Journal of Inflammation Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Association of Systemic Immune Inflammation Index with All-Cause, Cardiovascular Disease, and Cancer-Related Mortality in Patients with Cardiovascular Disease: A Cross-Sectional Study

Shengjue Xiao[1,*], Zhenwei Wang[1,*], Ronghua Zuo[2,*], Yufei Zhou[3], Yiqing Yang[1], Tian Chen[1], Naifeng Liu[1]

[1]Department of Cardiology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, People's Republic of China; [2]Department of Anesthesiology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, People's Republic of China; [3]Department of Cardiology, Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital and Institutes of Biomedical Sciences, Fudan University, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Naifeng Liu, Department of Cardiology, Zhongda Hospital, School of Medicine, Southeast University, 87 Dingjiaqiao, Nanjing, 210009, People's Republic of China, Tel +86 025 8327 2002, Email liunf@seu.edu.cn

Objective: Our research was designed to investigate the relationship between systemic immune inflammation (SII) index and all-cause, cardiovascular disease (CVD), and cancer-related mortality in patients with CVD.

Methods: We used the National Health and Nutrition Examination Survey data from 1999 to 2018 to conduct this study. The association between SII index and all-cause, CVD, and cancer-related mortality in patients with CVD was examined using restricted cubic splines (RCS), Cox proportional hazard models, and subgroup analysis, respectively. CVD was defined as a composite of five outcomes of CVD, including coronary heart disease (CHD), congestive heart failure (CHF), angina pectoris, myocardial infarction, and stroke. Additionally, the link between SII index and all-cause, CVD, and cancer-related mortality in patients with a composite of five outcomes of CVD was also explored.

Results: In total, 5329 participants were included. The RCS also showed a U-curve correlation between SII index and the all-cause, CVD, and cancer-related mortality in patients with CVD. As compared with the individuals with lowest quartile of SII index, hazard ratios with 95% confidence intervals for all-cause, CVD, and cancer-related mortality across the quartiles were (1.202 (0.981, 1.474), 1.184 (0.967, 1.450), and 1.365 (1.115, 1.672)), (1.116 (0.815, 1.527), 1.017 (0.740, 1.398), and 1.220 (0.891, 1.670)), and (1.202 (0.981, 1.474), 1.184 (0.967, 1.450), and 1.365 (1.115, 1.672)), respectively, in the full-adjusted model. The SII index also had a U-shaped relationship with all-cause, CVD, and cancer-related mortality in patients with CHD, angina, and myocardial infarction. Additionally, the U-shaped relationship between SII index and all-cause, and cancer-related mortality also exists in CHF, and stroke. However, there was a positive linear correlation between SII index and CVD mortality in patients with CHF, and stroke.

Conclusion: In the United States general population, the correlation between SII index and all-cause, CVD, and cancer-related mortality showed a U-shaped curve in patients with CVD.

Keywords: all-cause mortality, cross-sectional study, cardiovascular disease mortality, cancer-related mortality, systemic immune inflammatory index

Introduction

Worldwide, cardiovascular diseases (CVD) are responsible for nearly one-third of all deaths and account for the majority of disease burdens.[1,2] There are many types of CVD, including heart vascular diseases, heart structure and function diseases, heart conduction system diseases.[3] Among them, congestive heart failure (CHF), coronary heart disease (CHD), angina pectoris, myocardial infarction (MI), and stroke are all CVD. Systemic inflammation caused by metabolic or

Received: 6 January 2023
Accepted: 24 February 2023
Published: 6 March 2023

immunological conditions is strongly linked to cardiovascular disease.[4] In addition, after CVD, cancer is the second leading cause of death in the world.[5] Similar to CVD, chronic inflammation is often associated with cancer initiation and progression.[6]

Systemic immune inflammation (SII) index is a measure of systemic inflammation based on neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio and has been shown to be promising.[7,8] There is a correlation between changes in gene expression in peripheral blood cells and various forms of systemic inflammation and immunosuppression, such as CVD.[9] Wingrove JA has found that peripheral-blood cell gene expression reflects coronary artery disease (CAD) severity and presence.[10] In addition, an analysis of gene expression and demographic characteristics could be useful for identifying obstructive CAD among nondiabetics without known CAD.[11] Deng MC and his team revealed that the expression of genes in peripheral blood mononuclear cells can be used to detect moderate/severe rejection in cardiac allograft recipients.[12] Additionally, Baechler EC also found global gene expression profiling of peripheral blood mononuclear cells was used to identify distinct gene expression patterns that differentiate most systemic lupus erythematosus patients from healthy controls.[13] A recent study shows major cardiovascular events after coronary intervention were better predicted by SII index than traditional risk factors in CAD patients.[14] In addition, the SII index has recently been shown to have independent prognostic value in several cancer types.[15] Silva-Vaz P also found that SII index is exclusively used for assessing prognosis and therapeutic outcomes in a variety of cancers.[16]

At present, the relationship between SII index and mortality (all-cause, cardiovascular disease (CVD), and cancer) is unclear in United States (US) general population. Therefore, SII index in population-based cohorts throughout the US general population was analyzed using the National Health and Nutrition Examination Survey (NHANES) 1999–2018 to explore the association of SII index with all-cause mortality, CVD, and cancer-related mortality.

Materials and Methods

Study Population

The current cross-sectional research was based on the NHANES, a survey of nutrition and health in the United States that is representative nationwide.[17] In the total sample of 106,203 participants, there were 11,312 without SII index data. Furthermore, we excluded participants who did not have CVD data (n =88,259) and mortality data (n =1303). Finally, 5329 participants were included in the final analysis. The NHANES website (https://www.cdc.gov/nchs/nhanes/) has comprehensive information on the survey's design, methodology, and statistics. The National Center for Health Statistics Research Ethics Review Board approved all protocols, and informed permission was acquired from all participants included in the investigation.[18]

Calculation of the SII Index

The blood samples were collected from fasting participants in the study. The automated hematology analyzing devices (Coulter® DxH 800 analyzer) were used to measure blood count (neutrophil, lymphocyte, and platelet counts). In this study, we calculated SII index for each participant as follows: SII index ($\times 10^9$/L) = neutrophil count ($\times 10^9$/L)/lymphocyte count ($\times 10^9$/L) × platelet count ($\times 10^9$/L).[19] Furthermore, SII index was categorized into quartiles: Q1 (4.056–349.500), Q2 (349.501–508.800), Q3 (508.801–736.154), and Q4 (376.155–11,700.000).

All-Cause, CVD, and Cancer-Related Mortality

Overall mortality was the primary outcome and defined as death due to any cause during follow-up, including diseases of heart (I00-I09, I11, I13, I20-I51), malignant neoplasms (C00-C97), chronic lower respiratory diseases (J40-J47), accidents (unintentional injuries) (V01-X59, Y85-Y86), cerebrovascular diseases (I60-I69), Alzheimer's disease (G30), Diabetes mellitus (E10-E14), influenza and pneumonia (J09-J18), nephritis, nephrotic syndrome and nephrosis (N00-N07, N17-N19, N25-N27), all other causes (residual). Follow-up commenced at the baseline examination date. CVD mortality was considered as the secondary outcome and included death due to diseases of heart (I00-I09, I11, I13, I20-I51). The comprehensive information on this program and its procedures were published on the NHANES website (https://www.cdc.gov/nchs/nhanes/).

Table 1 Characteristics of the Study Population Based on SII Index Quartiles

SII Index	Total	Q1	Q2	Q3	Q4	*P*-value
Age, years	64.70 ± 0.29	64.24 ± 0.45	63.58 ± 0.54	64.91 ± 0.47	66.12 ± 0.55	0.006
Sex, %						0.005
Male	2997 (56.2%)	784 (15.1%)	736 (13.8%)	736 (13.8%)	717 (13.5%)	
Female	2332 (43.8%)	549 (10.3%)	572 (10.7%)	596 (11.2%)	615 (11.5%)	
Race/ethnicity, %						< 0.001
Mexican American	594 (11.1%)	133 (2.5%)	161 (3.0%)	161 (3.0%)	139 (2.6%)	
Other Hispanic	326 (6.1%)	92 (1.7%)	86 (1.6%)	79 (1.5%)	69 (1.3%)	
Non-Hispanic Black	1106 (20.8%)	417 (7.8%)	269 (5.0%)	236 (4.4%)	184 (3.5%)	
Non-Hispanic White	3000 (56.3%)	600 (11.3%)	736 (13.8%)	797 (15.0%)	867 (16.3%)	
Other race	303 (5.7%)	91 (1.7%)	80 (1.5%)	59 (1.1%)	73 (1.4%)	
Family PIR	2.57 ± 0.04	2.67 ± 0.07	2.65 ± 0.06	2.60 ± 0.06	2.37 ± 0.06	< 0.001
Education level, %						0.664
High school	1892 (35.5%)	489 (9.2%)	484 (9.1%)	460 (8.6%)	459 (8.6%)	
College	558 (10.5%)	160 (3.0%)	136 (10.2%)	141 (10.6%)	121 (2.3%)	
Graduate	2879 (54.0%)	684 (12.8%)	712 (13.4%)	731 (13.7%)	752 (14.1%)	
Marital status, %						<0.001
Having a partner	2876 (55.8%)	759 (14.2%)	798 (15.0%)	731 (13.7%)	688 (12.9%)	
No partner	1988 (37.3%)	469 (8.8%)	453 (8.5%)	514 (9.6%)	552 (10.4%)	
Unmarried	365 (6.8%)	105 (2.0%)	81 (1.5%)	87 (1.6%)	92 (1.7%)	
Hypertension, %						0.010
No	1048 (19.7%)	257 (4.8%)	300 (5.6%)	254 (4.8%)	237 (4.4%)	
Yes	4281 (80.3%)	1076 (20.2%)	1032 (19.4%)	1078 (20.2%)	1095 (20.5%)	
DM, %						0.203
No	3214 (60.3%)	817 (15.3%)	819 (15.4%)	798 (15.0%)	780 (14.6%)	
Yes	2115 (39.7%)	516 (9.7%)	513 (9.6%)	534 (10.0%)	552 (10.4%)	
Smoker, %						0.339
No	2106 (39.5%)	567 (10.6%)	536 (10.1%)	526 (9.9%)	477 (9.0%)	
Former	2167 (40.7%)	507 (9.5%)	552 (10.4%)	530 (9.9%)	578 (10.8%)	
Now	1056 (19.8%)	259 (4.9%)	244 (4.6%)	276 (5.2%)	277 (5.2%)	
Alcohol user, %						0.078
Never	830 (15.6%)	209 (3.9%)	209 (3.9%)	222 (4.2%)	190 (3.6%)	
Former	1745 (32.7%)	406 (7.6%)	416 (7.8%)	427 (8.0%)	496 (9.3%)	
Mild	1797 (33.7%)	469 (8.8%)	453 (8.5%)	457 (8.6%)	418 (7.8%)	
Moderate	432 (8.1%)	114 (2.1%)	113 (2.1%)	95 (1.8%)	110 (2.1%)	
Heavy	525 (9.9%)	135 (2.5%)	141 (2.6%)	131 (2.5%)	118 (2.2%)	
CVD, %						< 0.001
No	4364 (81.9%)	1140 (21.4%)	1091 (20.5%)	1101 (20.7%)	1032 (19.4%)	
Yes	965 (18.1%)	193 (3.6%)	241 (18.1%)	231 (4.3%)	300 (5.6%)	
CHD, %						0.563
No	3337 (62.6%)	823 (15.4%)	823 (15.4%)	831 (15.6%)	860 (16.1%)	
Yes	1992 (37.4%)	510 (9.6%)	509 (38.2%)	501 (9.4%)	472 (8.9%)	
CHF, %						0.011
No	3796 (71.2%)	958 (18.0%)	980 (18.4%)	963 (18.1%)	895 (16.8%)	
Yes	1533 (28.8%)	375 (7.0%)	352 (6.6%)	369 (6.9%)	437 (8.2%)	
Angina pectoris						0.597
No	3955 (74.2%)	981 (18.4%)	992 (18.6%)	993 (18.6%)	989 (18.6%)	
Yes	1374 (25.8%)	352 (6.6%)	340 (6.4%)	339 (6.4%)	343 (6.4%)	
MI						0.620
No	3228 (60.6%)	795 (14.9%)	802 (15.0%)	842 (15.8%)	789 (14.8%)	
Yes	2101 (39.4%)	538 (10.1%)	530 (9.9%)	490 (9.2%)	543 (10.2%)	
Stroke, %						0.059
No	3456 (64.9%)	904 (17.0%)	846 (15.9%)	855 (16.0%)	851 (16.0%)	
Yes	1873 (35.1%)	429 (8.1%)	486 (9.1%)	477 (9.0%)	481 (9.0%)	
BMI, kg/m^2	30.21 ± 0.13	30.01 ± 0.20	30.11 ± 0.23	30.53 ± 0.28	30.16 ± 0.26	0.496
Waist circumference, cm	105.27 ± 0.31	104.97 ± 0.46	104.87 ± 0.56	106.03 ± 0.68	105.20 ± 0.56	0.524
SBP, mmHg	130.24 ± 0.40	129.99 ± 0.78	129.60 ± 0.76	130.98 ± 0.75	130.41 ± 0.75	0.608

(*Continued*)

Table 1 (Continued).

SII Index	Total	Q1	Q2	Q3	Q4	*P*-value
DBP, mmHg	68.44 ± 0.28	69.10 ± 0.48	68.78 ± 0.52	68.94 ± 0.51	66.90 ± 0.48	0.003
FBG, mg/mL	119.46 ± 0.76	117.82 ± 1.17	119.38 ± 1.74	119.85 ± 1.47	120.75 ± 1.47	0.476
HbA1c, %	6.06 ± 0.02	6.01 ± 0.04	6.09 ± 0.05	6.06 ± 0.04	6.09 ± 0.04	0.415
CRP, mg/dL	2.16 ± 0.13	1.54 ± 0.16	1.96 ± 0.27	2.31 ± 0.17	2.85 ± 0.33	0.001
Mean Energy Intake, kcal	1880.65 ± 15.67	1903.52 ± 31.80	1920.30 ± 29.73	1903.72 ± 29.03	1791.66 ± 24.27	< 0.001
AST, U/L	25.45 ± 0.26	27.74 ± 0.50	25.31 ± 0.50	24.67 ± 0.56	24.16 ± 0.52	< 0.001
ALT, U/L	24.06 ± 0.36	25.80 ± 0.59	24.39 ± 0.68	23.11 ± 0.71	23.02 ± 1.06	0.008
Albumin, g/L	41.42 ± 0.07	41.61 ± 0.13	41.81 ± 0.12	41.48 ± 0.14	40.74 ± 0.15	< 0.001
Hb, g/dL	14.02 ± 0.04	14.03 ± 0.06	14.16 ± 0.07	14.11 ± 0.06	13.76 ± 0.07	< 0.001
Plt, 1000 cells/ul	236.69 ± 1.49	191.22 ± 1.80	223.03 ± 1.95	245.12 ± 2.16	287.15 ± 2.86	< 0.001
Lym, 1000 cells/ul	2.10 ± 0.04	2.77 ± 0.16	2.11 ± 0.03	1.92 ± 0.02	1.61 ± 0.02	< 0.001
Neu, 1000 cells/ul	4.55 ± 0.03	3.27 ± 0.04	4.05 ± 0.03	4.79 ± 0.04	6.08 ± 0.07	< 0.001
BUN, mg/dL	17.33 ± 0.14	16.52 ± 0.24	16.96 ± 0.26	17.43 ± 0.27	18.41 ± 0.33	< 0.001
UA, mg/dL	5.92 ± 0.03	5.93 ± 0.05	5.82 ± 0.05	5.91 ± 0.06	6.02 ± 0.06	0.071
Scr, mg/dL	1.06 ± 0.01	1.06 ± 0.02	1.01 ± 0.01	1.06 ± 0.02	1.14 ± 0.02	< 0.001
eGFR, mL/min/1.73m^2	74.15 ± 0.41	75.97 ± 0.80	76.43 ± 0.88	73.64 ± 0.86	70.49 ± 0.83	< 0.001
TC, mg/dL	186.40 ± 0.99	185.63 ± 1.72	186.11 ± 1.79	186.37 ± 1.83	187.52 ± 1.76	0.895
TG, mg/dL	151.62 ± 2.08	148.61 ± 4.37	153.30 ± 4.17	153.72 ± 3.42	150.59 ± 2.98	0.753
HDL-C, mg/dL	50.25 ± 0.33	50.62 ± 0.66	49.70 ± 0.57	49.99 ± 0.59	50.74 ± 0.53	0.437
All-cause mortality, %						<0.001
No	2981 (55.9%)	870 (16.3%)	777 (14.6%)	756 (14.2%)	578 (10.8%)	
Yes	2348 (44.1%)	463 (8.7%)	555 (10.4%)	576 (10.8%)	754 (14.1%)	
CVD mortality, %						<0.001
No	4364 (81.9%)	1140 (21.4%)	1091 (20.5%)	1101 (20.7%)	1032 (19.4%)	
Yes	965 (18.1%)	193 (3.6%)	241 (4.5%)	231 (4.3%)	300 (5.6%)	
Cancer-related mortality, %						0.004
No	4936 (92.6%)	1249 (23.4%)	1249 (23.4%)	1246 (23.4%)	1192 (22.4%)	
Yes	393 (7.4%)	84 (1.6%)	83 (1.6%)	86 (1.6%)	140 (2.6%)	

Note: Q1, 4.056–349.500; Q2, 349.501–508.800; Q3, 508.801–736.154; Q4, 376.155–11,700.000.

Abbreviations: SII index, systemic immune inflammation index; CVD, cardiovascular disease; CHD, coronary heart disease; CHF, congestive heart failure; MI, myocardial infarction; DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fast glucose; HbA1c, glycohemoglobin; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hb, hemoglobin; Plt, platelet; Lym, lymphocyte; Neu, neutrophils; BUN, blood urea nitrogen; UA, uric acid; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein-cholesterol.

Ascertainment of CVD

CVD was defined as a composite of self-reported doctor diagnoses of CHF, CHD, angina pectoris, MI, and stroke. NHANES surveys asked about the five diseases used to define CVD.[20]

Covariates

The following covariates were considered in the study: age, sex, race/ethnicity, family poverty income ratio (PIR), education level, marital status, the complication of hypertension, and diabetes mellitus (DM), smoker, drinker, body mass index (BMI), waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean energy intake, hemoglobin (Hb), fast glucose (FBG), glycosylated hemoglobin (HbA1c), alanine transaminase (Alt), aspartate aminotransferase (Ast), albumin, total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), uric acid (UA), blood urea nitrogen (BUN), serum creatinine (Scr), and estimated glomerular filtration rate (eGFR). Individuals who have smoked less than 100 cigarettes in their lifetime/smoked less than 100 cigarettes in their lifetime, do not smoke at all at present/smoked more than 100 cigarettes in their lifetime, and smoke some days or every day were defined as never smoke, former smokers, and now smokers, respectively. There are three categories of drinkers: current heavy alcohol consumption were defined as ≥3 drinks per day for females, ≥4 drinks per day for males, or binge drinking [≥4 drinks on same occasion for females, ≥5 drinks on same occasion for males] on 5 or more days per month; current moderate alcohol consumption were

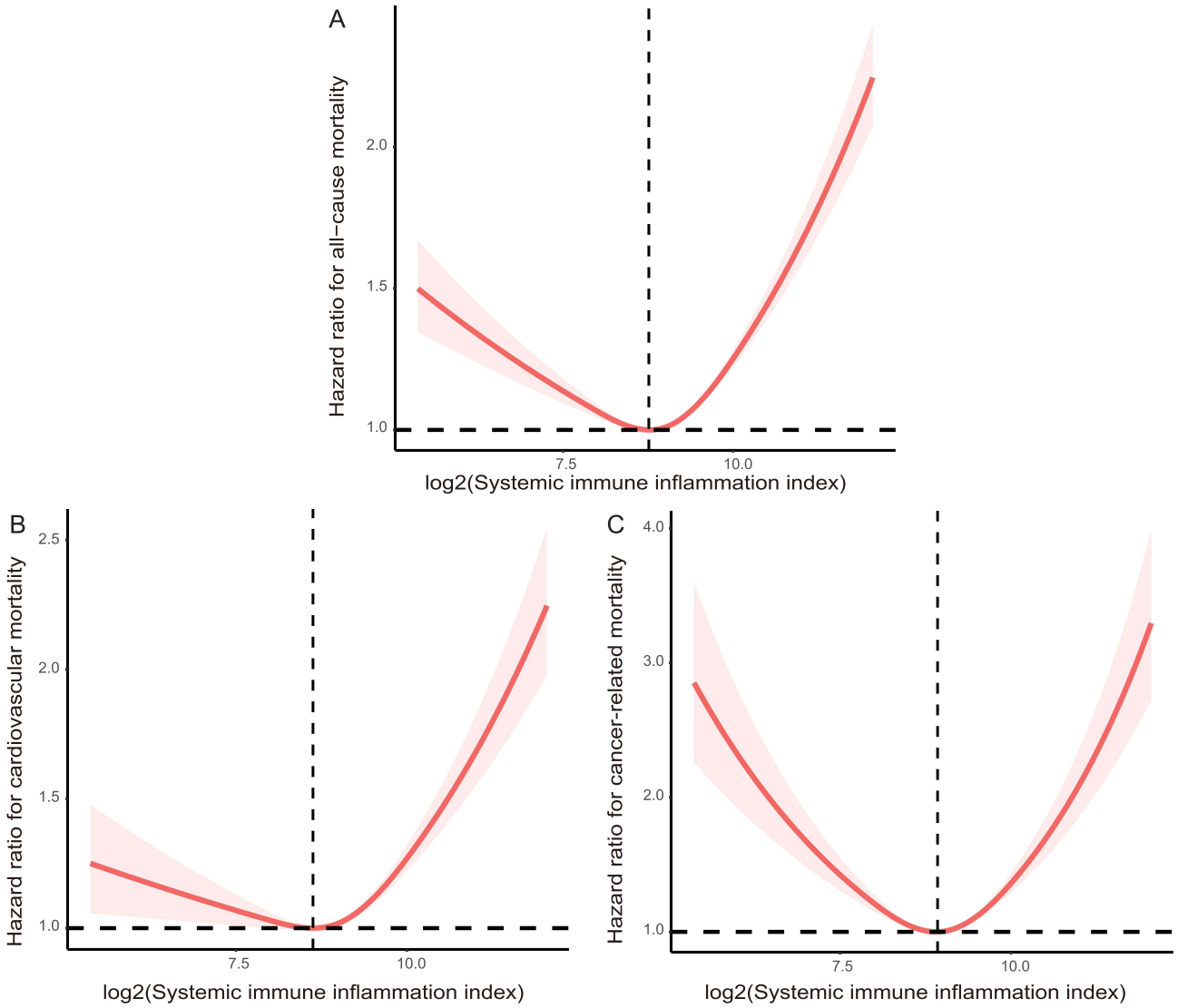

Figure 1 The RCS curve of the association between SII index and all-cause (**A**), CVD (**B** and **C**) cancer-related mortality in CVD patients.
Abbreviations: RCS, restricted cubic spline; SII index, systemic immune inflammation index; CVD, cardiovascular disease.

defined as ≥2 drinks per day for females, ≥3 drinks per day for males, or binge drinking ≥2 days per month. Those who did not meet the above criteria were classified as current mild alcohol user.[21] Hypertension was defined as an average systolic blood pressure more than 140 mmHg/diastolic blood pressure greater than 90 mmHg or self-reported use of antihypertensive medication. DM will be assessed by measures of blood glycohemoglobin, fasting plasma glucose, 2-hour glucose (Oral

Table 2 Cox Regression Analysis of SII Index for All-Cause, CVD, and Cancer-Related Mortality in CVD Patients

Mortality	Model 1	*P* for Trend	Model 2	*P* for Trend	Model 3	*P* for Trend
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
All-cause		<0.001		<0.001		0.005
Q1	1.00		1.00		1.00	
Q2	1.259 (1.032, 1.537)*		1.194 (0.976, 1.460)		1.202 (0.981, 1.474)	
Q3	1.191 (0.976, 1.454)		1.150 (0.940, 1.407)		1.184 (0.967, 1.450)	
Q4	1.762 (1.454, 2.315)***		1.521 (1.248, 1.854) ***		1.365 (1.115, 1.672)**	

(*Continued*)

Table 2 (Continued).

Mortality	Model 1	*P* for Trend	Model 2	*P* for Trend	Model 3	*P* for Trend
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
CVD		0.004		0.081		0.314
Q1	1.00		1.00		1.00	
Q2	1.174 (0.864, 1.594)		1.108 (0.813, 1.511)		1.116 (0.815, 1.527)	
Q3	1.060 (0.778, 1.445)		1.016 (0.743, 1.389)		1.017 (0.740, 1.398)	
Q4	1.609 (1.197, 2.161)**		1.355 (0.999, 1.838)		1.220 (0.891, 1.670)	
Cancer-related		0.137		0.403		0.005
Q1	1.00		1.00		1.00	
Q2	0.869 (0.543, 1.389)		0.825 (0.513, 1.326)		1.202 (0.981, 1.474)	
Q3	1.005 (0.641, 1.576)		0.960 (0.609, 1.514)		1.184 (0.967, 1.450)	
Q4	1.347 (0.868, 2.092)		1.152 (0.731, 1.816)		1.365 (1.115, 1.672) **	

Notes: Model 1: age and sex. Model 2: model 1 variables plus race/ethnicity, education level, marital status, family poverty–income ratio, hypertension, diabetes mellitus, smoker, alcohol user; Model 3 was adjusted for model 2 variables plus body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, mean energy intake, hemoglobin, fast glucose, glycosylated hemoglobin, alanine transaminase, aspartate aminotransferase, albumin, blood urea nitrogen, uric acid, serum creatinine, estimated glomerular filtration rate, total cholesterol, triglyceride, and high-density lipoprotein-cholesterol. Q1, 4.056–349.500; Q2, 349.501–508.800; Q3 508.801–736.154; Q4, 376.155–11,700.000; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Abbreviations: SII index, systemic immune inflammation index; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval.

Glucose Tolerance Test), serum insulin in participants aged 12 years and over. Hb, FBG, HbA1c, Alt, Ast, albumin, TC, TG, HDL-C, UA, BUN, Scr, and eGFR were all determined in the laboratory. More information regarding the variables used is available at https://www.cdc.gov/nchs/nhanes/index.htm.

Statistical Analysis

Mean (standard deviation) and quantity (percentage, %) are used to represent continuous and categorical variables, respectively. For continuous variables, Student's *t*-test or one-way ANOVA were used. In addition, to compare the constituent ratios between each group, the chi-square test was performed. The SII index was divided into four groups: Q1 (4.056–349.500), Q2 (349.501–508.800), Q3 (508.801–736.154), and Q4 (376.155–11,700.000), with Q1 serving as the reference group. Cox regression analysis was used to examine the relationship between SII index and all-cause, cardiovascular, and cancer-related mortality in patients with CVD. First, model 1 was adjusted for age and sex. Second, model 2 was further adjusted for race/ethnicity, education level, marital status, family PIR, the complication of hypertension, and DM, smoker, and drinker. Finally, model 3 was further adjusted for BMI, waist circumference, mean energy intake, SBP, DBP, Hb, FBG, HbA1c, Alt, Ast, albumin, TC, TG, HDL-C, UA, BUN, Scr, and eGFR, as our final model. Then, using the above methods and models, we also explored the relationship between SII index and all-cause, CVD, and cancer-related mortality in patients with a composite of 5 CVD outcomes (CHF, CHD, angina pectoris, MI, and stroke). All statistical analyses were performed using the "survey", "openxlsx", "dplyr", "reshape2", and "do" packages of R version 3.6.4 (R Foundation for Statistical Computing, Vienna, Austria), Stata version 13.0 (Stata Corporation, College Station, TX, USA), and SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Two-side *P*-value <0.05 was regarded as statistically significant.

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of included participants. The all-cause, CVD, and cancer-related mortality were 44.1%, 18.1, and 7.4%, respectively. The average age of included 5329 participants in our study was 64.70 ± 0.29 years, with 2997 (56.2%) were male. The education level, the complication of DM, smoke status, drink status, the prevalence of CHD, Angina, MI, and Stroke, BMI, waist circumference, SBP, FBG, HbA1c, UA, TC, TG, and HDL-C had no significant difference among Q1, Q2, and Q3, and Q4 group. Individuals in Q2 group were the youngest, with

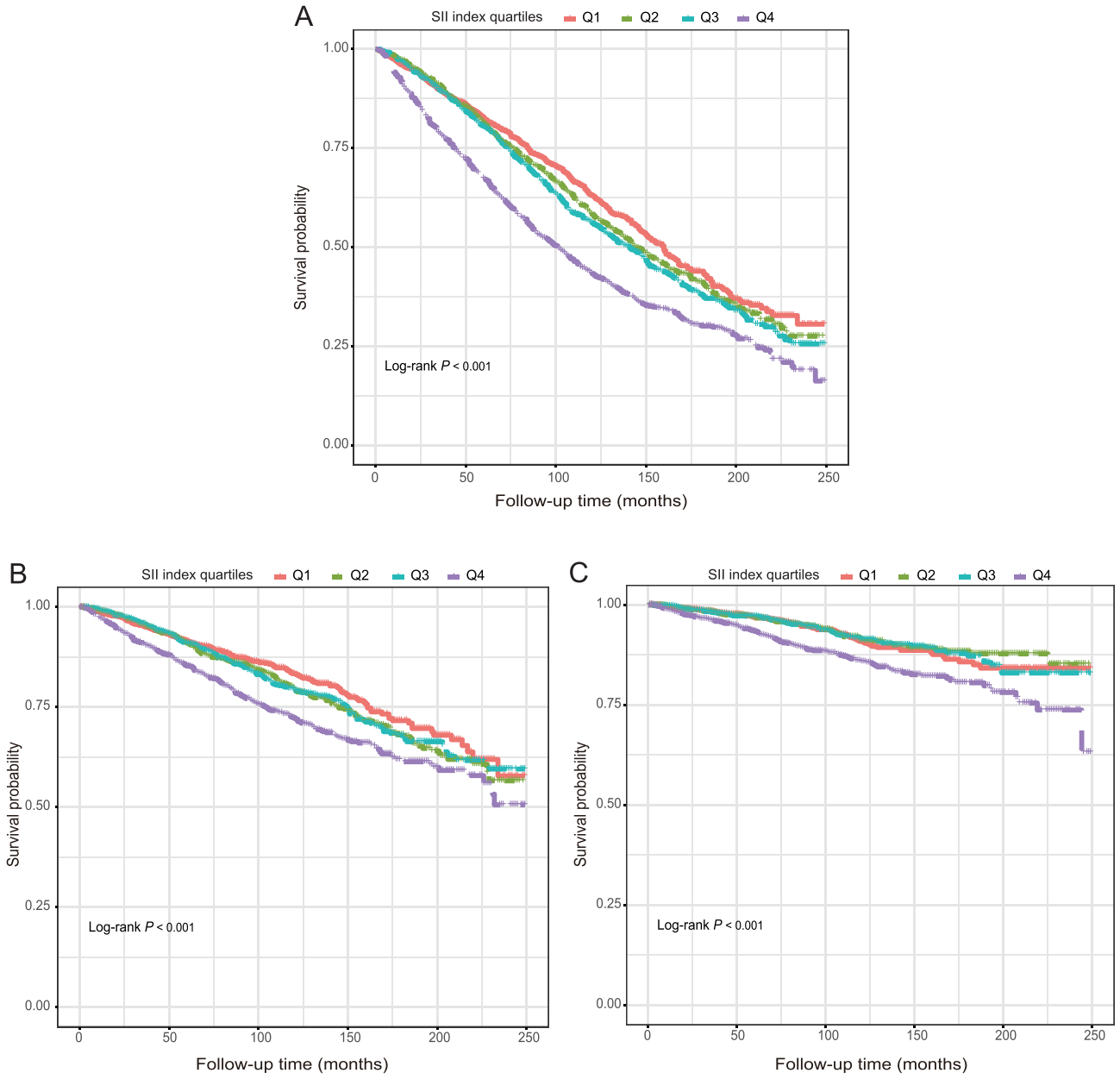

Figure 2 Kaplan-Meier survival curve for all-cause (**A**), CVD (**B** and **C**) cancer-related mortality in CVD patients.
Abbreviation: CVD, cardiovascular disease.

13.8% of males. Q2 group occupied the lowest proportion of hypertension, DM, CHF, MI, and cancer-related mortality, and the highest proportion of stroke. And, Q2 group had the highest level of HbA1c, mean energy intake, albumin, Hb, and eGFR, and the lowest level of waist circumference, SBP, DBP, mmHg, UA, Scr, and HDL-C. In addition, participants in Q3 group occupied a lowest proportion of angina pectoris, and had the highest level of BMI, waist circumference, SBP, and TG. Compared with the Q1, Q2, and Q3 group, individuals in Q4 occupied a highest proportion of CVD, CHF, MI, all-cause mortality, CVD mortality, and cancer-related mortality, and had the highest level of FBG, CRP, BUN, UA, Scr, TC, and HDL-C.

Associations of SII Index with All-Cause, CVD, and Cancer-Related Mortality in CVD

According to Figure 1A–C, the restricted cubic spline (RCS) curve illustrates the U-shaped association between SII index and all-cause, CVD, and cancer-related mortality in participants with CVD (*P* for nonlinearity <0.05). After adjusting for underlying

Table 3 Subgroups Analysis for the Associations of SII Index with All-Cause Mortality in CVD Patients

	Q1 OR (95% CI)	Q2 OR (95% CI)	Q3 OR (95% CI)	Q4 OR (95% CI)	*P* for Trend	*P* for Interaction
Age						0.107
< 60	1.00	1.440 (0.705, 2.941)	0.816 (0.350, 1.902)	1.767 (0.794, 3.929)	0.356	
≥ 60	1.00	1.178 (0.952, 1.459)	1.188 (0.960, 1.472)	1.330 (1.076, 1.645)	0.012	
Gender						0.309
Male	1.00	1.237 (0.962, 1.591)	1.278 (0.997, 1.638)	1.442 (1.128, 1.844)**	0.005	
Female	1.00	1.304 (0.894, 1.901)	1.016 (0.697, 1.480)	1.253 (0.859, 1.830)	0.534	
Hypertension						0.501
No	1.00	1.173 (0.658, 2.091)	1.118 (0.640, 1.955)	1.209 (0.666, 1.955)	0.603	
Yes	1.00	1.191 (0.954, 1.486)	1.189 (0.952, 1.486)	1.383 (1.110, 1.723)**	0.006	
DM						0.045
No	1.00	1.167 (0.886, 1.538)	1.130 (0.856, 1.491)	1.202 (0.904, 1.597)	0.292	
Yes	1.00	1.168 (0.853, 1.600)	1.128 (0.824, 1.544)	1.504 (1.117, 2.024)	0.010	
BMI						0.049
< 30 kg/m^2	1.00	1.064 (0.820, 1.379)	1.088 (0.837, 1.414)	1.332 (1.030, 1.721)*	0.025	
≥ 30 kg/m^2	1.00	1.378 (0.978, 1.940)	1.132 (0.805, 1.591)	1.313 (0.933, 1.847)	0.315	

Notes: Q1, 4.056–349.500; Q2, 349.501–508.800; Q3 508.801–736.154; Q4, 376.155–11,700.000; *P < 0.05; **P < 0.01. Analyses was adjusted for age and sex, race/ethnicity, education level, marital status, family poverty–income ratio, hypertension, diabetes mellitus, smoker, alcohol user, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, mean energy intake, hemoglobin, fast glucose, glycosylated hemoglobin, alanine transaminase, aspartate aminotransferase, albumin, blood urea nitrogen, uric acid, serum creatinine, estimated glomerular filtration rate, total cholesterol, triglyceride, and high-density lipoprotein-cholesterol.
Abbreviations: SII index, systemic immune inflammation index; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval.

Table 4 Subgroups Analysis for the Associations of SII Index with CVD Mortality in CVD Patients

	Q1 OR (95% CI)	Q2 OR (95% CI)	Q3 OR (95% CI)	Q4 OR (95% CI)	*P* for Trend	*P* for Interaction
Age						0.003
< 60	1.00	3.020 (1.490, 6.120) **	1.892 (0.903, 3.964)	2.763 (1.321, 5.779) **	0.043	
≥ 60	1.00	0.963 (0.786, 1.178)	0.970 (0.793, 1.187)	1.188 (0.977, 1.444)	0.063	
Gender						0.056
Male	1.00	1.038 (0.808, 1.334)	1.132 (0.881, 1.454)	1.314 (1.028, 1.679) *	0.017	
Female	1.00	1.274 (0.931, 1.744)	0.908 (0.662, 1.247)	1.311 (0.968, 1.776)	0.306	
Hypertension						0.028
No	1.00	0.865 (0.516, 1.448)	0.586 (0.335, 1.024)	0.854 (0.510, 1.432)	0.362	
Yes	1.00	1.100 (0.891, 1.357)	1.121 (0.909, 1.383)	1.354 (1.103, 1.663) **	0.004	
DM						0.134
No	1.00	1.240 (0.954, 1.611)	1.180 (0.906, 1.537)	1.413 (1.091, 1.830)	0.019	
Yes	1.00	0.923 (0.689, 1.237)	0.873 (0.650, 1.173)	1.203 (0.905, 1.599)	0.242	
BMI						0.021
< 30 kg/m^2	1.00	1.000 (0.786, 1.272)	1.040 (0.815, 1.328)	1.177 (0.927, 1.495)	0.145	
≥ 30 kg/m^2	1.00	1.290 (0.923, 1.803)	0.985 (0.708, 1.370)	1.470 (1.070, 2.020)	0.072	

Notes: Q1, 4.056–349.500; Q2, 349.501–508.800; Q3 508.801–736.154; Q4, 376.155–11,700.000; *P < 0.05; **P < 0.01. Analyses was adjusted for age and sex, race/ethnicity, education level, marital status, family poverty–income ratio, hypertension, diabetes mellitus, smoker, alcohol user, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, mean energy intake, hemoglobin, fast glucose, glycosylated hemoglobin, alanine transaminase, aspartate aminotransferase, albumin, blood urea nitrogen, uric acid, serum creatinine, estimated glomerular filtration rate, total cholesterol, triglyceride, and high-density lipoprotein-cholesterol.
Abbreviations: SII index, systemic immune inflammation index; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval.

confounding variables, compared to Q1 group, the hazard ratios (HRs) with 95% confidence intervals (CIs) for all-cause, CVD, and cancer-related mortality across rising quartiles were (1.202 (0.981, 1.474), 1.184 (0.967, 1.450), and 1.365 (1.115, 1.672)), (1.116 (0.815, 1.527), 1.017 (0.740, 1.398), and 1.220 (0.891, 1.670)), and (1.202 (0.981, 1.474), 1.184 (0.967, 1.450), and 1.365 (1.115, 1.672)) for SII index (Table 2). According to the SII index quartiles, the differences in survival rate of all-cause (Figure 2A), CVD (Figure 2B), and cancer-related (Figure 2C) mortality were shown in Kaplan–Meier survival curves.

Table 5 Subgroups Analysis for the Associations of SII Index with Cancer-Related Mortality in CVD Patients

	Q1 OR (95% CI)	Q2 OR (95% CI)	Q3 OR (95% CI)	Q4 OR (95% CI)	*P* for Trend	*P* for Interaction
Age						0.104
< 60	1.00	0.926 (0.372, 2.301)	0.870 (0.351, 2.158)	2.186 (0.975, 4.897)	0.043	
≥ 60	1.00	0.837 (0.602, 1.163)	0.848 (0.611, 1.177)	1.310 (0.967, 1.774)	0.046	
Gender						0.095
Male	1.00	0.732 (0.498, 1.075)	0.861 (0.591, 1.252)	1.330 (0.943, 1.875)	0.038	
Female	1.00	1.227 (0.714, 2.110)	1.030 (0.598, 1.776)	1.689 (1.016, 2.805)	0.062	
Hypertension						
No	1.00	0.920 (0.456, 1.860)	1.101 (0.544, 2.229)	1.030 (0.513, 2.071)	0.796	0.255
Yes	1.00	0.855 (0.603, 1.213)	0.898 (0.635, 1.271)	1.558 (1.136, 2.136)	0.002	
DM						0.406
No	1.00	0.914 (0.617, 1.355)	0.859 (0.576, 1.279)	1.483 (1.032, 2.131)	0.025	
Yes	1.00	0.874 (0.525, 1.455)	0.991 (0.607, 1.617)	1.539 (0.967, 2.451)	0.044	
BMI						0.001
< 30 kg/m^2	1.00	0.849 (0.549, 1.311)	1.044 (0.677, 1.609)	1.960 (1.335, 2.877)	<0.001	
≥ 30 kg/m^2	1.00	0.899 (0.574, 1.408)	0.738 (0.473, 1.152)	0.909 (0.583, 1.418)	0.504	

Notes: Q1, 4.056–349.500; Q2, 349.501–508.800; Q3 508.801–736.154; Q4, 376.155–11,700.000. Analyses was adjusted for age and sex, race/ethnicity, education level, marital status, family poverty–income ratio, hypertension, diabetes mellitus, smoker, alcohol user, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, mean energy intake, hemoglobin, fast glucose, glycosylated hemoglobin, alanine transaminase, aspartate aminotransferase, albumin, blood urea nitrogen, uric acid, serum creatinine, estimated glomerular filtration rate, total cholesterol, triglyceride, and high-density lipoprotein-cholesterol.
Abbreviations: SII index, systemic immune inflammation index; CVD, cardiovascular disease; CI, confidence interval; HR, hazard ratio.

Individuals in Q4 group had the highest risk of all-cause, CVD, and cancer-related mortality (Log-rank P <0.001, Log-rank P <0.001, and Log-rank P <0.001, respectively). Subgroup analysis for the associations of SII index with all-cause, cardiovascular, and cancer-related mortality was conducted based on age, sex, hypertension, DM, and BMI (Tables 3–5). Additionally, RCS curves for subgroup analysis were shown in Supplementary Figures 1–3.

Associations of SII Index with All-Cause, CVD, and Cancer-Related Mortality in CHD

There were the U-shaped relationships between SII index and all-cause, CVD, and cancer-related mortality in participants with CHD (Figure 3A–C, P for nonlinearity <0.05). After adjusting for underlying confounding variables, compared to Q1 group, the HRs with 95% CIs for all-cause, CVD, and cancer-related mortality across rising quartiles were (1.202 (0.981, 1.474), 1.184 (0.967, 1.450), and 1.365 (1.115, 1.672), 1.116 (0.815, 1.527), 1.017 (0.740, 1.398), and 1.220 (0.891, 1.670), and 0.808 (0.499, 1.308), 0.931 (0.586, 1.478), and 1.067 (0.668, 1.703)) for SII index (Supplementary Table 1). In accordance with the SII index quartiles, the differences in survival rate of all-cause (Figure 4A), cardiovascular (Figure 4B), and cancer-related (Figure 4C) mortality were shown in Kaplan–Meier survival curves. Individuals in Q4 group had the highest risk of all-cause, CVD, and cancer-related mortality (Log-rank P <0.001, Log-rank P <0.001, and Log-rank P =0.180, respectively). On the basis of age, gender, hypertension, DM, and BMI, subgroup analyses were performed to determine the relationships between the SII index and all-cause, CVD, and cancer-related mortality (Supplementary Tables 2–4). Moreover, RCS curves for subgroup analysis were shown in Supplementary Figures 4–6.

Associations of SII Index with All-Cause, CVD, and Cancer-Related Mortality in CHF

The RCS plot also shows the U-shaped association between SII index and all-cause, and cancer-related mortality in participants with CHF (Figure 5A, and C, P for nonlinearity <0.05). However, there was a positive and linear relationship between SII index and CVD mortality (Figure 5B). After adjusting for underlying confounding variables, compared to Q1 group, the HRs with 95% CIs for all-cause, CVD, and cancer-related mortality across rising quartiles were (1.040 (0.832, 1.299), 1.009 (0.813, 1.252), and 1.212 (0.987, 1.488)), (1.165 (0.825, 1.645), 1.058 (0.754, 1.484), and 1.292 (0.935, 1.785)), and (0.528 (0.293, 0.952), 0.632 (0.365, 1.093), and 0.942 (0.576, 1.541)) for SII index (Supplementary

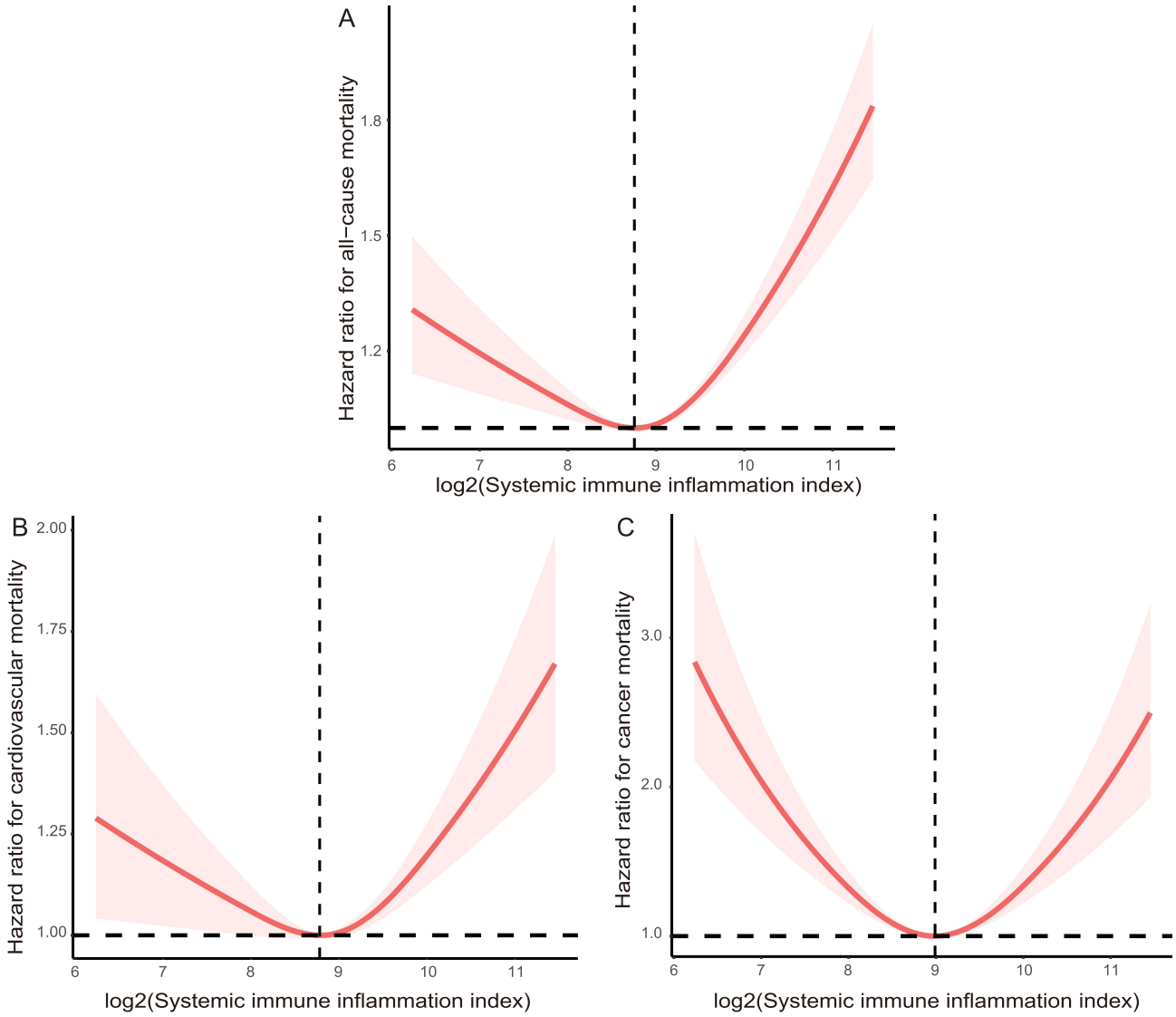

Figure 3 The RCS curve of the association between SII index and all-cause (**A**), CVD (**B** and **C**) cancer-related mortality in CHD patients.
Abbreviations: RCS, restricted cubic spline; SII index, systemic immune inflammation index; CVD, cardiovascular disease; CHD, coronary heart disease.

Table 5). Kaplan–Meier survival curves illustrated differences in survival rate of all-cause (Figure 6A), CVD (Figure 6B), and cancer-related (Figure 6C) mortality. Patients in Q4 group also had the highest risk of all-cause, CVD, and cancer-related mortality (Log-rank P <0.001, Log-rank P <0.001, and Log-rank P =0.009, respectively). Based on age, sex, hypertension, DM, and BMI, subgroup analysis for the correlations of SII index with all-cause, CVD, and cancer-related mortality was performed (Supplementary Tables 6–8). Additionally, Supplementary Figures 7–9 included RCS curves for subgroup analysis.

Associations of SII Index with All-Cause, CVD, and Cancer-Related Mortality in Angina Pectoris

As shown in Figure 7A–C, the RCS curve also indicates a U-shaped relationship between SII index and all-cause mortality, CVD, and cancer-related mortality (P for nonlinearity <0.05). After adjusting for underlying confounding variables, compared to Q1 group, the HRs with 95% CIs for all-cause, cardiovascular, and cancer-related mortality across rising quartiles were (0.972 (0.759, 1.244), 0.991 (0.777, 1.263), and 1.250 (0.987, 1.583)), (0.933 (0.641, 1.357), 0.877 (0.604, 1.273), and 1.204 (0.841, 1.722)), and (1.420 (0.752, 2.681), 1.287 (0.676, 2.449), and 1.761

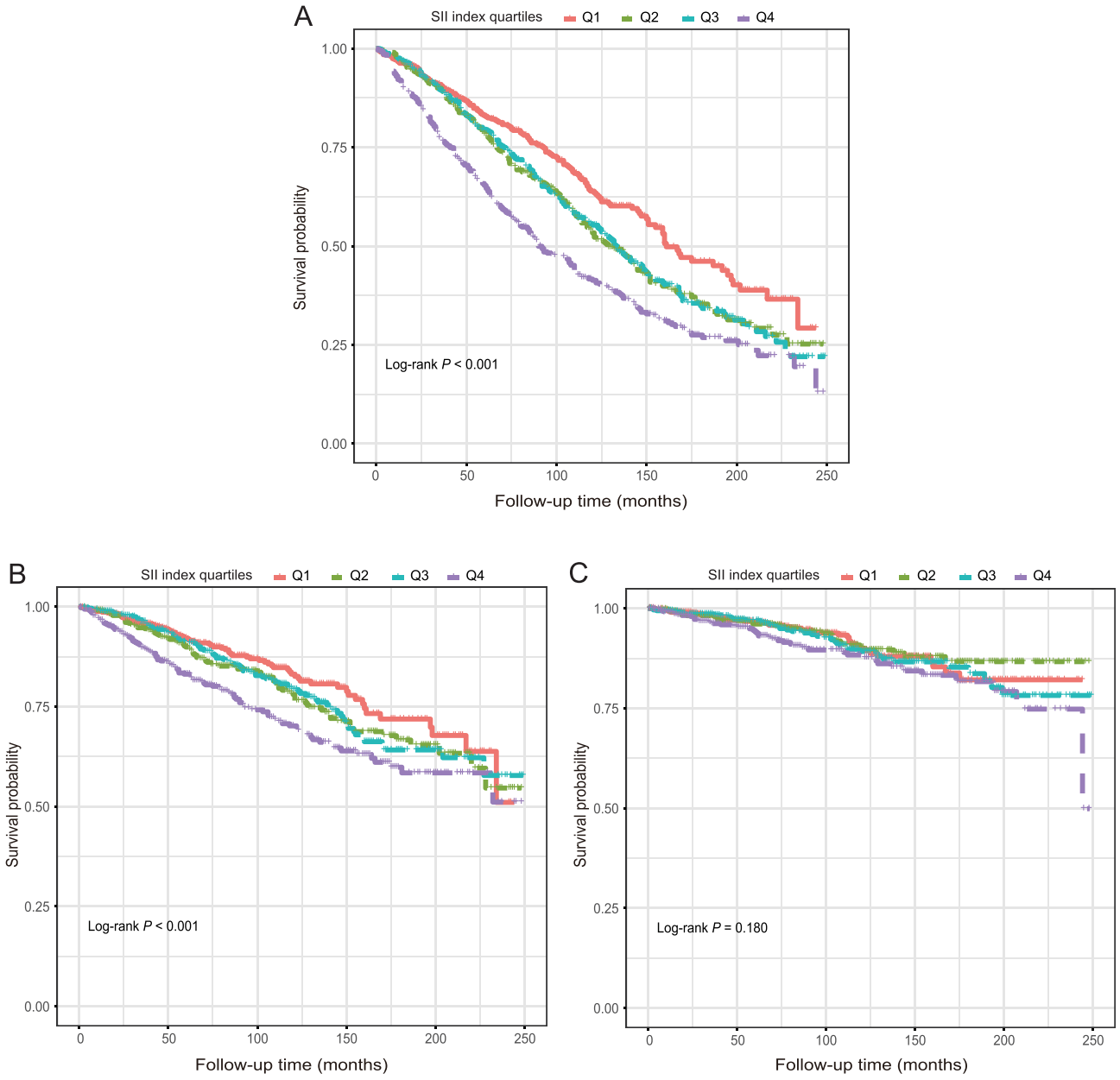

Figure 4 Kaplan-Meier survival curve for all-cause (**A**), CVD (**B** and **C**) cancer-related mortality in CHD patients.
Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.

(0.949, 3.269)) for SII index (Supplementary Table 9). The variations in survival rate of all-cause (Figure 8A), cardiovascular (Figure 8B), and cancer-related (Figure 8C) mortality were shown in Kaplan–Meier survival curves. Participants in Q4 group had the highest risk of all-cause, cardiovascular, and cancer-related mortality (Log-rank P <0.001, Log-rank P =0.013, and Log-rank P =0.079, respectively). Based on age, sex, hypertension, DM, and BMI, subgroup analysis was performed to determine the link between the SII index and all-cause, CVD, and cancer-related mortality (Supplementary Tables 10–12). In addition, RCS curves for subgroup analysis were also included in Supplementary Figures 10–12.

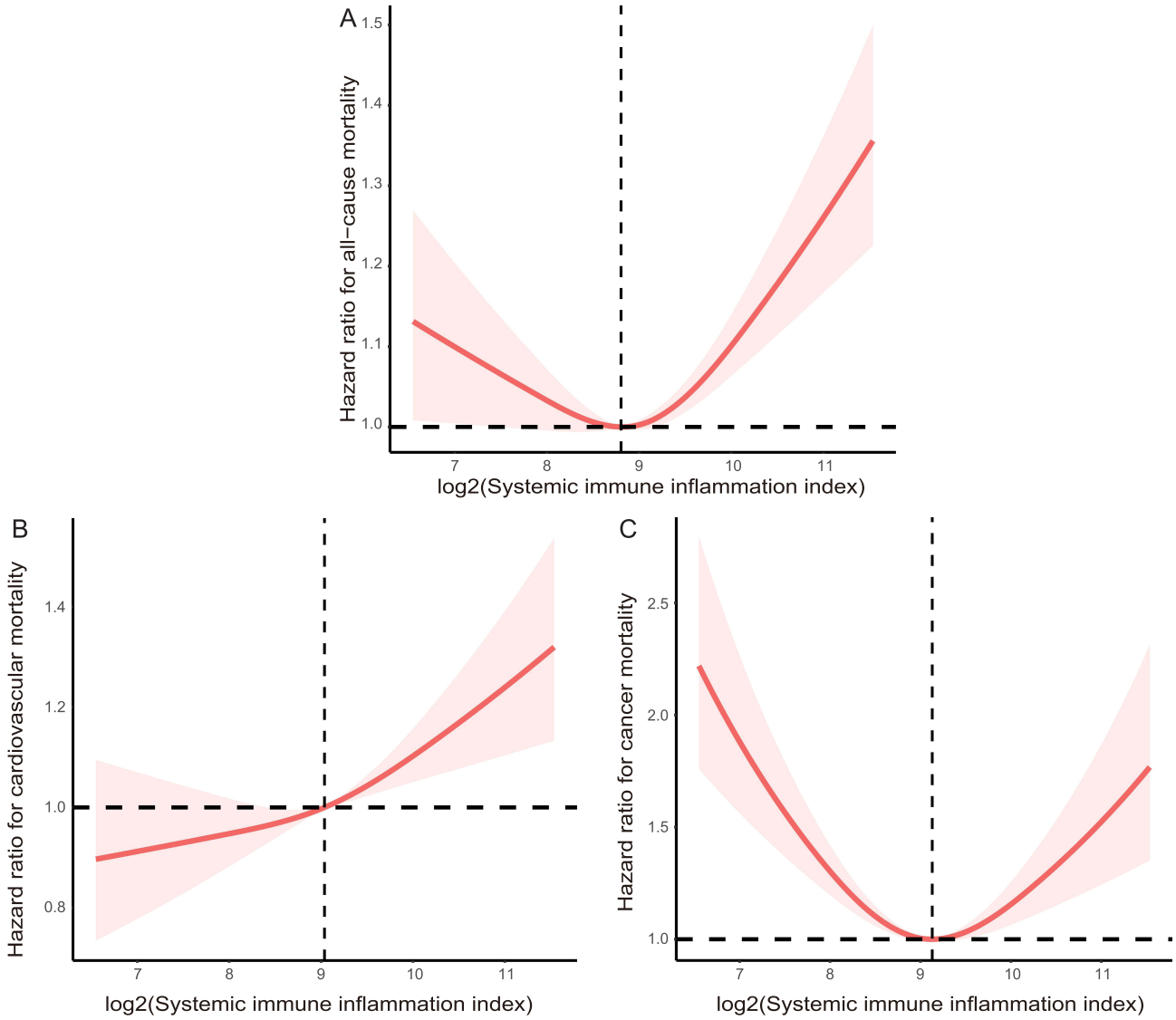

Figure 5 The RCS curve of the association between SII index and all-cause (**A**), CVD (**B** and **C**) cancer-related mortality in CHF patients.
Abbreviations: RCS, restricted cubic spline; SII index, systemic immune inflammation index; CVD, cardiovascular disease; CHF, congestive heart failure.

Associations of SII Index with All-Cause, CVD, and Cancer-Related Mortality in Myocardial Infarction

The correlation between the U-curve is also between SII index and all-cause, CVD, and cancer-related mortality in individuals with myocardial infarction (Figure 9A–C, *P* for nonlinearity <0.05). After adjusting for underlying confounding variables, compared to Q1 group, the HRs with 95% CIs for all-cause, CVD, and cancer-related mortality across rising quartiles were (1.096 (0.904, 1.328), 0.980 (0.803, 1.196), and 1.249 (1.035, 1.507), (1.090 (0.818, 1.453), 0.891 (0.657, 1.208), and 1.176 (0.886, 1.563)), and 0.815 (0.523, 1.270), 0.739 (0.469, 1.166), and 1.041 (0.685, 1.584)) for SII index (Supplementary Table 13). The differences in survival rate of all-cause (Figure 10A), cardiovascular (Figure 10B), and cancer-related (Figure 10C) mortality were shown in Kaplan–Meier survival curves. Q4 group had the highest risk of all-cause, cardiovascular, and cancer-related mortality (Log-rank *P* <0.001, Log-rank *P* <0.001, and Log-rank *P* =0.056, respectively). Subgroup analysis for SII index and all-cause, cardiovascular, and cancer-related mortality was done by age, sex, hypertension, DM, and BMI (Supplementary Tables 14–16). Moreover, Supplementary Figures 13–15 show RCS curves for subgroup analysis.

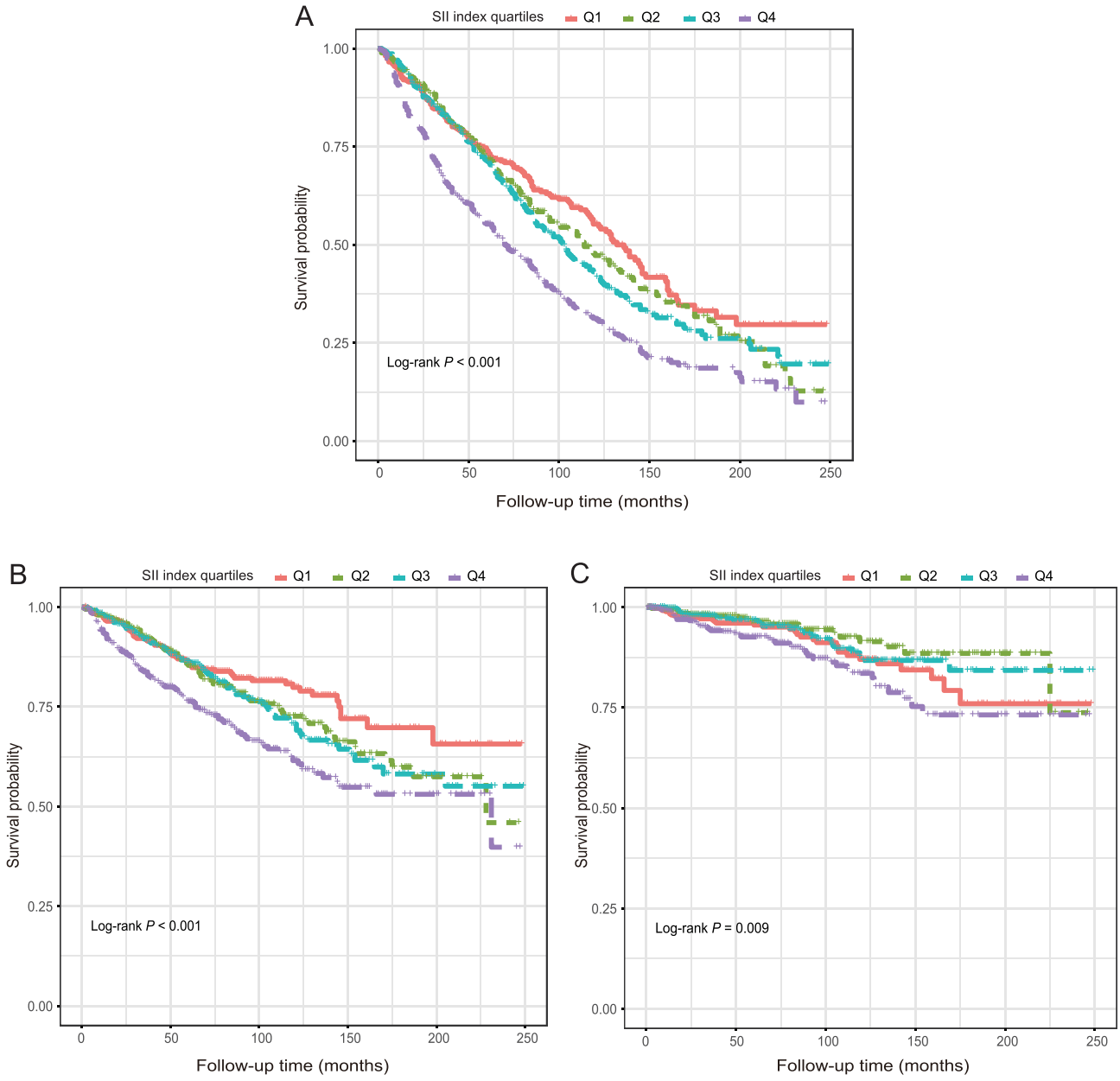

Figure 6 Kaplan-Meier survival curve for all-cause (**A**), CVD (**B** and **C**) cancer-related mortality in CHF patients.
Abbreviations: CVD, cardiovascular disease; CHF, congestive heart failure.

Associations of SII Index with All-Cause, CVD, and Cancer-Related Mortality in Stroke

The RCS plot demonstrates a U-shaped connection between SII index and all-cause, and cancer-related mortality in CHF patients (Figure 11A, and C; *P* for nonlinearity <0.05). However, SII index and CVD mortality were positively correlated (Figure 11B). After adjusting for underlying confounding variables, compared to Q1 group, the HRs with 95% CIs for all-cause, cardiovascular, and cancer-related mortality across rising quartiles were (1.022 (0.633, 1.650), 0.924 (0.567, 1.507), and 1.369 (0.847, 2.211), 1.514 (0.671, 3.4140), 1.200 (0.524, 2.748), and 1.925 (0.855, 4.333), and (0.440 (0.131, 1.474), 0.240 (0.063, 0.912), and 0.674 (0.202, 2.250)) for SII index (Supplementary Table 17). Kaplan–Meier survival curves showed the difference in survival rates between all-cause (Figure 12A), cardiovascular (Figure 12B), and cancer-related (Figure 12C) mortality. Patients with stroke in Q4 group had the highest risk of all-cause, cardiovascular, and cancer-related mortality (Log-rank *P* =0.200, Log-rank *P* =0.330, and Log-rank *P* =0.520, respectively). A subgroup analysis was conducted to examine the

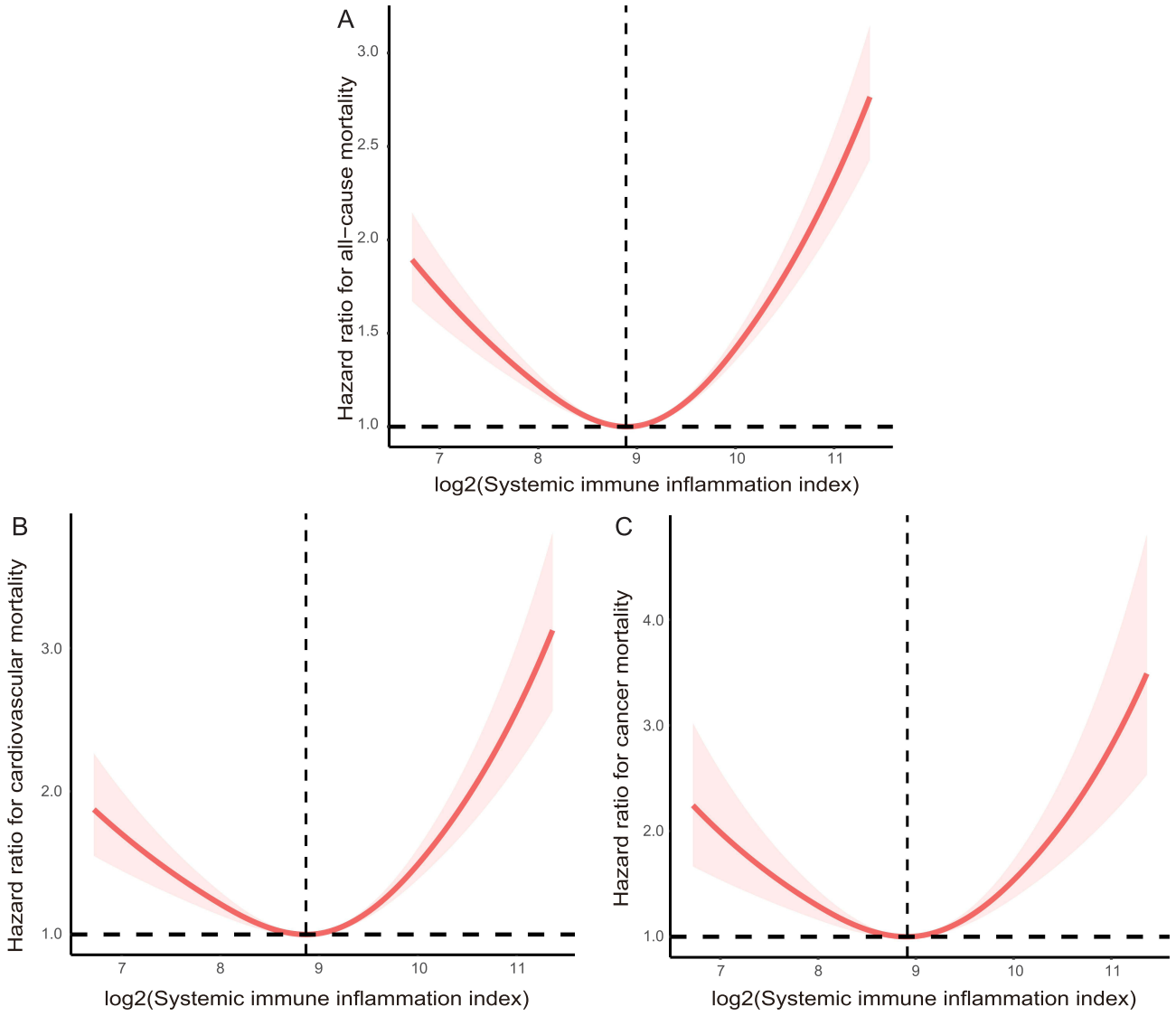

Figure 7 The RCS curve of the association between SII index and all-cause (**A**), CVD (**B** and **C**) cancer-related mortality in angina pectoris patients.
Abbreviations: RCS, restricted cubic spline; SII index, systemic immune inflammation index; CVD, cardiovascular disease.

associations between SII index and all-cause, CVD, and cancer-related mortality based on age, sex, hypertension, DM, and BMI (Supplementary Tables 18–20). Finally, Supplementary Figures 16–18 show RCS curves for subgroup analysis.

Discussion

Using the large general population dataset in the US, our study found that there was the U-shaped association between SII index and all-cause, CVD, and cancer-related mortality in participants with CVD. SII index, a novel inflammatory biomarker, might provide a more accurate and thorough evaluation of the immune and inflammatory responses.[22] In addition, clinical outcomes may be poor in diseases with high SII levels due to high inflammatory activity.[23] High SII levels have been shown to be an effective predictor of survival in cancer patients, chronic heart failure patients, and elderly non-ST-elevation myocardial infarction patients over the long run.[24,25] The platelets are essential for prothrombotic potential during arterial thrombosis, as well as in atherogenesis and inflammation. And, platelets are crucial for preserving hemostasis and coagulation as well as preventing bleeding.[26,27] By interacting with the endothelium, leukocytes, and non-activated platelets, platelets actively contribute to the inflammatory and atherosclerotic process and advance atherosclerosis.[28,29] Neutrophils, the most abundant subtype of white blood cell in the blood, are essential in

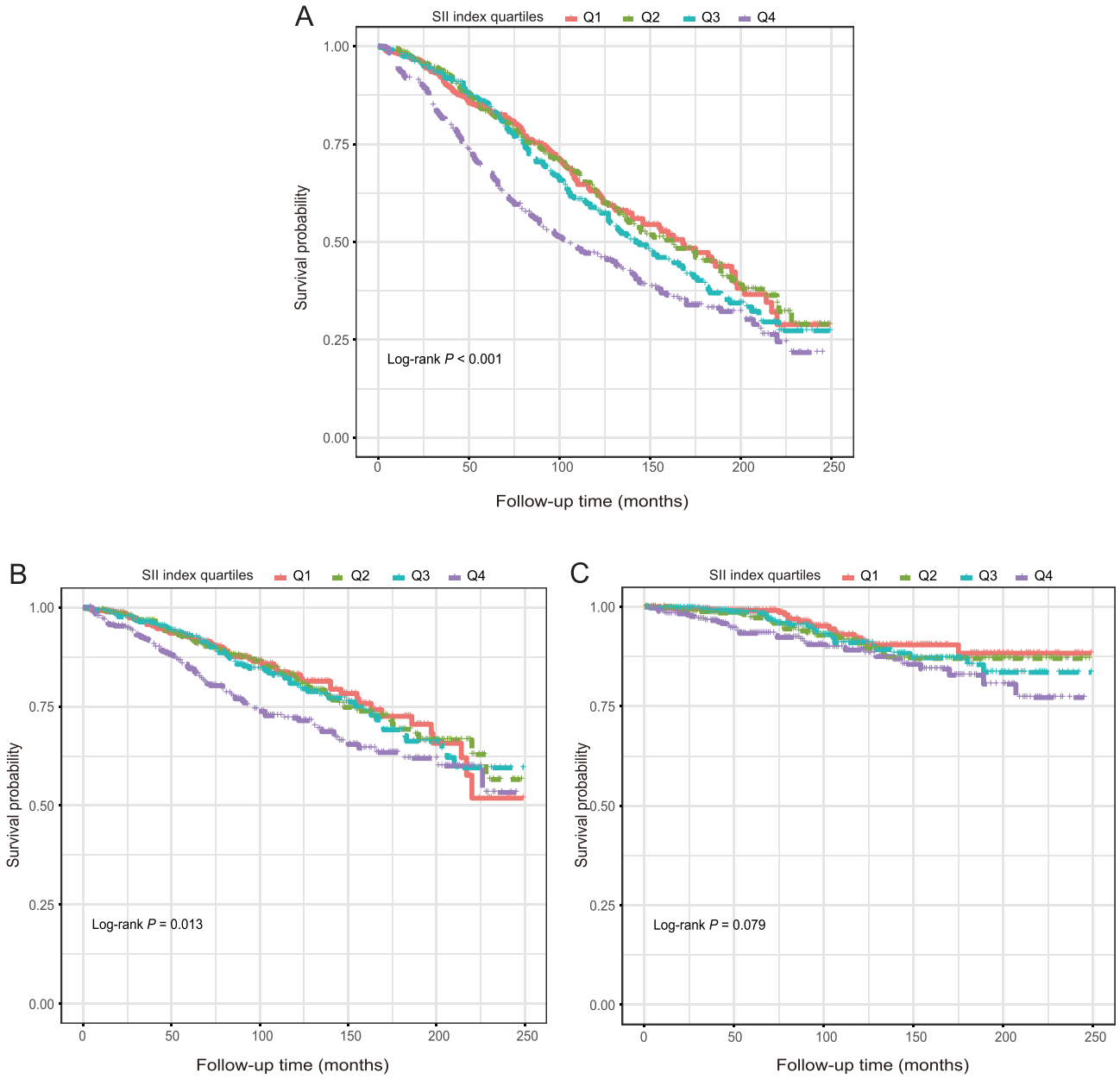

Figure 8 Kaplan-Meier survival curve for all-cause (**A**), CVD (**B** and **C**) cancer-related mortality in angina pectoris patients.
Abbreviation: CVD, cardiovascular disease.

mediating inflammation. By causing smooth muscle cells to lyse and die, neutrophils have been shown to cause tissue damage and inflammation in advanced stages of atherosclerosis.[30] Additionally, research has shown that neutrophils interact with platelets to influence important biological processes connected to atherosclerosis, thrombosis, and ischemic stroke.[31] Lymphocytes are essential for controlling the inflammatory response at every stage of the atherosclerotic process. The development of atherosclerosis is linked to low lymphocyte numbers. After lymphocytes undergo apoptosis, the lipid core of an atherosclerotic plaque ruptures and creates a thrombus.[32] Furthermore, Yao J and his team found that a low lymphocyte count is positively connected with cardiovascular events and is linked to a poor prognosis in a number of illnesses, including stable coronary artery disease.[33] Thus, based on the above-mentioned evidence, it is reasonable to suggest a U-shaped relationship between SII index and all-cause, CVD, and cancer-related mortality in patients with CVD in American population.

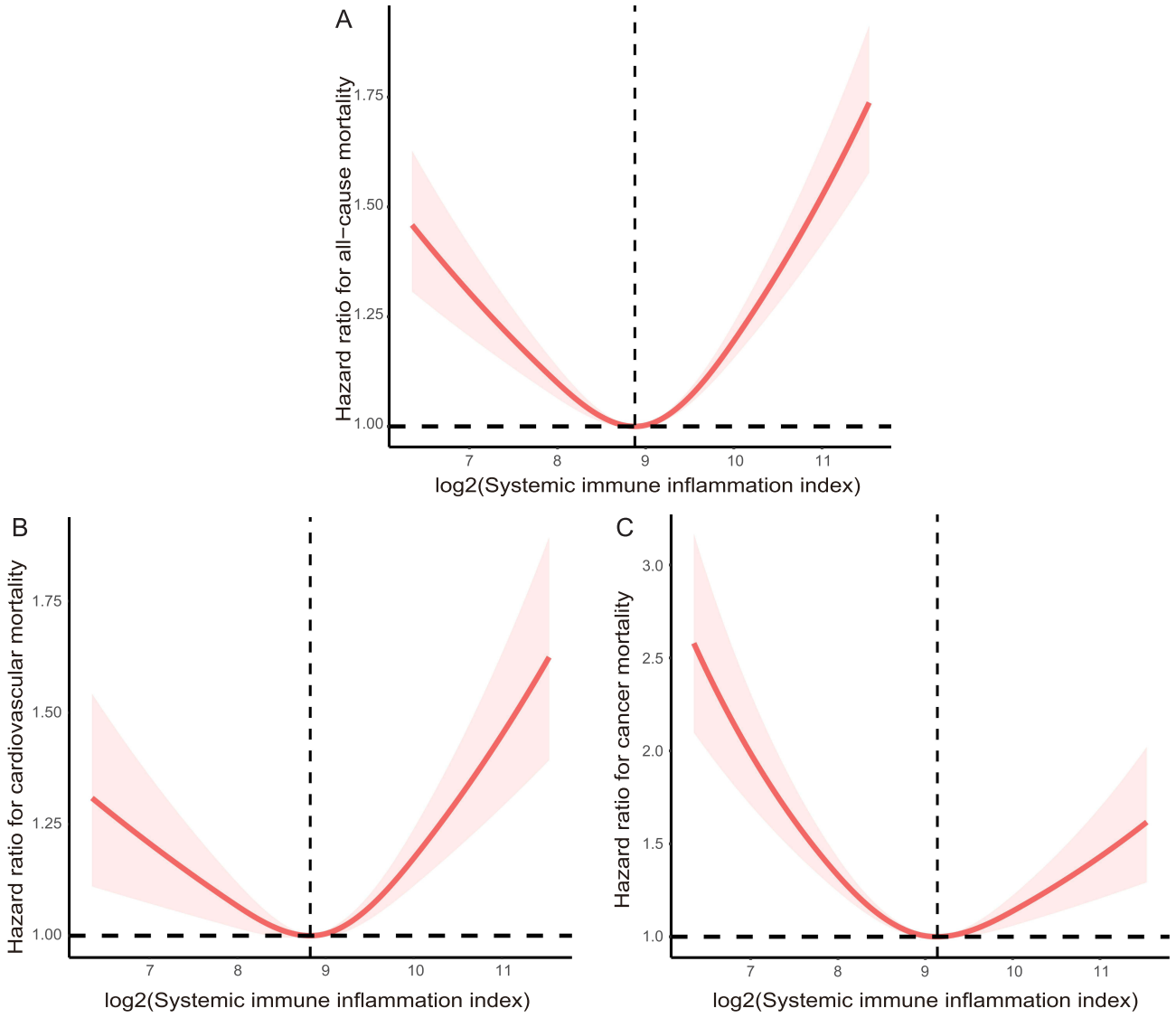

Figure 9 The RCS curve of the association between SII index and all-cause (**A**), CVD (**B** and **C**) cancer-related mortality in MI patients.
Abbreviations: RCS, restricted cubic spline; SII index, systemic immune inflammation index; CVD, cardiovascular disease; MI, myocardial infarction.

Previous research also shows various diseases have been linked to inflammation, such as CVD, and even cancer.[34] Karaaslan T found that COVID-19 mortality can be predicted independently using the SII index, a proinflammatory marker of systemic inflammation.[35] Among elderly non-ST-segment elevation myocardial infarction patients, Orhan AL demonstrated an independent link between SII index and in-hospital and long-term mortality.[25] He L and his team found that, in a US atherosclerotic cardiovascular disease population (ASCVD), there was a non-linear association between the SII index and all-cause mortality. Above the threshold value of 6.57 of SII index, ASCVD patients were associated with a higher probability of all-cause death.[36] The results of this study are consistent with this conclusion. In addition, as a result of Li H, they found that high SII index levels may contribute to an increase in all-cause and CVD mortality in general populations, while physical activity may have a beneficial effect on these relationships.[37] Accordingly, we concluded that maintaining appropriate levels of SII in vivo can effectively reduce the incidence of cardiovascular events. Meanwhile, Öcal L suggested that in patients with ST-segment elevation myocardial infarction, the systemic immune-inflammation index predicts in-hospital and long-term outcomes. According to Kaplan–Meier survival methods, Q1, Q2, Q3 and Q4 group had 97.6%, 96.9%, 91.6%, and 81.0% overall survival, respectively.[38] Compared to high levels of SII index, low levels of SII index can effectively reduce all-cause, and CVD mortality. However, there have been no studies

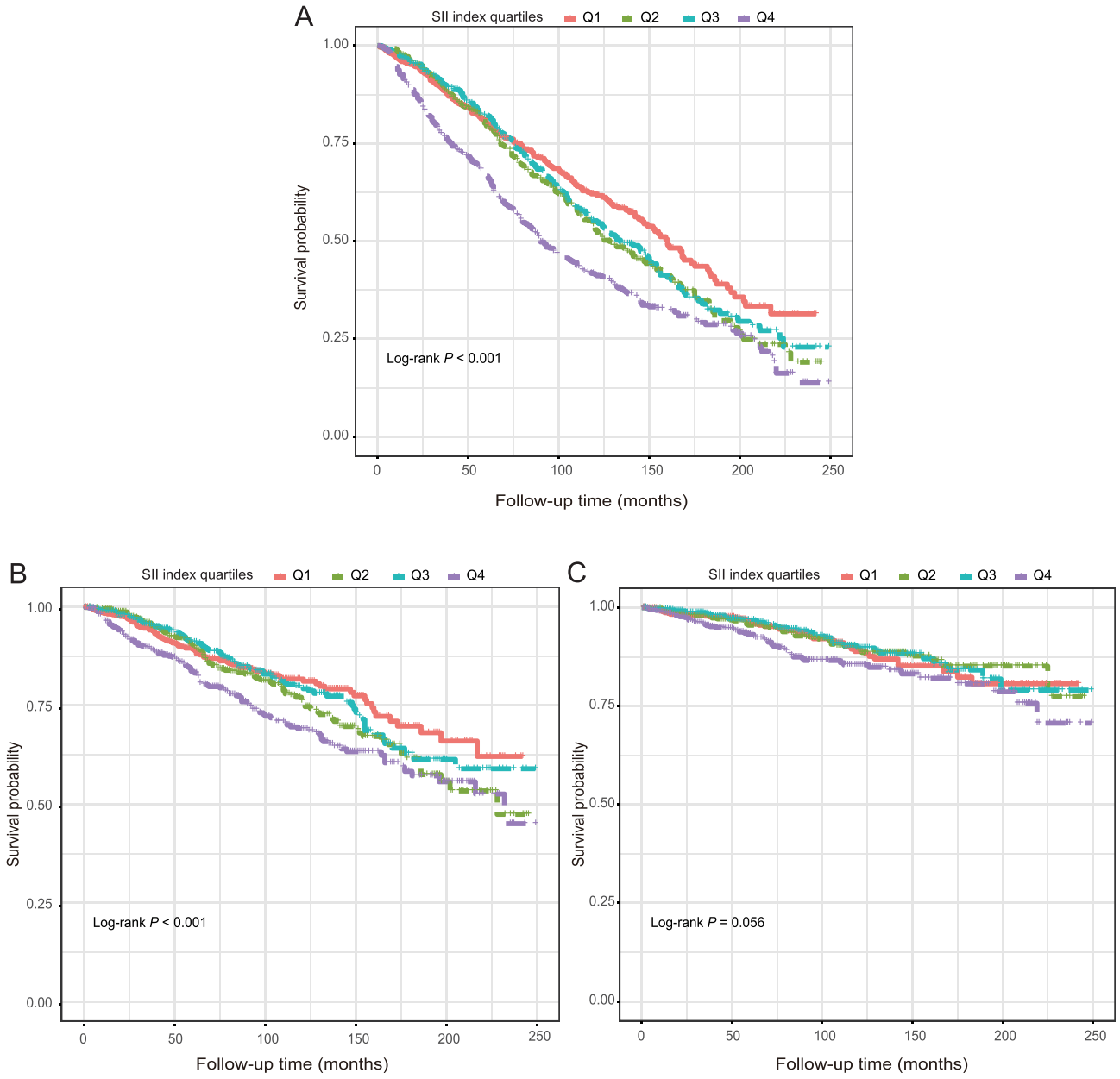

Figure 10 Kaplan-Meier survival curve for all-cause (**A**), CVD (**B** and **C**) cancer-related mortality in MI patients.
Abbreviations: CVD, cardiovascular disease; MI, myocardial infarction.

exploring the effect of further dividing low levels of SII on all-cause, and CVD mortality. Therefore, the effect of lowering SII index on all-cause, and CVD patients' survival requires further study. For the association between SII index and cancer-related mortality, Nøst TH observed that even out of 17 cancers had positive associations with SII index. Among them, colorectal and lung cancer showed the strongest associations.[39] In addition, Chen et al also revealed that patients with colorectal cancer benefit from SII in terms of predicting survival outcome and identifying high-risk patients.[40]

In addition, in the research, we also explored the link between SII index and all-cause, CVD, and cancer-related mortality in patients with a composite of five outcomes of CVD, including CHD, CHF, angina pectoris, myocardial infarction, and stroke. Yang YL found that in CAD patients after coronary angioplasty, SII index fared better than traditional risk factors in predicting major cardiovascular events.[14] In addition, an analysis of patients with segment elevation myocardial infarction undergoing percutaneous coronary intervention found that SII index was a better

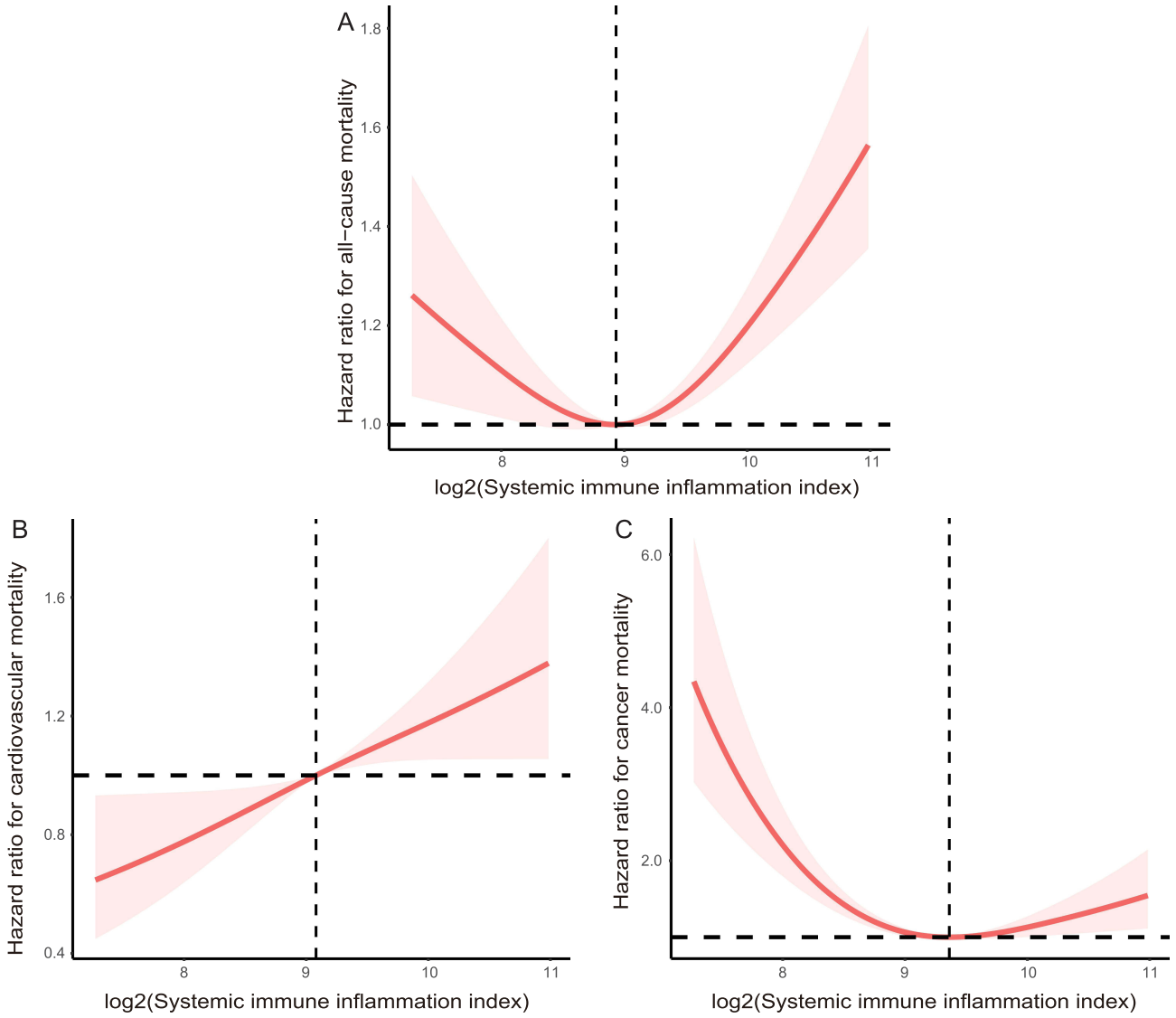

Figure 11 The RCS curve of the association between SII index and all-cause (**A**), CVD (**B** and **C**) cancer-related mortality in stroke patients.
Abbreviations: RCS, restricted cubic spline; SII index, systemic immune inflammation index; CVD, cardiovascular disease.

predictor of in-hospital and long-term outcomes than traditional risk factors.[38] Meanwhile, unselected patients with acute coronary syndromes may benefit from SII, which as a prognostic indicator.[41] Wang Z found that SII index was a significant risk factor for all-cause mortality in HCM patients.[42] Agus HZ also revealed that high SII levels are independently associated with in-hospital mortality and patients with infective endocarditis were predicted well by the SII index.[43] The high SII index levels can predict an increased risk of 30-day and 90-day in-hospital mortality, as well as major adverse cardiac events in critically ill CHF patients.[44] The 30-day all-cause mortality was higher in patients with acute ischemic stroke who had elevated SII. The SII may be useful in elucidating the role of inflammation, thrombocytosis, and immunity interaction in the development of acute ischemic stroke.[45]

Limitation

This study also had several limitations. Firstly, the samples we analyzed all came from the NHANES public database, which covered the years 1999–2018. There is a need to recruit participants from other nations in order to corroborate our findings, particularly the inflection point. Secondly, due to the limitation of the NHANES database, we did not have data on the medication duration and dosage of antiplatelet drug, antilipidemic drug, and antihypertensive drug, which may be

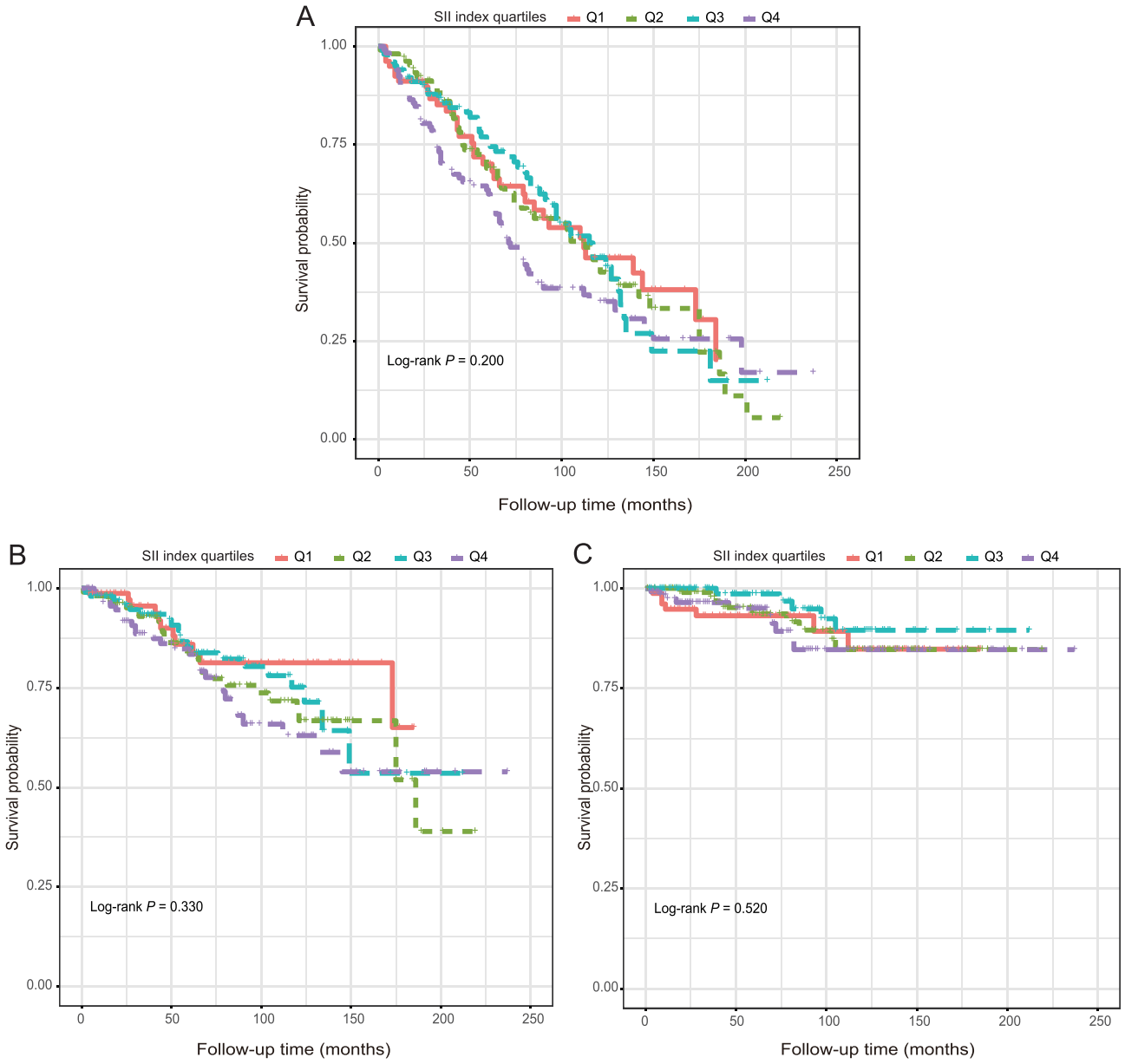

Figure 12 Kaplan-Meier survival curve for all-cause (**A**), CVD (**B** and **C**) cancer-related mortality in stroke patients.
Abbreviation: CVD, cardiovascular disease.

bias of the factors in the Cox regression models. Finally, as a retrospective study, the bias cannot be avoided to some relevant results, prospective studies are thus needed to validate the findings.

Conclusion

In US general population, there was U-shaped association between the SII index and all-cause mortality, CVD, and cancer-related mortality in patients with CVD. In addition, this correlation was also found in patients with CHD, angina pectoris, and myocardial infarction. The association between SII and all-cause, and cancer-related mortality in patients with CHF, and stroke was also U-shaped. However, with the increase of SII index, CVD mortality also increased in patients with CHF, and stroke. The SII index might be used as a clinical predictor for all-cause, CVD, and cancer-related mortality in patients with CVD. The potential mechanisms of SII index in all-cause, CVD, and cancer-related mortality need further exploration.

Data Sharing Statement

The survey data are publicly available on the Internet for data users and researchers throughout the world https://www.cdc.gov/nchs/nhanes/.

Acknowledgments

The authors thank the staff and the participants of the NHANES study for their valuable contributions.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Natural Science Foundation of China (81770451).

Disclosure

The authors declare that they have no competing interests.

References

1. Roth GA, Johnson C, Abajobir A, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol*. 2017;70(1):1–25. doi:10.1016/j.jacc.2017.04.052
2. Wong ND. Epidemiological studies of CHD and the evolution of preventive cardiology. *Nat Rev Cardiol*. 2014;11(5):276–289.
3. El Harane N, Kervadec A, Bellamy V, et al. Acellular therapeutic approach for heart failure: in vitro production of extracellular vesicles from human cardiovascular progenitors. *Eur Heart J*. 2018;39(20):1835–1847.
4. Panahi M, Papanikolaou A, Torabi A, et al. Immunomodulatory interventions in myocardial infarction and heart failure: a systematic review of clinical trials and meta-analysis of IL-1 inhibition. *Cardiovasc Res*. 2018;114(11):1445–1461.
5. Basmaeil Y, Al Subayyil A, Abumaree M, Khatlani T. Conditions mimicking the cancer microenvironment modulate the functional outcome of human chorionic villus mesenchymal stem/stromal cells in vitro. *Front Cell Dev Biol*. 2021;9:650125.
6. Li M, Li S, Zhou H, et al. Chemotaxis-driven delivery of nano-pathogenoids for complete eradication of tumors post-phototherapy. *Nat Commun*. 2020;11(1):1126.
7. Dionisie V, Filip GA, Manea MC, et al. Neutrophil-to-lymphocyte ratio, a novel inflammatory marker, as a predictor of bipolar type in depressed patients: a quest for biological markers. *J Clin Med*. 2021;10:9.
8. Yan X, Li G. Preoperative systemic immune-inflammation index predicts prognosis and guides clinical treatment in patients with non-small cell lung cancer. *Biosci Rep*. 2020;40:3.
9. Beineke P, Fitch K, Tao H, et al. A whole blood gene expression-based signature for smoking status. *BMC Med Genomics*. 2012;5:58.
10. Wingrove JA, Daniels SE, Sehnert AJ, et al. Correlation of peripheral-blood gene expression with the extent of coronary artery stenosis. *Circ Cardiovasc Genet*. 2008;1(1):31–38.
11. Rosenberg S, Elashoff MR, Beineke P, et al. Multicenter validation of the diagnostic accuracy of a blood-based gene expression test for assessing obstructive coronary artery disease in nondiabetic patients. *Ann Intern Med*. 2010;153(7):425–434.
12. Deng MC, Eisen HJ, Mehra MR, et al. Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling. *Am J Transplant*. 2006;6(1):150–160.
13. Baechler EC, Batliwalla FM, Karypis G, et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. *Proc Natl Acad Sci USA*. 2003;100(5):2610–2615.
14. Yang YL, Wu CH, Hsu PF, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. *Eur J Clin Invest*. 2020;50(5):e13230.
15. Lu Y, Xin D, Wang F. Predictive significance of preoperative systemic immune-inflammation index determination in postoperative liver metastasis of colorectal cancer. *Onco Targets Ther*. 2019;12:7791–7799.
16. Silva-Vaz P, Abrantes AM, Morgado-Nunes S, et al. Evaluation of prognostic factors of severity in acute biliary pancreatitis. *Int J Mol Sci*. 2020;21:12.
17. Ahluwalia N, Dwyer J, Terry A, Moshfegh A, Johnson C. Update on NHANES dietary data: focus on collection, release, analytical considerations, and uses to inform public policy. *Adv Nutri*. 2016;7(1):121–134.
18. Zipf G, Chiappa M, Porter KS, Ostchega Y, Lewis BG, Dostal J. National health and nutrition examination survey: plan and operations, 1999–2010. Vital and health statistics Ser 1, Programs and collection procedures. *Chemosphere*. 2013;3(56):1–37.
19. Hu B, Yang XR, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. *Clin Cancer Res*. 2014;20(23):6212–6222.
20. Liao S, Zhang J, Shi S, et al. Association of aldehyde exposure with cardiovascular disease. *Ecotoxicol Environ Saf*. 2020;206:111385.

21. Rattan P, Penrice DD, Ahn JC, et al. Inverse association of telomere length with liver disease and mortality in the US population. *Hepatol Commun*. 2022;6(2):399–410.
22. Fest J, Ruiter R, Ikram MA, Voortman T, van Eijck CHJ, Stricker BH. Reference values for white blood-cell-based inflammatory markers in the Rotterdam Study: a population-based prospective cohort study. *Sci Rep*. 2018;8(1):10566.
23. Huang J, Zhang Q, Wang R, et al. Systemic immune-inflammatory index predicts clinical outcomes for elderly patients with acute myocardial infarction receiving percutaneous coronary intervention. *Med Sci Monit*. 2019;25:9690–9701.
24. Wang Z, Qin Z, Yuan R, et al. Systemic immune-inflammation index as a prognostic marker for advanced chronic heart failure with renal dysfunction. *ESC Heart Fail*. 2022;2022:1.
25. Orhan AL, Şaylık F, Çiçek V, Akbulut T, Selçuk M, Çınar T. Evaluating the systemic immune-inflammation index for in-hospital and long-term mortality in elderly non-ST-elevation myocardial infarction patients. *Aging Clin Exp Res*. 2022;34(7):1687–1695.
26. Li Z, Yang F, Dunn S, Gross AK, Smyth SS. Platelets as immune mediators: their role in host defense responses and sepsis. *Thromb Res*. 2011;127 (3):184–188.
27. Ho-Tin-Noé B, Carbo C, Demers M, Cifuni SM, Goerge T, Wagner DD. Innate immune cells induce hemorrhage in tumors during thrombocytopenia. *Am J Pathol*. 2009;175(4):1699–1708.
28. Pasalic L, Wang SS, Chen VM. Platelets as biomarkers of coronary artery disease. *Semin Thromb Hemost*. 2016;42(3):223–233.
29. Gawaz M, Langer H, May AE. Platelets in inflammation and atherogenesis. *J Clin Invest*. 2005;115(12):3378–3384.
30. Silvestre-Roig C, Braster Q, Wichapong K, et al. Externalized histone H4 orchestrates chronic inflammation by inducing lytic cell death. *Nature*. 2019;569(7755):236–240.
31. Jickling GC, Liu D, Ander BP, Stamova B, Zhan X, Sharp FR. Targeting neutrophils in ischemic stroke: translational insights from experimental studies. *J Cereb Blood Flow Metab*. 2015;35(6):888–901.
32. Núñez J, Miñana G, Bodí V, et al. Low lymphocyte count and cardiovascular diseases. *Curr Med Chem*. 2011;18(21):3226–3233.
33. Ommen SR, Gibbons RJ, Hodge DO, Thomson SP. Usefulness of the lymphocyte concentration as a prognostic marker in coronary artery disease. *Am J Cardiol*. 1997;79(6):812–814.
34. Yao J, Cheng Y, Zhou M, et al. ROS scavenging Mn(3)O(4) nanozymes for in vivo anti-inflammation. *Chem Sci*. 2018;9(11):2927–2933.
35. Karaaslan T, Karaaslan E. Predictive value of systemic immune-inflammation index in determining mortality in COVID-19 patients. *J Crit Care Med*. 2022;8(3):156–164.
36. He L, Xie X, Xue J, Xie H, Zhang Y. Association of the systemic immune-inflammation index with all-cause mortality in patients with arteriosclerotic cardiovascular disease. *Front Cardiovasc Med*. 2022;9:952953.
37. Li H, Wu X, Bai Y, et al. Physical activity attenuates the associations of systemic immune-inflammation index with total and cause-specific mortality among middle-aged and older populations. *Sci Rep*. 2021;11(1):12532.
38. Öcal L, Keskin M, Cerşit S, et al. Systemic immune-inflammation index predicts in-hospital and long-term outcomes in patients with ST-segment elevation myocardial infarction. *Coron Artery Dis*. 2022;33(4):251–260.
39. Nøst TH, Alcala K, Urbarova I, et al. Systemic inflammation markers and cancer incidence in the UK Biobank. *Eur J Epidemiol*. 2021;36 (8):841–848.
40. Chen JH, Zhai ET, Yuan YJ, et al. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. *World J Gastroenterol*. 2017;23(34):6261–6272.
41. Su G, Zhang Y, Xiao R, Zhang T, Gong B. Systemic immune-inflammation index as a promising predictor of mortality in patients with acute coronary syndrome: a real-world study. *J Int Med Res*. 2021;49(5):3000605211016274.
42. Wang Z, Ruan H, Li L, et al. Assessing the relationship between systemic immune-inflammation index and mortality in patients with hypertrophic cardiomyopathy. *Ups J Med Sci*. 2021;2021:126.
43. Agus HZ, Kahraman S, Arslan C, et al. Systemic immune-inflammation index predicts mortality in infective endocarditis. *J Saudi Heart Assoc*. 2020;32(1):58–64.
44. Tang Y, Zeng X, Feng Y, et al. Association of systemic immune-inflammation index with short-term mortality of congestive heart failure: a retrospective cohort study. *Front Cardiovasc Med*. 2021;8:753133.
45. Wu S, Shi X, Zhou Q, Duan X, Zhang X, Guo H. The association between systemic immune-inflammation index and all-cause mortality in acute ischemic stroke patients: analysis from the MIMIC-IV database. *Emerg Med Int*. 2022;2022:4156489.