional file 1: Table S1-Table S6).

Discussion

This study investigated the association between SII and SIRI with mortality in patients with DN. The results of the multivariate Cox regression analysis indicated that for each unit increase in SII and SIRI levels, the risk of all-cause mortality increased by 1% and 16%, respectively, and the risk of cardiovascular mortality increased by 1% and 14%, respectively, in patients with DN. For each unit increase in SIRI levels, there was a 25% increased risk of kidney disease mortality. Furthermore, the risk of all-cause mortality in patients in the highest quartile for SII and SIRI was 1.49 and 1.62 times higher, respectively, than that in patients in the lowest quartile. Similarly, the risk of cardiovascular mortality in patients in the highest quartile for SII and SIRI was 1.31 and 1.73 times that of patients in the lowest quartile. The risk of kidney disease mortality in patients in the highest quartile of SIRI was 2.74 times higher than that in patients in the lowest quartile. Moreover, Kaplan-Meier survival curves and RCS analysis confirmed the positive association between SII and SIRI and mortality. The results of the incremental prediction analyses indicated that incorporating SII and SIRI into the baseline model could lead to a notable enhancement in predicting mortality risk among patients with DN. These findings indicate that SII and SIRI may serve as biomarkers for predicting the risk of death in patients with DN.

SII and SIRI are emerging as comprehensive indicators integrating three separate leukocyte subpopulations and platelet counts to provide a comprehensive picture of the body's inflammatory state and immune response [10–12]. Compared to conventional indices such as the platelet-to-lymphocyte ratio (PLR) and the neutrophil-to-lymphocyte ratio (NLR), SII and SIRI have exhibited enhanced reliability and are more indicative of the inflammatory state and thrombotic risk [21, 22]. A substantial body of existing research has demonstrated a robust correlation between SII and SIRI and the prognosis of various diseases. Specifically, elevated SII levels have been linked to

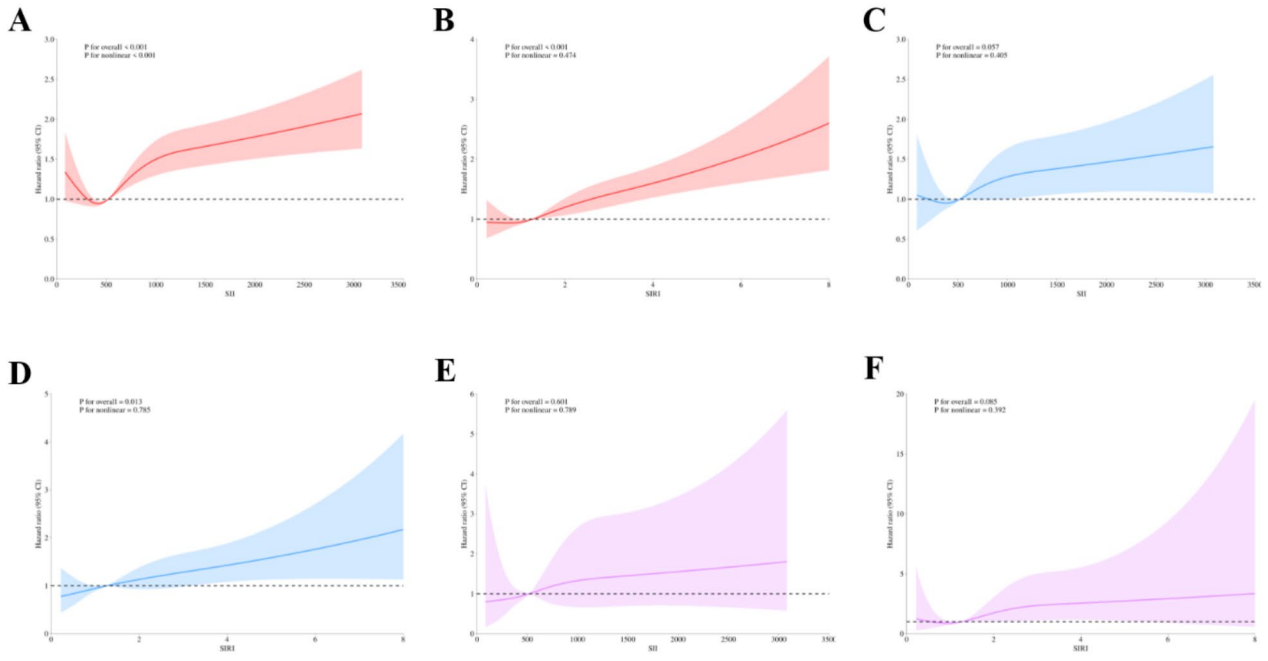

Fig. 4 Restricted cubic spline fitting for the association between mortality and the SII and SIRI. **A**, **B**: all-cause mortality according to the SII and SIRI; **C**, **D**: cardiovascular mortality according to the SII and SIRI. **E**, **F**: kidney disease mortality according to the SII and SIRI. Solid lines indicate HR, and shaded areas indicate 95% CI. These analyses were adjusted according to Model 3. Abbreviations: SII: Systemic immune inflammation index; SIRI: Systemic inflammation response index; HR: Hazard ratio; CI: Confidence interval

Table 5 Incremental predictive power of SII and SIRI for mortality in patients with diabetic nephropathy

	C-statistic	*P*	NRI	*P*	IDI	*P*
All-cause mortality						
Baseline model	0.746		Reference		Reference	
Baseline model + SII	0.758	**< 0.001**	0.038	**0.001**	0.019	0.112
Baseline model + SIRI	0.756	**0.003**	0.024	**0.038**	0.023	0.054
Cardiovascular mortality						
Baseline model	0.665		Reference		Reference	
Baseline model + SII	0.683	**0.021**	0.054	**0.012**	0.025	0.132
Baseline model + SIRI	0.684	**0.017**	0.054	**0.014**	0.026	0.121
Kidney disease mortality						
Baseline model	0.657		Reference		Reference	
Baseline model + SII	0.698	0.189	0.022	0.757	-0.006	0.733
Baseline model + SIRI	0.703	**0.047**	0.062	0.297	0.003	0.863

The bold values indicated statistically significant

Abbreviations: SII: Systemic immune inflammation index; SIRI: Systemic inflammation response index; NRI: Net reclassification improvement; IDI: Integrated discrimination improvement

unfavorable outcomes in patients with coronary artery disease [13]. At the same time, both SII and SIRI have been identified as independent predictors of functional prognosis in patients with cerebral hemorrhage and acute ischemic stroke [16, 23]. In patients with chronic heart failure, there was a significant correlation between SIRI and SII and the risk of mortality [24]. Elevated preoperative SII and SIRI levels were found to be strongly associated with an increased risk of mortality in patients presenting with acute ST-segment elevation myocardial infarction [17, 25]. Moreover, additional research has demonstrated that SII and SIRI are significantly correlated with the risk of developing cardiovascular disease and the risk of mortality from any cause [26, 27]. In patients with chronic kidney disease, there was a robust correlation between SII and SIRI levels and mortality [28, 29]. It is noteworthy that in the obese population, SIRI and SII have been identified as independent risk factors for all-cause mortality and cardiovascular mortality [30]. Moreover, studies conducted in the general population

have also identified a significant association between SII and all-cause mortality and cardiovascular mortality [31]. Nevertheless, the current body of research evidence on the role of SII versus SIRI in all-cause and cardiovascular mortality in patients with DN remains insufficient. Our study effectively addresses this knowledge gap and provides a new empirical basis that emphasizes the critical role of SII and SIRI in mortality in patients with DN.

The findings of this study further substantiate the critical role of the inflammatory response in the pathogenesis of DN. Various pathological processes in DN are associated with inflammation, including tubular fibrosis, inflammatory cell infiltration, extracellular matrix accumulation, and podocyte autophagy [32, 33]. Elevated levels of SII and SIRI may indicate a persistent inflammatory response in the body. This inflammatory response is not only directly involved in the pathophysiological processes of DN, such as promoting glomerulosclerosis and tubulointerstitial fibrosis, but also may further exacerbate renal damage by activating oxidative stress, induction of apoptosis, and other pathways. This further increases the risk of death in patients [34–36]. Furthermore, the inflammatory response may be closely associated with the development of other chronic complications, such as hypertension, coronary artery disease, and stroke. This can create a vicious cycle that collectively endangers the lives of patients [37]. Furthermore, inflammation is intricately linked to the pathogenesis of cardiovascular diseases such as atherosclerosis and thrombosis. This may indirectly impact the prognosis of patients with DN by increasing the risk of cardiovascular events [38]. The present study revealed a positive correlation between elevated SIRI and CKD stage, indicating that SIRI levels increased significantly as CKD worsened. This finding further corroborates the hypothesis that systemic inflammation may play a pivotal role in the progression of DN.

The dose-response relationship between SII and SIRI and mortality in patients with DN was further investigated through RCS modeling. The results demonstrated a statistically significant nonlinear relationship between SII and all-cause mortality, whereas the relationship between SIRI and all-cause and cardiovascular mortality tended to be linear. This finding offers a novel perspective for more comprehensively understanding the prognostic role of SII and SIRI in patients with DN. When evaluating the predictive value of SII and SIRI, it is recommended that consideration be given not only to their absolute levels but also to their trends and dose effects.

The incremental prediction analysis revealed that incorporating SII markedly enhanced the predictive precision of the baseline model for all-cause mortality and cardiovascular mortality. Furthermore, the introduction of SIRI also positively impacted the predictive performance of the baseline model, significantly improving the prediction accuracy of all-cause mortality and extending it to the prediction of cardiovascular mortality and kidney disease mortality. Furthermore, the joint application of SII and SIRI to the baseline model resulted in a significant enhancement in the risk reclassification ability of the model for all-cause mortality and cardiovascular mortality. This indicates that combining these two metrics enables the more accurate identification of patients in different risk tiers, thereby facilitating the implementation of personalized risk management strategies in clinical decision-making.

Additionally, this study identified that the relationships between SII and SIRI and the mortality risk in patients with DN exhibited some degree of heterogeneity across different subgroups. For instance, the correlation between SII and all-cause mortality were more pronounced in Mexican American and Non-Hispanic Black participants, participants with higher education levels, and participants with lower family PIR. In contrast, in the analysis of cardiovascular mortality and kidney disease mortality, although the associations of SII and SIRI differed across subgroups, none exhibited significant intergroup discrepancies. These findings indicate the necessity of considering individual differences and clinical characteristics when assessing the predictive value of SII and SIRI to develop a more precise risk assessment strategy. Furthermore, this study offers a novel foundation for future research endeavors. It may delve deeper into the predictive value of SII and SIRI and their underlying mechanisms across diverse patient subgroups.

The present study demonstrated a significant positive correlation between SII and SIRI levels and mortality in patients with DN. This finding underscores the potential of SII and SIRI as valuable biomarkers for evaluating the prognosis of patients with DN. By integrating multiple leukocyte counts, SII and SIRI can reflect the body's inflammatory state and immune function more comprehensively, thereby enabling more accurate prediction of the risk of death in patients. This result expands our understanding of prognostic factors in DN and provides a scientific basis for clinicians to develop more individualized treatment plans and follow-up strategies. Furthermore, SII and SIRI are well-suited for large-scale screening and routine monitoring, as they are readily accessible, cost-effective, and indicate systemic inflammatory status [10, 12]. They have a broad range of applications in both clinical and research settings.

It should be noted that this study is not without limitations. First, although the NHANES database provides large-scale cross-sectional survey data, there may be potential limitations, such as bias in data collection and imperfect handling of missing values. Furthermore, the findings may not fully apply in other countries and regions, given that the data were derived from the U.S.

population. Secondly, this study was observational and, therefore, unable to directly infer a causal relationship between SII and SIRI and mortality in patients with DN. Third, despite using various statistical techniques to minimize the impact of confounding factors, it was not feasible to eliminate the potential for unknown variables to influence the results. Fourth, although the study followed up on data through December 31, 2019, the follow-up period may still be insufficient for some patients to reflect their long-term prognosis fully. Furthermore, the scope of the database survey was limited, which prevented the inclusion of additional factors such as B-type natriuretic peptide and C-reactive protein in the comparative study. This, in turn, impacts the comprehensive evaluation of the predictive capacity of SII and SIRI. Ultimately, while the study examined the correlation between SII and SIRI and mortality in patients with DN, as well as the underlying mechanisms, further comprehensive investigations are necessary to elucidate the precise mechanisms through which these biomarkers contribute to the progression of DN.

Conclusion

In conclusion, this study's findings offer preliminary evidence that SII and SIRI may predict mortality risk in patients with DN. The clinical application of these biomarkers can potentially enhance these patients' prognostic assessment and management. Further research is required to elucidate SII and SIRI's mechanistic role in DN and determine the most effective means of applying these indicators in clinical practice.

Abbreviations

BMI	Body mass index
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CKD	Chronic kidney disease
DM	Diabetes mellitus
DN	Diabetic nephropathy
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
FPG	Fasting plasma-glucose
HbA1c	Hemoglobin A1c
HDL-c	High-density lipoprotein cholesterol
HR	Hazard ratio
IDI	Integrated discriminant improvement
MEC	Mobile Examination Center
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
NLR	Neutrophil-to-lymphocyte ratio
NRI	Net reclassification improvement
PIR	Poverty-to-Income Ratio
PLR	Platelet-to-lymphocyte ratio
PLT	Platelet count
RCS	Restricted cubic spline
SII	Systemic immune-inflammation index
SIRI	Systemic inflammation response index
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TC	Total cholesterol
TG	Triglyceride
UACR	Urine albumin-to-creatinine ratio

Supplementary Information

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Supplementary Material 1

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Author contributions

Conceptualization and methodology, F.Z. and W.L.; project administration, data curation, and investigation, F.Z., Y.M., and Y.H.; formal analysis, F.Z. and W.L.; visualization and supervision, W.L.; Writing - original draft, F.Z. and Y.H.; Writing - review and editing, W.L.; funding acquisition, F.Z.; All authors have read and agreed to the published version of the manuscript.

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Data availability

The National Health and Nutrition Examination Survey dataset is publicly available at the National Center for Health Statistics of the Centers for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes/index.htm).

Declarations

Ethics approval and consent to participate

The studies involving humans were approved by National Center for Health Statistics Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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