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Association between systemic immune-inflammation index and the risk of all-cause, cancer and non-cancer mortality in the general population: results from national health and nutrition examination survey 2005–2018

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Summary

Background Inflammation plays an important role in the progression of cancer and other diseases, such as diabetes and cardiovascular and cerebrovascular diseases. The systemic immune-inflammation index (SII) was recognized as an objective biomarker reflecting immunoinflammatory status. This study aimed to identify the association between SII with all-cause, cancer and non-cancer mortality among general population in the United States.

Methods 25,955 participants (≥ 20 years) were included from 2005 to 2018 National Health and Nutrition Examination Survey (NHANES) and were divided into four groups according to the SII quartiles. Weighted multivariate Cox regression was used to assess the correlation between SII and mortality. Subgroup analyses were conducted to identify the effects of other covariates on the relationship between SII and mortality. A restricted cubic spline (RCS) model was subsequently used to explore the dose-response relationship between SII and mortality. Survival analysis was assessed using Kaplan-Meier method.

Results In fully adjusted model, the adjusted hazard ratio (aHR) and 95% confidence intervals (CIs) of individuals in Q4 were 1.24 (1.09, 1.41) for all-cause mortality and 1.41 (1.23, 1.63) for non-cancer mortality compared with Q1. Besides, the aHR and 95% CIs in Q2 of SII were 0.70 (0.50, 0.99) and in Q3 were 0.68 (0.52, 0.87) compared with Q1 for cancer mortality. In RCS analysis, non-linear relationships of J-shaped curves were observed in the association between SII with all-cause and non-cancer mortality. Additionally, a U-shaped curve was identified between SII and cancer mortality with a threshold value of 445.22.

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Conclusion Our findings imply that SII can serve as a potential prognosis indicator among general population. Elevated SII is associated with higher all-cause and non-cancer mortality. Furthermore, both the lowest and highest quartiles of the SII exhibit a correlation with heightened cancer mortality.

Keywords Systemic immune-inflammation index, Mortality, NHANES, Prospective cohort study, Non-linear relationship

Background

Inflammation holds a crucial position in the progression of cancer [1, 2] and other diseases, such as diabetes [3] and cardiovascular and cerebrovascular diseases [4, 5]. Several environmental factors, including carcinogenic microorganisms, pollutants, tissue-damaging radiation, tobacco smoke, diesel engine exhaust, particulate matter and dietary factors, can induce chronic inflammation in multiple organ systems, which is a key factor in the progression of tumors [6]. Chronic inflammation and the release of inflammatory cytokines stimulate cancer cell proliferation, invasion and metastasis, while concurrently aiding in the evasion of immune surveillance by tumor cells [1, 7]. A low degree of chronic inflammation and several mediators such as interleukin-1, interleukin-6 and tumor necrosis factor-α are associated with insulin resistance, and the heightened ROS production in the inflammatory microenvironment contributes to beta-cell damage and diabetes worsening [3, 8]. Additionally, in the context of cardiovascular and cerebrovascular disease development, the distinct microenvironment of atherosclerotic plaques and adjacent tissues is marked by repeated inflammatory and reparative reaction [9].

Systemic inflammation can be evaluated with diverse haematological indicators, which are frequently analyzed in routine blood tests or through the calculation of ratios based on these measurements [10]. Systemic immune-inflammation index (SII, platelets count × neutrophil/lymphocyte ratio), regarded as an objective marker that reflects the balance between host inflammatory and immune response status, was initially introduced as a tool for assessing the prognosis of hepatocellular carcinoma [11]. Recently, SII has been reported to be associated with adverse outcomes in various diseases [12–15]. The preoperative SII was identified as a valuable prognostic indicator for predicting long-term outcomes in breast cancer patients undergoing surgical intervention. Specifically, an elevated SII was an independent worse prognostic factor for both disease-free survival (DFS), with a hazard ratio (HR) of 4.530 (95% confidence interval [CI], 3.279–6.258; $P < 0.001$), and overall survival (OS), with an HR of 3.825 (95% CI, 2.594–5.640; $P < 0.001$) [16]. In patients with cardiovascular disease, compared to individuals in the lowest quartile of the SII ($4.056 \le SII < 349.500$), those in the highest quartile ($376.155 \le SII < 11{,}700.000$) exhibited an increased risk of all-cause, cancer, and CVD mortality by 20.2% (95%CI, 0.981–1.474), 36.5% (95%CI, 1.115–1.672)) and 18.4% (95%CI, 0.967–1.450), respectively [17].

However, the relationship between SII and mortality in general population was not well studied. To fill the knowledge gap, we aimed to explore the association of SII with all-cause mortality, cancer mortality, and non-cancer mortality using a nationally-representative sample of adults (≥ 20 years) in the United States.

Materials and methods

Sample sources

The US National Center for Health Statistics' National Health and Nutrition Examination Survey (NHANES) was utilized to conduct this prospective cohort study. As a continuous survey (1999 - present), NHANES employs a stratified, multi-phase probability sampling framework, which entails the selection of counties, blocks, households and individuals, aiming to provide a representative depiction of the civilian, non-institutionalized segment of American population. All the participants were required to take household questionnaires and then to undergo standardized physical examinations in mobile examination centers, and the processes were performed by well-trained interviewers and medical personnel. Besides, all the individuals enrolled have written informed consent [18, 19].

Study population

As shown in the flowchart (Fig. 1), we collected data from 2005 to 2018 with a total of 70,190 participants. After excluding participants less than 20 years old ($n = 30441$) and with missing data on SII ($n = 3559$), mortality information ($n = 73$) and other covariates ($n = 10162$), 25,955 participants were enrolled ultimately.

Assessment of SII

Serving as the explanatory factor, the value of SII is based on the counts of platelet, neutrophil and lymphocyte. After participants were enrolled in the study, blood samples were collected on mobile examination centers and then blood cell counts were measured by the automated hematological analyzer (a CoulterDxH 800 analyzer) [20, 21]. SII was expressed as 1000 cells/μl and calculated as follows: SII = platelet count × absolute neutrophil count / absolute lymphocyte count [11, 20–22].

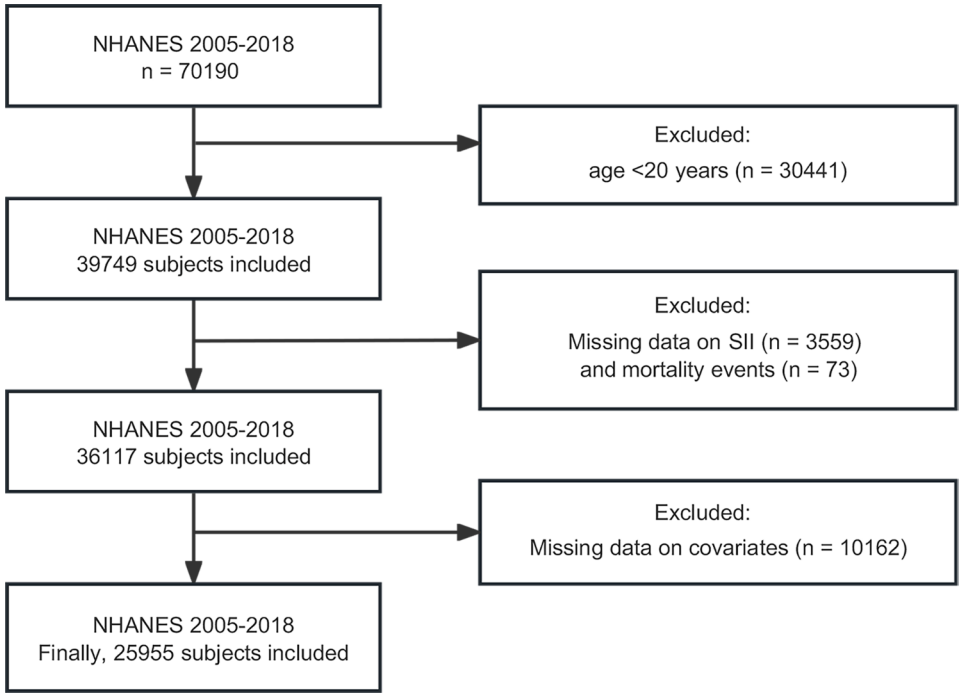

Fig. 1 Flowchart of included participants

Covariates

Self-reported sociodemographic characteristics included age, gender (male or female), race (non-Hispanic white, non-Hispanic black, Mexican American and other), education attainment (< high school, high school, > high school), marital status (married, single), family poverty income ratio (PIR), body mass index (BMI) (< 25, 25–30, > 30). In terms of smoking status, never smoker was defined as fewer than 100 cigarettes in entire life; former smoker as more than 100 cigarettes during life but not at all currently smoking; and current smoker as more than 100 cigarettes during life and smoking some days or every day in the recent year. In alcohol drinking status, never drinker was defined as fewer than 12 alcoholic beverages in entire life; former drinker as more than 12 alcoholic beverages during life but not at all currently drinking; and current drinker as more than 12 alcoholic beverages during life and drinking several days or every day in the past year. The definitions of hypertension, diabetes and dyslipidemia were reported in previous literature [23].

Assessment of mortality

Mortality outcomes were ascertained using death certificates records from the National Death Index. Death from all reasons was defined as all-cause mortality. Cancer mortality was defined as any death related to cancer, as indicated by the ICD-10 codes C00-C97, otherwise, deaths were defined as non-cancer mortality. The time in months from the household interview to death or to the end of the study period on December 31, 2019, whichever came first, was assessed as the follow-up time.

Statistical analysis

All statistical analysis used proper NHANES sample weights and accounted for the complex multistage subgroup survey. Participants were grouped by the quartile of SII, and differences between groups were evaluated using weighted linear regression for continuous variables or weighted chi-square testing for categorical variables. Multivariate cox regression analysis was used to investigate the association between SII and mortality and its components in three distinct models. Age was adjusted in model 1. Age, gender, race, education attainment, marital status, PIR, BMI, smoking status, alcohol drinking status were made to model 2. Based on model 2, model 3 was further adjusted for the status of hypertension, diabetes and dyslipidemia. Subgroup analysis of the association between SII and mortality was performed using stratifed factors including the covariates mentioned above. The interaction analysis was introduced to identify the mutual effect of SII and the covariates. The nonlinear relationships between SII with a series of mortality were tested using restricted cubic spline (RCS) regression. Survival analysis was constructed using Kaplan-Meier methodology. To test the robustness of our findings, two sensitivity analysis were performed. First, participants who died within 2-year of follow-up were removed to eliminate the potential reverse causality. Second, multiple imputation was conducted for variables with missing data. Then, the

relationship between SII and mortality was retested in the the new population or in imputed complete datasets.

R software (version 4.3.2) was used for all analysis. A two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 25,955 participants (weighted population of 156,150,8941) were included, with mean (SD) aged 47.0 (31.2, 59.0) years, 13,210 (51.3%) women and 11,878 (70.2%) non-Hispanic white participants. SII was grouped into Q1 ($1.53 \le SII < 337.87$), Q2 ($337.87 \le SII < 476.00$), Q3 ($476.00 \le SII < 676.42$) and Q4 ($SII \ge 676.42$) categories, and the participant characteristics were presented by the SII groups in Table 1. Participants with higher SII were more likely to be female, white people, with an education background of more than high school, married, never smoker but current drinker, BMI > 30 and with dyslipidemia. During 90.46 (47.99) months of follow-up, 3047 of 25,955 participants died. A total of 781 deaths occurred due to cardiovascular diseases and 717 due to cancer (Table S1 in the Supplement).

Association between SII and mortality

The relationships between SII and mortality were presented in Fig. 2. In minimally adjusted model, the adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) in Q4 of SII were 1.34 (1.19, 1.50) for all-cause

Table 1 Baseline characteristics of included participants

Characteristic	Overall *N* = 25,955 (100%)[1]	SII				*P* Value[2]
		Q1 *N* = 6577 (23%)[1]	Q2 *N* = 6562 (26%)[1]	Q3 *N* = 6532 (26%)[1]	Q4 *N* = 6284 (25%)[1]	
Age (years)	47.0 (31.2, 59.0)	46.7 (32.3, 59.1)	46.0 (34.6, 59.2)	47.4 (35.8, 61.5)	46.7 (32.2, 59.8)	**< 0.001**
Gender (%)						**< 0.001**
female	13,210 (51.3%)	2,994 (45.6%)	3,204 (49.2%)	3,442 (51.7%)	3,570 (58.3%)	
male	12,745 (48.7%)	3,583 (54.4%)	3,358 (50.8%)	3,090 (48.3%)	2,714 (41.7%)	
Race (%)						**< 0.001**
Non-Hispanic White	11,878 (70.2%)	2,305 (61.8%)	2,973 (70.7%)	3,211 (72.1%)	3,389 (75.3%)	
Non-Hispanic Black	5,279 (10.4%)	2,152 (18.2%)	1,231 (9.3%)	1,023 (7.8%)	873 (6.9%)	
Mexican American	4,059 (8.0%)	889 (8.0%)	1,060 (7.9%)	1,120 (8.5%)	990 (7.6%)	
Other	4,739 (11.5%)	1,231 (12.1%)	1,298 (12.2%)	1,178 (11.6%)	1,032 (10.2%)	
education attainment (%)						**< 0.001**
< High school	6,329 (15.9%)	1,623 (16.8%)	1,571 (14.7%)	1,605 (16.0%)	1,530 (16.3%)	
High school	5,944 (22.5%)	1,490 (21.8%)	1,442 (21.2%)	1,496 (22.8%)	1,516 (24.3%)	
> High school	13,682 (61.5%)	3,464 (61.4%)	3,549 (64.1%)	3,431 (61.2%)	3,238 (59.4%)	
Marital status						**< 0.001**
Married	15,642 (64.2%)	3,958 (65.0%)	4,097 (67.0%)	3,951 (63.8%)	3,636 (61.2%)	
Single	10,313 (35.8%)	2,619 (35.0%)	2,465 (33.0%)	2,581 (36.2%)	2,648 (38.8%)	
Family poverty income ratio	3.02 (1.64)	2.98 (1.64)	3.09 (1.64)	3.05 (1.64)	2.96 (1.63)	**< 0.001**
Smoking status (%)						**< 0.001**
Current	5,446 (20.6%)	1,305 (18.7%)	1,285 (19.0%)	1,380 (21.0%)	1,476 (23.8%)	
Former	6,418 (25.0%)	1,563 (24.5%)	1,614 (24.8%)	1,595 (24.5%)	1,646 (26.3%)	
Never	14,091 (54.3%)	3,709 (56.8%)	3,663 (56.2%)	3,557 (54.5%)	3,162 (49.9%)	
Alcohol drinking status (%)						**< 0.001**
Current	15,681 (67.7%)	3,910 (67.4%)	4,052 (69.7%)	4,018 (68.1%)	3,701 (65.6%)	
Former	2,918 (9.4%)	746 (9.3%)	681 (8.0%)	717 (9.7%)	774 (10.6%)	
Never	7,356 (22.9%)	1,921 (23.3%)	1,829 (22.3%)	1,797 (22.3%)	1,809 (23.7%)	
BMI (%)						**< 0.001**
< 25	7,484 (30.1%)	2,058 (33.1%)	1,913 (31.4%)	1,776 (27.9%)	1,737 (28.2%)	
25–30	8,625 (33.2%)	2,305 (35.3%)	2,235 (34.0%)	2,164 (33.5%)	1,921 (30.3%)	
> 30	9,846 (36.7%)	2,214 (31.6%)	2,414 (34.6%)	2,592 (38.6%)	2,626 (41.5%)	
Hypertension (%)	11,140 (38.3%)	2,799 (36.3%)	2,659 (35.4%)	2,806 (38.6%)	2,876 (42.9%)	**< 0.001**
Diabetes (%)	4,883 (14.4%)	1,200 (13.2%)	1,186 (13.2%)	1,191 (14.3%)	1,306 (16.8%)	**< 0.001**
Dyslipidemia (%)	18,957 (72.6%)	4,583 (69.0%)	4,781 (71.7%)	4,891 (74.7%)	4,702 (74.5%)	**< 0.001**
SII (1,000 cells/μL)	480.73 (349.18, 675.11)	268.40 (218.40, 303.88)	406.40 (372.75, 439.37)	561.08 (515.29, 612.00)	857.65 (749.55, 1,057.99)	**< 0.001**

[1]Median (IQR) for numeric variables; n (%) for categorical variables

[2]Wilcoxon rank-sum test for complex survey samples; chi-squared test with Rao & Scott's second-order correction

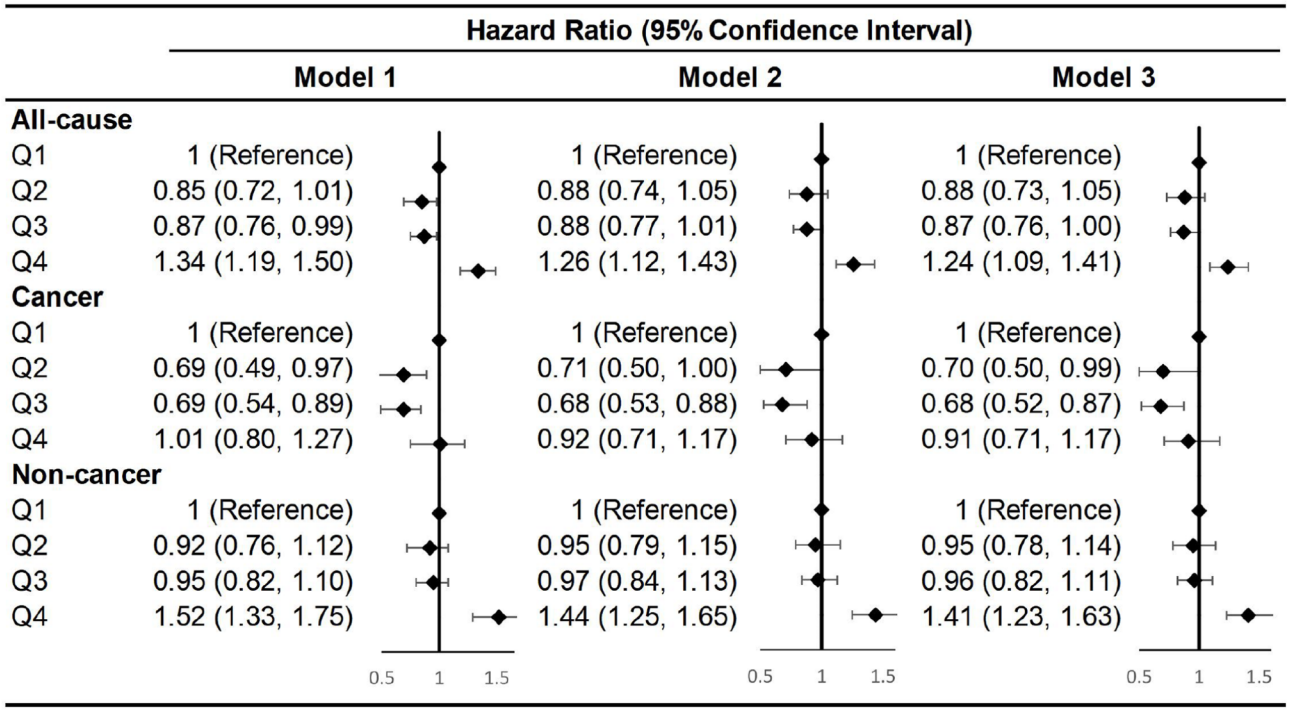

Fig. 2 Associations of SII with all-cause, cancer and non-cancer mortality
Model 1: Age was adjusted
Model 2: Age, gender, race, education attainment, marital status, family poverty income ratio, body mass index, smoking status, alcohol drinking status were adjusted
Model 3: Based on model 2, the status of hypertension, diabetes and dyslipidemia were further adjusted

mortality and 1.52 (1.33, 1.75) for non-cancer mortality compared with Q1. The magnitudes of the association attenuated when the model was fully adjusted but remain statistically significant, with the aHRs and 95% CIs in Q4 of SII were 1.24 (1.09, 1.41) for all-cause mortality and 1.41 (1.23, 1.63) for non-cancer mortality compared with Q1. Notably, for cancer mortality in fully adjusted model, the aHRs and 95% CIs in Q2 of SII were 0.70 (0.50, 0.99) and in Q3 were 0.68 (0.52, 0.87) compared with Q1 (Fig. 2). All trends remained similar after imputing the missing data or after excluding deaths that occurred within the initial 2-year follow-up (Fig. S1 and Fig. S2 in the Supplement).

Subgroup analysis

The subgroup analysis was shown in Fig. 3. Participants who were more than 60 years, non-Hispanic black, other races, with an education background less than high school, married, never drinker, with hypertension or diabetes showed statistically significant association between SII and all-cause mortality. In addition, participants who were male, more than 60 years, non-Hispanic black, other races, with an education background less than high school, married, never smoker and never drinker, BMI < 25 or > 30, with hypertension, with diabetes, with and without dyslipidemia showed positive association between SII with non-cancer mortality (Fig. 3). Interaction tests revealed no significant difference in the correlation between SII and all-cause mortality for age, gender, race, education attainment, marital status, PIR, smoking status, alcohol drinking status, the prevalence of hypertension and dyslipidemia (P for interaction > 0.05). However, BMI and the prevalence of diabetes may influence the positive correlation between SII and all-cause mortality (P for interaction < 0.05).

Analysis of RCS model

After adjusting all the covariates, non-linear relationships of J-shaped curves were observed between SII with all-cause and non-cancer mortality in RCS regression ($P < 0.001$, Fig. 4). Higher SII was significantly associated with higher all-cause mortality or non-cancer mortality after SII reaching 406.00 or 410.58, respectively. Besides, a U-shaped association between SII and cancer mortality was observed. The risk of cancer mortality decreased with SII below the threshold of 445.22, and the decreasing trend reversed after SII exceeding the threshold.

Kaplan-Meier survival analysis

Participants in the Q4 of SII had a higher cumulative hazard for all-cause mortality and non-cancer mortality than those in the Q1 of SII (Q4 vs. Q1, $P < 0.001$, Fig. 5A

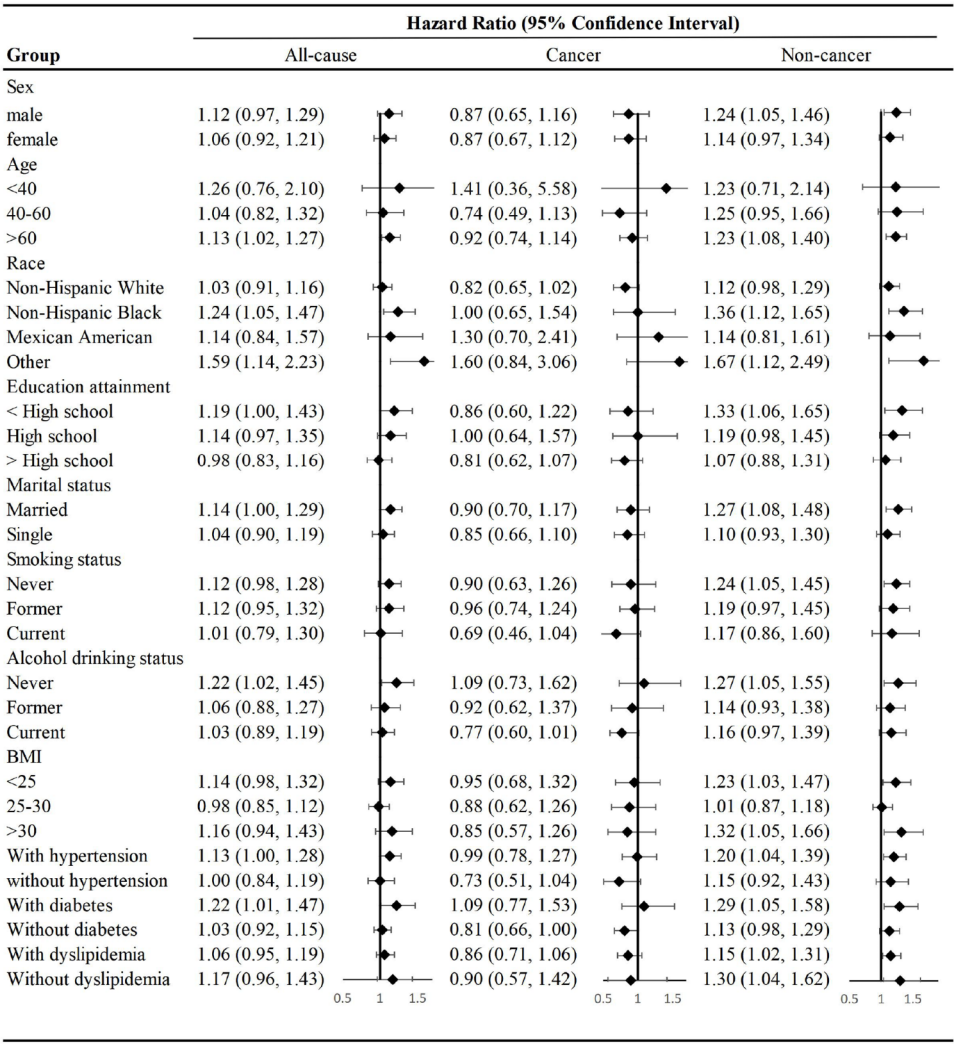

Fig. 3 Subgroup analysis of the association between SII with all-cause, cancer and non-cancer mortality. Each stratum was adjusted for age, gender, race, education attainment, marital status, family poverty income ratio, body mass index, smoking status, alcohol drinking status, hypertension, diabetes and dyslipidemia

and C). For cancer mortality, there was no significant difference in the cumulative hazard between the Q1 and Q4 populations (Q1 vs. Q4, $P > 0.05$), but the cumulative hazards for both were higher than that for the Q2 or Q3 populations, with a statistically significant difference (Q1 vs. Q2 or Q3, $P < 0.001$, Q4 vs. Q2 or Q3, $P < 0.001$, Fig. 5B). Furthermore, SII of Q2 and Q3 were combined into one group. The participants with SII of Q1 had a higher cumulative hazard (Q1 vs. Q2 + Q3, $P = 0.0019$, Fig. 5D), and those with SII of Q4 had the similar trend (Q4 vs. Q2 + Q3, $P < 0.001$, Fig. 5D) than counterparts with median SII values (Q2 + Q3).

Discussion

In this nationally representative cohort of US adults aged 20 years or older, elevated SII was significantly associated with higher all-cause and non-cancer mortality. Compared with SII of Q1, individuals with SII of Q4 were associated with a higher death risk of 24% for all-cause mortality and 41% for non-cancer mortality. However, for cancer mortality, there was no significant difference between SII of Q1 and Q4 populations, and those with SII of Q2 and Q3 had 30% and 32% lower death risk, respectively. The U-shaped curve observed in RCS analysis provided comprehensive verification of this trend.

SII was regarded as an objective marker that reflects the balance between host inflammatory and immune response status [11]. A recent study reported that individuals with higher SII had a higher risk of death from all-cause with aHR and 95% CI of 1.48 (1.48–1.48) and cardiovascular mortality with aHR and 95% CI of 1.60 (1.60–1.61) compared with those with lower SII level among participants aged more than 20 years [24]. In addition, participants with higher SII scores had a higher

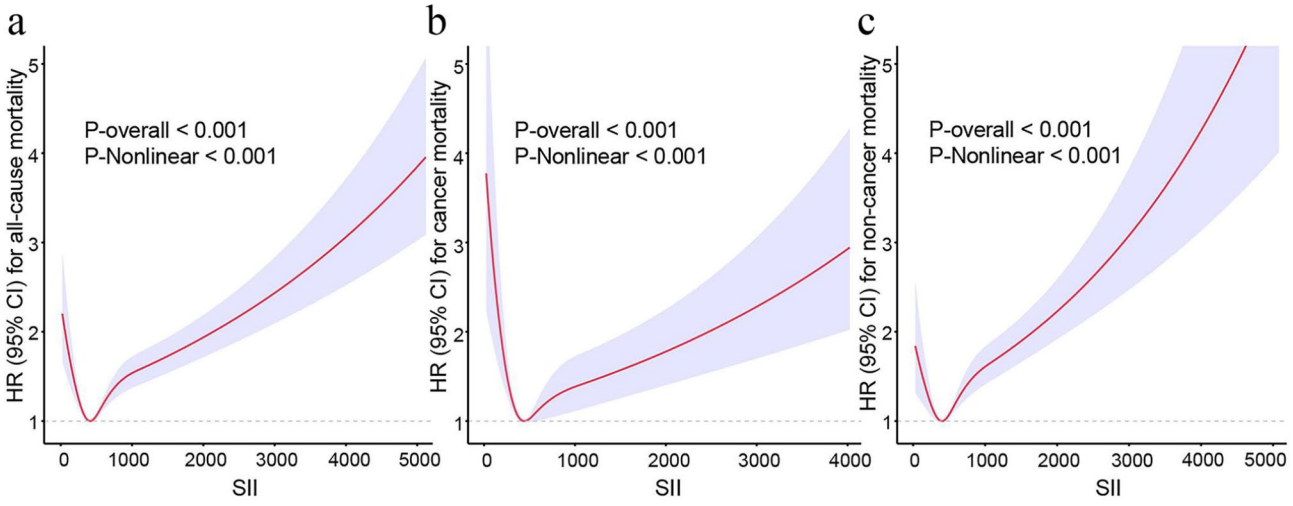

Fig. 4 Non-linear relationships between SII with all-cause, cancer and non-cancer mortality. **(A)** all-cause mortality, **(B)** cancer mortality, **(C)** non-cancer mortality

HR, hazard ratio; CI confidence interval. HRs (solid lines) and 95% CIs (shaded areas) were adjusted for age, gender, race, education attainment, marital status, family poverty income ratio, body mass index, smoking status, alcohol drinking status, hypertension, diabetes and dyslipidemia. Vertical dotted lines suggested the minimal threshold for the beneficial association with estimated HR = 1

chance of developing metabolic syndrome with odds ratio (OR) and 95%CI of 1.33 (1.14–1.55) [25]. Furthermore, metabolic syndrome was turned out to be associated with higher all-cause, heart disease, and diabetes mortality with significantly elevated aHRs and 95% CIs of 1.24 (1.16, 1.33), 1.44 (1.25, 1.66) and 5.15 (3.15, 8.43) [26].

The U-shaped RCS curve complicates the analysis of the association between SII with cancer mortality. The same trend was reported in the association between SII with the mortality among patients with primary central nervous system lymphoma [27]. The patients with SII < 450 or SII > 890 had a worse OS ($P < 0.0001$) and progression-free survival ($P = 0.0016$) than those with median SII values (450 < SII < 890). As reported in the previous literature, neutrophils play contradictory roles in cancer progression. On the one hand, neutrophils inhibit the anti-tumor immune responses [28], and the formation of neutrophils extracellular traps (NETs) induces the epithelialization of cancer cells and promotes the angiogenesis in tumor tissues, assisting tumor cells in detaching from the primary tumor, surviving in the blood circulation and ultimately colonizing distant organs [29–32]. On the other hand, neutrophils exhibit the capacity to suppress early-stage tumor progression through eliciting the detachment of cancer cells from the basement membrane. Besides, neutrophils secrete nitric oxide to directly eliminate cancer cells and modify the anti-tumor microenvironment in a manner that manifests anticancer efficacy [29]. Plateletsplay a crucial role in the initiation and progression of cancer. Not only can platelets protect tumor cells from immune surveillance, but also stimulate angiogenesis in tumor tissues by promoting the release of angiogenic factors [33]. Furthermore, platelets can facilitate the aggregation of inflammatory cells in tumor tissues, and jointly induce the generation of NETs with tumor cells, promoting the aggression of tumor cells and accelerating the progression of cancer [34, 35]. Lymphocytes are essential tools in the anti-tumor immune response [36]. Cytotoxic T cells (TCLs) can directly kill tumor cells through the mechanism involving the recognition of antigens presented on the surface of tumor cells and the secretion of cytotoxic molecules such as perforin and granzyme B [37–39]. The increased number of lymphocytes in the tumor microenvironment is associated with improved survival rates among cancer patients [40]. Additionally, regulatory T cells (Tregs) can reduce the accumulation of effector T cells in tumor tissues through the expression of immunosuppressive receptors and the secretion of related cytokines, which are significantly correlated with a poor prognosis [41]. The different subpopulations and functions of these hemocytes in tumor tissues may account for the U-shaped relationship between SII and cancer mortality. As reported in the previous literature, patients exhibiting an elevated preoperative SII often present with thrombocytopenia, neutrophilia or lymphopenia, indicating a heightened inflammatory status and a compromised immune response [11]. However, whether the alteration in the immune cell composition primarily manifests as an expansion of cancer-promoting neutrophils and a reduction in effector T cells still requires further research.

There are several strengths in our study. First, the research was conducted in a nationally representative sample, which can be generalized to larger population. Second, prospective cohort study with well-designed

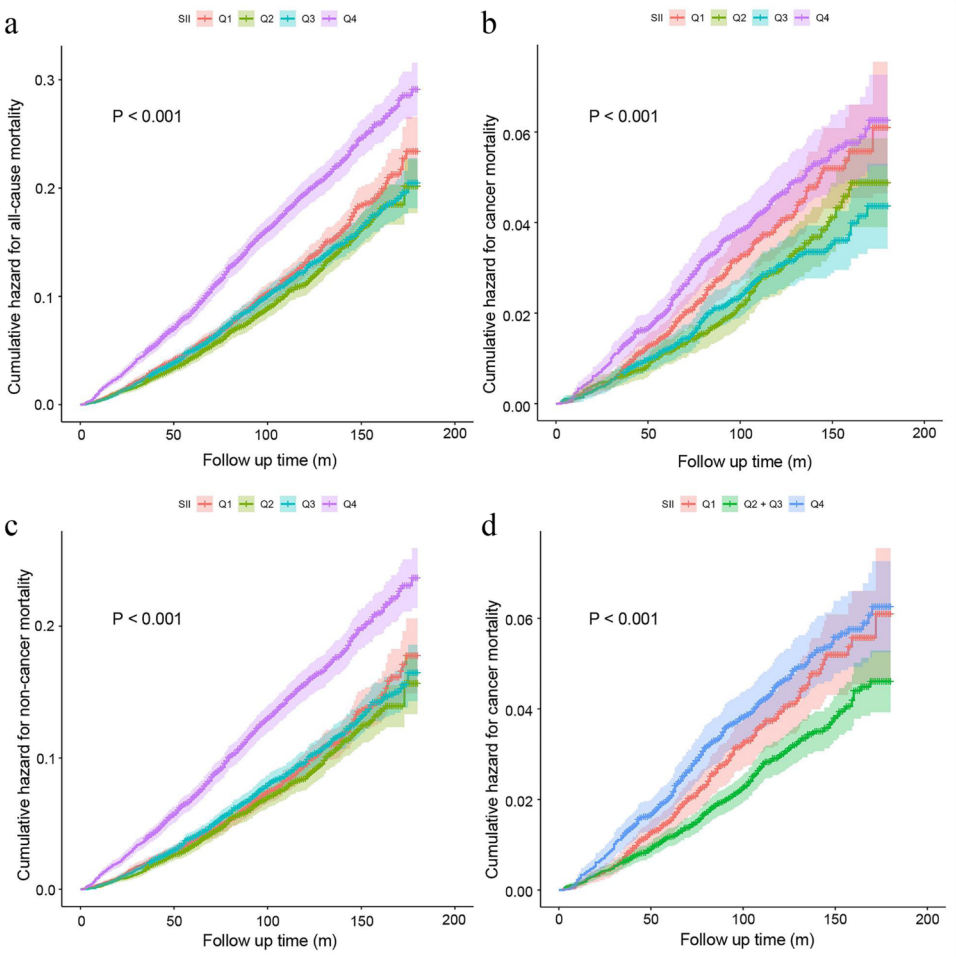

Fig. 5 Kaplan-Meier analysis estimates all-cause, cancer and non-cancer mortality according to SII levels. **(A)** All-cause mortality according to Q1-Q4 of four SII levels. **(B)** Cancer mortality according to Q1-Q4 of four SII levels. **(C)** Non-cancer mortality according to Q1-Q4 of four SII levels. **(D)** Cancer mortality according to Q1 or Q4, and Q2 + Q3 of three SII levels

protocols provides a firm evidence of the association between SII with mortality. Third, SII is an objective index based on blood cells counts assessed by hemocytometer, so that recall bias can be avoided to the maximum extent. Finally, we reshaped the non-linear relationship between predictor with outcomes using RCS curve in the Cox proportional hazards regression models.

There also exist several limitations. First, this is an observational research and no causal inferences was be conducted. Second, although numerous demographic factors, behavior risk factors and comorbidity have been adjusted, potential residual confounding cannot be entirely ruled out. Third, considering the demographic characteristics reflected in NHANES, the sample was representative of the American population, thus rendering the generalization of findings to other populations infeasible. Fourth, a single measurement of SII is susceptible to infection, stress and other abnormal factors, which may influence the results. Thus, using average value obtained from multiple measurements in further analysis will lead to more robust results.

Overall, our findings suggest that SII could be considered as a potential prognosis indicator among general population. Elevated SII is associated with higher all-cause and non-cancer mortality. Furthermore, both the lowest and highest quartiles of the SII exhibit a correlation with heightened cancer mortality.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-21423-1.

Fig S1. Associations of SII with all-cause, cancer, non-cancer mortality, sensitivity analysis##imputed the missing data by multiple imputation methodModel 1: Age was adjustedModel 2: Age, gender, race, education attainment, marital status, family poverty income ratio, body mass index, smoking status, alcohol drinking status were adjustedModel 3: Based on model 2, the status of hypertension, diabetes and dyslipidemia were further adjusted

Fig S2. Associations of SII with all-cause, cancer, non-cancer mortality, sensitivity analysis##excluded participants who died within the initial

2-year follow-upModel 1: Age was adjustedModel 2: Age, gender, race, education attainment, marital status, family poverty income ratio, body mass index, smoking status, alcohol drinking status were adjustedModel 3: Based on model 2, the status of hypertension, diabetes and dyslipidemia were further adjusted

Table S1. Death events observed among enrolled participants in NHANES 2005-2018

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Not applicable.

Author contributions
P.X designed the study. S.W and Z.L collected and analyzed data. X.L and S.G provided results visualization. S.W and P.X wrote the paper. All authors read and approved the final manuscript.

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Data availability
The NHANES data utilized in this study are accessible to the public and available for download from this location: https://wwwn.cdc.gov/nchs/nhanes.

Declarations

Ethics approval and consent to participate
The research was carried out following the Declaration of Helsinki and received approval from the NCHS Ethics Review Board. The NCHS IRB/ERB Protocol Number or Description of NHANES 2005–2006, NHANES 2007–2008, NHANES 2009–2010, NHANES 2011–2012, NHANES 2013–2014 and NHANES 2015–2016 were Protocol #2005-06, Continuation of Protocol #2005-06, Continuation of Protocol #2005-06, Protocol #2011-17, Continuation of Protocol #2011-17 and Continuation of Protocol #2011-17. Besides, the NCHS IRB/ERB Protocol Number or Description of NHANES 2017–2018 were Continuation of Protocol #2011-17 (Effective through October 26, 2017) and Protocol #2018-01 (Effective beginning October 26, 2017). 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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