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Relationship between systemic immune-inflammation index and long-term all-cause and cause-specific mortality among adult asthma patients: a population—based study

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Abstract

Background Persistent inflammation in the airways is a hallmark of asthma, and researchers have extensively explored various inflammatory indicators that contribute to the condition. Despite this, there is limited research on the relationship between the systemic immune-inflammation index (SII), a novel marker of inflammation, and overall mortality rates as well as mortality rates due to specific causes in individuals with asthma.

Methods We analyzed data from the National Health and Nutrition Examination Survey (NHANES) covering a 20-year period, from 1999 to 2018. To examine the association between SII and mortality rates in asthma patients, we used a combination of statistical methods, including weighted Kaplan-Meier analysis and multivariate-adjusted Cox analysis. Additionally, we applied restricted cubic spline (RCS) analysis to investigate the potential non-linear relationship between these variables. To further validate our findings, we performed subgroup and sensitivity analyses to ensure the reliability of the results.

Results This study analyzed data from 5,384 individuals with asthma, finding a link between increased SII levels and a higher risk of death from all-cause, cardiovascular disease and respiratory disease, but no association with cancer mortality. There were J-shaped non-linear relationships between SII and all-cause, cardiovascular and respiratory diseases mortality in asthma patients. The inflection points were 326, 350 and 355, respectively. Below these inflection points, each 100-unit increase in SII was associated with a decrease in mortality by 8%, 11% and 10%, while above these thresholds, mortality rates increased by 4%, 4%, and 3%, respectively. Subgroup analyses showed that SII was a significant predictor of all-cause mortality across various subgroups, and sensitivity analyses confirmed these findings, with the highest SII group consistently showing higher mortality rates for all-cause, cardiovascular, and respiratory disease mortality in the fully adjusted model.

Conclusions Our study initially demonstrated a strong link between elevated SII levels and a higher risk of death from all-cause, cardiovascular disease, and respiratory disease in individuals with asthma. Furthermore, our analysis

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showed that the relationship between SII and mortality rates in asthma patients followed a non-linear, J-shaped pattern for all-cause, cardiovascular, and respiratory disease mortality.

Clinical trial number Clinical trial number not applicable.

Keywords Systemic immune-inflammation index(SII), Asthma, Mortality, Population-based study, NHANES

Introduction

Asthma is a complex and multifaceted condition characterized by bronchial hyperresponsiveness, reversible airflow obstruction, and chronic inflammation. People with asthma often experience a range of symptoms, including chest tightness, breathlessness, and wheezing [1, 2]. The illness has a significant impact on patients' daily activities and long-term health, marked by frequent exacerbation, unpredictable treatment outcomes, and a variable disease trajectory. Globally, asthma affects about 300 million individuals and is a widespread chronic respiratory illness with high morbidity and mortality [3]. It is estimated that at least 250,000 deaths were attributed to the disease each year in the world [4]. Inflammation plays a pivotal role in the process of developing asthma [5]. Both local and systemic inflammation are involved in the development of asthma [6, 7]. Therefore, inflammatory markers may serve as prognostic indicators for patients with asthma.

An ideal prognostic biomarker can provide easily recognizable prognostic indicators at the time of diagnosis, maintain good cost-effectiveness, and ensure accessibility and affordability, making it widely applicable in clinical practice. The Systemic Immune-inflammation Index (SII) is acknowledged as a reliable and accurate tool for indicating overall immune responses and inflammation levels, whether systemic or localized. It mirrors the increase in absolute neutrophil and platelet counts, along with a decrease in lymphocyte count [8]. The SII has emerged as a widely studied metric in the field of disease diagnosis and prediction. Its utility has been demonstrated in numerous studies, where it has been shown to be a valuable predictor of patient outcomes and mortality rates for a range of diseases, including various types of cancer [9–11], spontaneous cerebral hemorrhage [12], ischemic stroke [13, 14] and cardiovascular disorders [15, 16]. The application of SII has been expanded in recent years, with studies showing its promise in predicting disease severity and evaluating the effectiveness of treatments [17–21]. By providing an accurate measurement of a patient's inflammatory response, SII can help healthcare professionals gain a deeper understanding of the patient's condition and create a tailored treatment strategy. Additionally, researches have demonstrated the value of SII in assessing the severity and progression of chronic inflammatory conditions like asthma [22, 23]. Notably, another study found that elevated SII levels were associated with a higher risk of mortality, suggesting that regular SII assessments could be a useful prognostic tool for older adults with asthma [24]. These findings highlight the potential of SII as a valuable indicator for monitoring inflammation and disease activity in patients with asthma.

Currently, researchers have not yet used the National Health and Nutrition Examination Survey (NHANES) database to study the relationship between the SII and mortality risk in asthma patients. Since there is a critical need for affordable and accessible prognostic indicators for asthma patients, our research sought to investigate the association between SII level and the risk of mortality from all-causes, as well as cardiovascular diseases, respiratory diseases and cancers. We hypothesized that higher SII levels would be linked to an increased risk of mortality. Our study analyzed a nationally representative cohort of American adults with asthma, utilizing data from the NHANES database [25].

Methods

Study population

Every two years, the Centers for Disease Control and Prevention (CDC) carries out the NHANES to collect data on the nutrition and health status of the Americans. This survey uses a complex sampling methodology to select representative cohort of non-institutionalized citizens that accurately reflect the population. The study underwent ethical scrutiny by the National Center for Health Statistics (NCHS) in the United States, and all participants provided their consent to take part in the research.

The NHANES data can be obtained from the NHANES website (http://www.cdc.gov/nchs/nhanes.htm).

Data from two decades of survey cycles, spanning from 1999 to 2000 to 2017–2018, was retrieved from the NHANES database for analysis in this research. We focused on adults aged ≥ 20 years who were diagnosed with asthma and provided complete data for SII and had available data on mortality information. Initially, a total of 101,316 participants were collected. Participants with unavailable asthma data (n = 4,506), SII data (n = 14,070), mortality data (n = 29,541), laboratory data (n = 1,014) and other covariates data (n = 13,995) were excluded. Furthermore, 32,806 participants without asthma were also excluded. Finally, a total of 5,384 qualified individuals were selected for the study. The detailed process of

participant selection, including the criteria for inclusion and exclusion, is illustrated in Fig. 1.

Systemic immune-inflammation index and other covariates

Lymphocyte, neutrophil, and platelet counts (expressed as $\times 10^3$cells/ml) were measured using the UniCel DxH 800 analyzer by trained personnel. In our study, we utilized specific formulas to calculate the SII level, which is determined by multiplying platelet counts with neutrophil counts and then dividing by lymphocyte (platelet*neutrophil/lymphocyte). The SII was specifically chosen as the variable of interest in our research. Demographic information and laboratory results were collected from the NHANES database across ten consecutive NHANES cycles. Demographic characteristics encompassed the following variables: age (continuous variable in years), gender (male/female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American and others), education level (less than high school, completed high school, and more than high school), and the family poverty-to-income ratio (PIR) (<1.3, 1.3–3.5, and >3.5) which was employed to assess the economic status. Marital statuses were grouped into married/living with partner, widowed/divorced, or never married. Lifestyle factors included body mass index (BMI) (continuous), self-reported smoking habits (never smoker (smoked fewer than 100 cigarettes in their lifetime), former smoker (smoked over 100 cigarettes but no longer smoke at all), and current smoker (had smoked over 100 cigarettes in

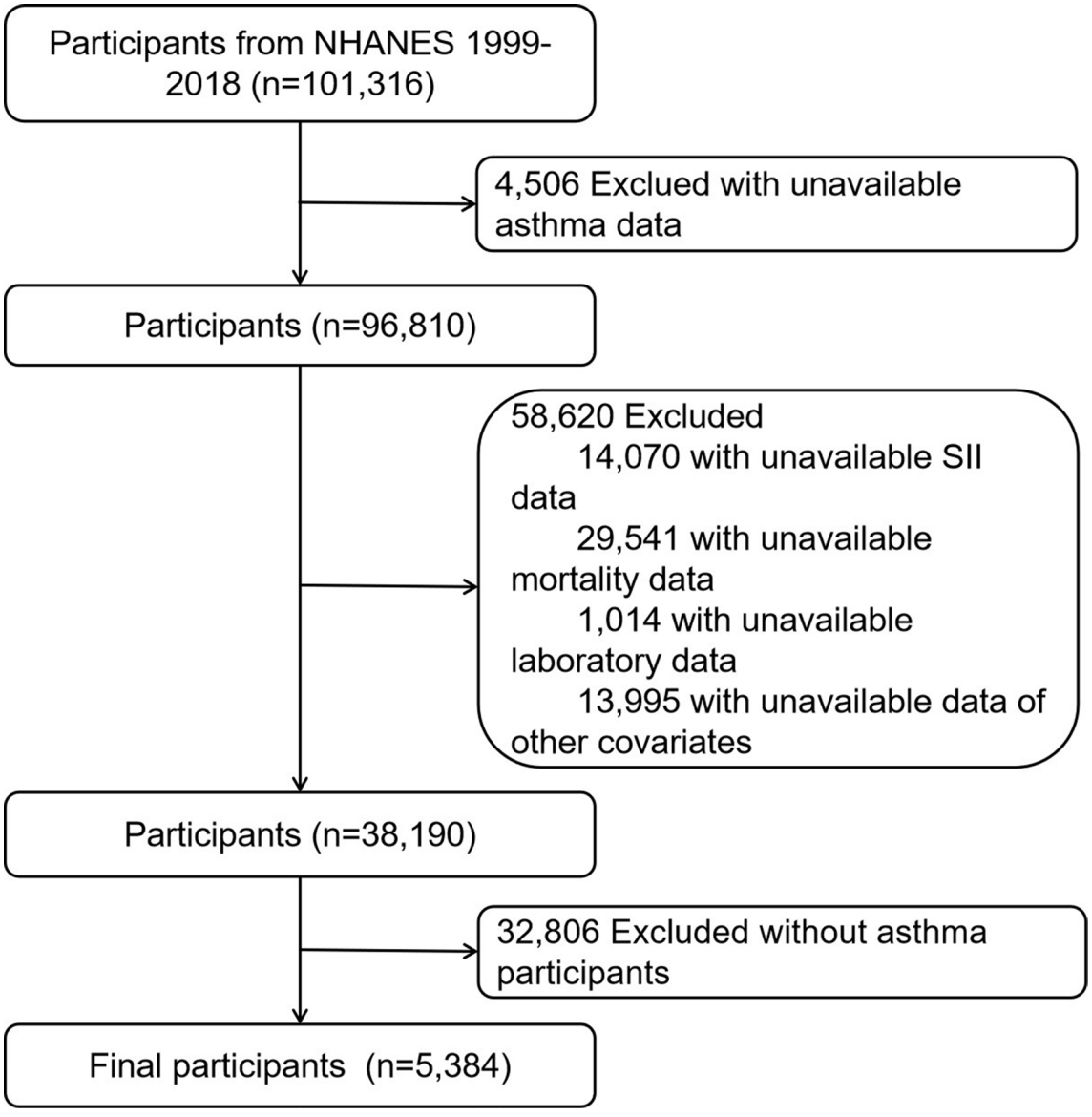

Fig. 1 Flow chart of study participants

life and currently smoke) [26], and drinking status which was categorized as never drinker (had less than 12 drinks in their lifetime), former drinker (had at least 12 drinks in one year but did not drink in the last year, or had not drank in the last year but had at least 12 drinks in their lifetime), current heavier drinker (consuming three or more drinks per day for females, four or more drinks per day for males, or engaging in binge drinking (four or more drinks on same occasion for females, five or more drinks on same occasion for males) on 5 or more days per month), or current mild/moderate drinker (consuming two or fewer drinks per day for females, three or fewer drinks per day for males, or engaging in binge drinking on two or fewer days per month) [27, 28].

Medical status variables taken into account included hypertension, cardiovascular disease (CVD) and diabetes mellitus (DM). Diabetes mellitus (DM) was diagnosed as a condition identified by a doctor or other medical provider, glycated hemoglobin level of over 6.5%, random blood glucose level of 11.1 mmol/L or higher, two-hour OGTT blood glucose level of 11.1 mmol/L or higher, or the use of diabetes medication or insulin [29]. Individuals who reported being diagnosed by a doctor with conditions such as coronary heart disease, heart attack, congestive failure, angina or stroke were categorized as having cardiovascular disease [27]. Hypertension was identified as systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher, or the use of medication to manage blood pressure [27]. Furthermore, data on albumin levels, neutrophil counts, lymphocyte counts, platelet counts, NLR (neutrophil-to-lymphocyte ratio), PLR (platelet-to-lymphocyte ratio), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine (Cr) were obtained from laboratory tests.

Assessment of asthma

Individuals were categorized as having asthma if they fulfilled any of the criteria listed below [30]: (1) positive answer to the question "Has a doctor or other health professional ever told you that you have asthma?"; (2) taking anti-asthmatic drugs, such as leukotriene modifiers, or bronchodilator/inhaled corticosteroids, and had no prior smoking habits, chronic bronchitis, or emphysema.

All-cause and cause-specific mortality

The study defined the outcome as the mortality rate, which includes death from all causes, as well as three specific causes for death. Cause-specific mortality was categorized based on the International Classification of Diseases, Tenth Revision (ICD-10). It included mortality due to cardiovascular diseases (coded I00- I09, I11, I13, I20-I51, and I60-I69), cancer (coded C00-C97), and respiratory diseases (coded J09-J18, J40-J47), using the data retrieved from NHANES linked Public-Use Linked Mortality Files up to December 31, 2019. Individuals coded as MORTSTAT = 0 were presumed to have survived through the end of 2019. The study's observation period began on the date of their NHANES enrollment and terminated either on the date of their death or on December 31, 2019, if they remained alive.

Statistical analysis

In accordance with the NHANES analysis guidelines, all statistical analyses took into consideration the stratified survey design factors. The participants were divided into four groups based on the quartiles the SII due to the absence of a standard cutoff value for SII. Categorical variables were expressed as frequencies (percentages) and continuous variables as means (standard error, SE) if conformed to a normal distribution, and median (interquartile range, IQR) when non-normally distributed in the analysis of baseline characteristics. The chi-square test and one-way ANOVA were employed to identify significant differences between groups for categorical and continuous variables, respectively.

Kaplan-Meier analysis was used to initially explore the connections between SII levels and all-cause and cause-specific mortality among patients with asthma. Weighted univariable and multivariable Cox proportional hazards models were used to further explore the association of the SII with all-cause and cause-specific mortality in asthma adults. The analysis was adjusted for various factors that could influence the results. The hazard ratio (HR) was calculated along with its 95% confidence interval (CIs). Four different models were created during the study. The first model, referred crude model, implying that no adjustments were made for confounders. Model 1 was adjusted for race/ethnicity, age, and sex, education level, marital status and PIR. Model 2 built upon Model 1 by incorporating adjustments for body mass index (BMI), alcohol consumption, smoking status, DM, CVD and hypertension. Finally, adjustments were implemented on Model 3 using Model 2 involved adjustments such as albumin levels, neutrophil counts, lymphocyte counts, platelet counts, NLR, PLR, ALT, AST, and serum creatinine (Cr). Interaction and subgroup analyses were conducted to elucidate the association between SII and all-cause and cause-specific mortality within different subgroups. These subgroups were determined based on different age groups (20–39 40–59, 60 years and older), gender (male, female), ethnicity (Non-Hispanic White, Other), smoking habits (never smoker, former smoker, current smoker), BMI (<30, ≥ 30 kg/m^2), marital status (married/living with partner, widowed/divorced, never married), DM, CVD, hypertension. We conducted all aforementioned analyses employing data weighted with

NHANES recommended weights and all the statistical analyses of the present study were under weighted case.

We combined restricted cubic spline analysis with a multivariate-adjusted Cox regression model to assess the non-linear relationships between SII levels and mortality rates from various causes, including all-cause, cardiovascular, cancer, and respiratory diseases, in patients with asthma. In cases where the relationship was not linear, we used a recursive algorithm to identify the inflection points. To further investigate the impact of specific thresholds, we applied piecewise Cox regression models to analyze the data. Furthermore, we took the SII levels of each participant and divided them by 100 before including them as continuous factors in a multivariable Cox regression analysis. This analysis was conducted to assess the influence of a 100-unit alteration in SII on mortality related to all-cause, cardiovascular, cancer, and respiratory diseases in individuals with asthma. This method aims to better quantify the impact of changes in SII levels on the prognosis of patients with asthma, providing more comprehensive insights (both quartile SII and per 100-unit SII increment). It is also beneficial for clinicians to dynamically assess the prognosis of asthma patients based on SII levels.

To further validate our findings, we performed three sensitivity analyses to test the robustness of our results. Firstly, we removed participants who died within a two-year follow-up period to minimize the impact of potential reverse causality. Secondly, we recognized the potential influence of pre-existing CVD on mortality rates, so we conducted an extra sensitivity analysis by excluding those who had a previous history CVD. Thirdly, we limited our study to individuals aged 45 and above to examine this relationship. Finally, after excluding patients with other chronic respiratory diseases, including COPD and chronic bronchitis, we reevaluated the associations between SII levels and risks of cause mortality in patients with asthma. All analyses were performed using R 4.2.3, with a two-tailed P-value below 0.05 deemed statistically significant.

Results

Baseline characteristics

A total of 5,384 subjects were enrolled in this study. The demographic characteristics and laboratory results of the study participants are presented in Table 1. The participants in the research were divided into four groups according to quartiles of the SII, with the specific cutoff values of 349.5, 495.9, and 696.0: the first quartile group (Q1, $n=1346$; SII ≤ 349.5), the second quartile group (Q2, $n=1346$; 349.5 < SII ≤ 495.9), the third quartile group (Q3, $n=1348$; 495.9 < SII ≤ 696.0) and the fourth quartile group (Q4, $n=1344$; SII > 696.0). The cohort had a mean age of 45.07 years, with males making up 41.68% of the group. The mean SII was 582.18, with a Standard Error of 5.83.

The Q2, Q3, and Q4 groups displayed notable differences in their characteristics when compared with the Q1 group: They tend to be older in age; They had a higher BMI value; In terms of gender distribution, the proportion of women was found to be higher; Non-Hispanic white individuals made up a larger percentage; They tend to be widowed/divorced; There was an increased percentage of individuals with now or former smoking; A higher percentage with former alcohol use; In terms of laboratory results, they had higher levels of albumin, Cr, neutrophil count, platelet count, as well as NLR and PLR, conversely, lower levels of AST and lymphocyte count. Moreover, there was a rise in the occurrence of hypertension and cardiovascular disease as the SII levels elevated. Similar PIR, education level, DM status and ALT were observed, as detailed in Table 1.

Kaplan-Meier analysis

Out of the 5,384 individuals included in the study, over a median follow-up of 4.13 years, there were 802 all-cause deaths, including 241 deaths due to cardiovascular diseases, 171 deaths related to cancer, and 119 deaths related to respiratory diseases. To initially assess the relationship between SII levels and mortality rates from all causes, cardiovascular diseases, cancer, and respiratory diseases in asthma patients, a Kaplan-Meier analysis was employed. The results shown in Fig. 2A-C indicate that elevated SII levels were associated with higher all-cause, cardiovascular diseases and respiratory diseases mortality in asthma patients ($P<0.0001$, $P=0.002$, $P<0.0001$ respectively). In contrast, no association was found between SII levels and cancer-related mortality ($P=0.113$), as demonstrated in Supplementary Figure S1.

SII and mortality

Table 2 displayed the results of Cox regression analysis examining the relationship between SII and all-cause mortality and mortality related to specific causes in adults diagnosed with asthma. Both crude and multivariate adjusted models revealed a notable correlation between elevated SII levels and an increased risk of death from all cause in individuals with asthma. In comparison to the Q1 group, the HR (95% CI) for the Q2, Q3, and Q4 groups were 1.15 (1.12–1.50), 1.52 (1.36–1.72), and 2.24 (1.91–2.71), respectively (P trend = 0.01) in the fully adjusted model (Model 3). Likewise, high quartile levels of SII were observed as a key factor in predicting mortality from cardiovascular diseases in asthma participants. The HR (95% CI) for the Q2, Q3, and Q4 groups were 1.60 (1.30–2.84), 1.70 (1.31–3.91), 1.75 (1.29–2.86), respectively (P trend = 0.02) in Model 3. In terms of mortality from respiratory diseases, a similar pattern was

Table 1 Cohort characteristics at baseline for study participants according to quartiles of SII

Variable	Total	Q1 [18.7, 349.5]	Q2 (349.5, 495.9]	Q3 (495.9, 696.0]	Q4 (696.0, 5821.8]	*P* value
Participants, n	5384	1346	1346	1348	1344	
Age, years	45.07(0.32)	43.58(0.59)	43.60(0.56)	45.85(0.57)	47.05(0.49)	< 0.0001
BMI, kg/m^2	28.40 (24.30,33.80)	26.60 (24.01,32.50)	27.50 (23.80,33.01)	29.20 (24.73,34.38)	29.30 (24.79,35.60)	< 0.0001
Sex, n(%)						< 0.0001
Female	3060(58.32)	686(52.58)	732(53.61)	830(62.95)	812(63.36)	
Male	2324(41.68)	660(47.42)	614(46.39)	518(37.05)	532(36.64)	
Race, n(%)						< 0.0001
Mexican American	544(4.51)	121(4.36)	133(4.19)	152(5.08)	138(4.37)	
non-Hispanic black	1228(11.40)	471(19.60)	303(10.80)	260(9.59)	194(6.84)	
non-Hispanic white	2738(72.64)	529(63.34)	693(74.79)	715(73.42)	801(77.62)	
others	874(11.45)	225(12.69)	217(10.22)	221(11.92)	211(11.16)	
Marital status, n (%)						0.01
Married/living with partner	2941(59.57)	729(60.39)	764(61.98)	738(59.01)	710(57.02)	
Widowed/divorced	1350(20.49)	314(17.57)	325(18.22)	332(21.84)	379(23.93)	
Never married	1093(19.94)	303(22.05)	257(19.81)	278(19.15)	255(19.06)	
PIR, n (%)						0.22
<1.3	1862(24.54)	453(25.17)	454(23.24)	469(24.71)	486(25.13)	
1.3–3.5	1880(34.02)	478(34.85)	458(31.95)	463(33.34)	481(36.06)	
>3.5	1642(41.45)	415(39.97)	434(44.81)	416(41.95)	377(38.81)	
Educational level, n (%)						0.30
More than high school	2999(63.16)	762(62.98)	776(65.11)	759(64.11)	702(60.41)	
Completed high school	1188(22.23)	292(21.57)	273(20.80)	298(21.68)	325(24.78)	
Less than high school	1197(14.61)	292(15.46)	297(14.09)	291(14.21)	317(14.82)	
Smoking status, n (%)						0.01
Now	1304(23.91)	294(22.08)	311(23.13)	336(23.35)	363(26.97)	
Former	1444(26.33)	328(23.56)	361(26.07)	360(26.57)	395(28.70)	
Never	2636(49.76)	724(54.36)	674(50.80)	652(50.08)	586(44.33)	
Alcohol user, n (%)						0.01
Current heavier drinker	1093(22.10)	273(23.31)	257(20.22)	289(21.31)	274(23.76)	
Current light/moderate drinker	2672(53.49)	683(53.64)	701(56.63)	663(54.71)	625(48.93)	
Former	986(15.23)	225(13.27)	228(13.61)	243(15.40)	290(18.43)	
Never	633(9.17)	165(9.78)	160(9.54)	153(8.58)	155(8.88)	
CVD, n (%)						0.01
No	4553(88.04)	1154(89.39)	1163(89.26)	1148(88.50)	1088(85.07)	
Yes	831(11.96)	192(10.61)	183(10.74)	200(11.50)	256(14.93)	
DM, n (%)						0.08
No	4329(85.79)	1110(86.86)	1083(87.06)	1100(85.83)	1036(83.57)	
Yes	1055(14.21)	236(13.14)	263(12.94)	248(14.17)	308(16.43)	
Hypertension, n (%)						< 0.001
No	2895(60.29)	762(60.89)	742(58.51)	731(57.42)	660(54.52)	
Yes	2489(39.71)	574(39.11)	614(41.48)	617(42.58)	684(45.48)	
ALT, U/L	25.73(0.38)	26.30(0.59)	26.41(0.66)	24.85(0.56)	25.43(0.90)	0.16
AST, U/L	25.22(0.25)	26.30(0.44)	25.12(0.38)	24.61(0.40)	24.02(0.61)	0.03
Albumin, g/dL	4.36(0.01)	4.28(0.01)	4.31(0.01)	4.35(0.01)	4.59(0.01)	< 0.0001
Cr, umol/L	77.36(0.66)	75.26(0.98)	76.73(0.66)	78.46(0.81)	79.14(1.95)	0.04
Lymphocyte count (1000 cell/mL)	2.17(0.02)	2.48(0.04)	2.23(0.02)	2.14(0.02)	1.86(0.02)	< 0.0001
Neutrophil count (1000 cell/mL)	4.43(0.03)	3.04(0.04)	3.87(0.03)	4.69(0.04)	5.94(0.06)	< 0.0001
Platelet count (1000 cell/mL)	259.92(1.23)	215.58(1.64)	245.01(2.06)	268.99(2.06)	303.67(2.50)	< 0.0001
NLR	2.00 (1.54,2.65)	1.25 (1.03,1.48)	1.75 (1.53,2.00)	2.19 (1.92,2.54)	3.12 (2.62,3.80)	< 0.0001

Table 1 (continued)

Variable	Total	Q1 [18.7, 349.5]	Q2 (349.5, 495.9]	Q3 (495.9, 696.0]	Q4 (696.0, 5821.8]	*P* value
PLR	122.31 (97.39,154.55)	91.74 (73.33,109.41)	111.50 (94.35,132.80)	130.00 (106.67,154.23)	164.62 (136.67,205.63)	< 0.0001
SII	582.18(5.83)	265.12(2.14)	421.69(1.33)	586.48(1.91)	969.68(11.40)	< 0.0001

SII, systemic immune-inflammation index; PIR, family poverty-to-income ratio; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; DM, diabetes mellitus; CVD, cardiovascular disease; Q1, Quartile 1; Q2, Quartile 2; Q3, Quartile 3; Q4, Quartile 4

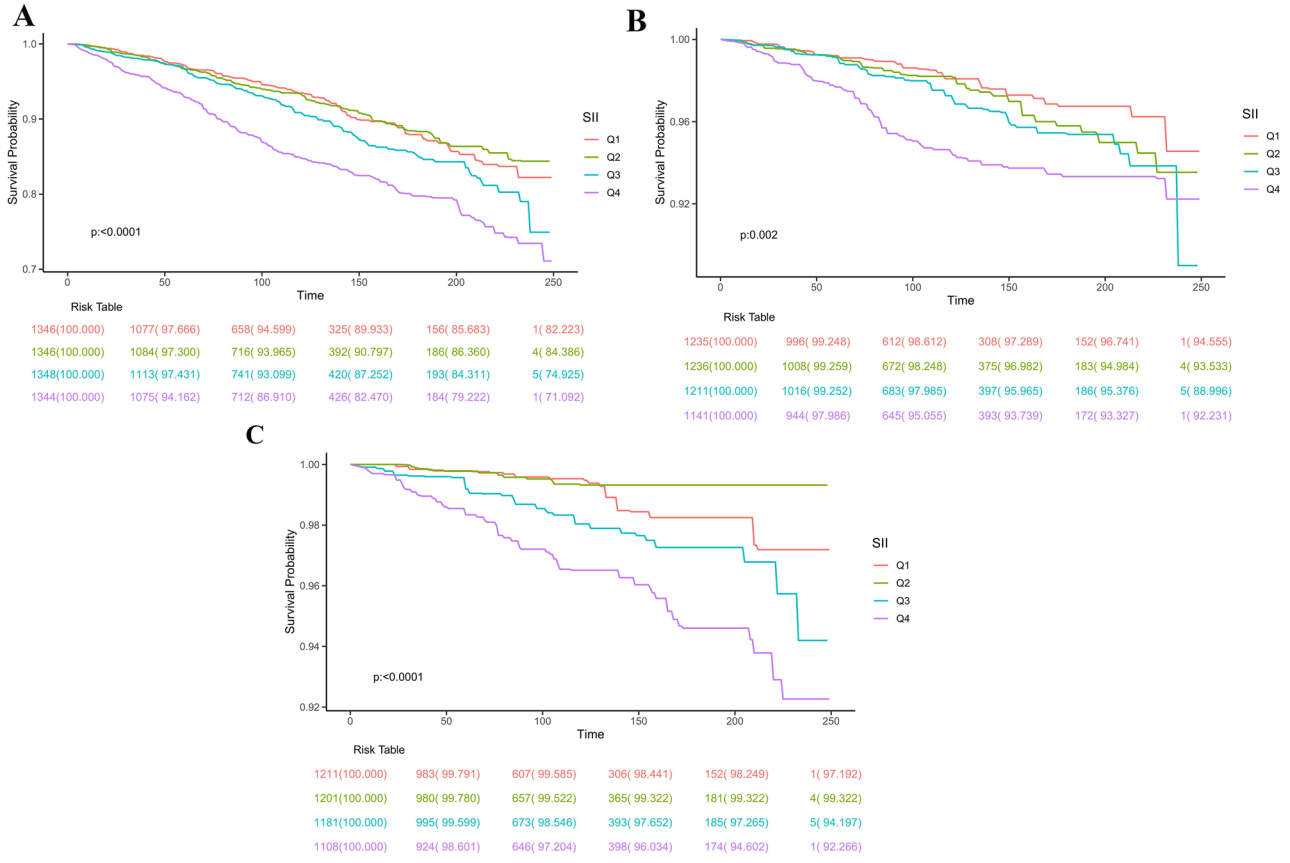

Fig. 2 The Kaplan-Meier curves display the long-term all-cause mortality (**A**), cardiovascular diseases mortality (**B**) and respiratory diseases mortality (**C**) differences by SII in patients with asthma (weighted). SII: systemic immune-inflammation index; Q1, Quartile 1; Q2, Quartile 2; Q3, Quartile 3; Q4, Quartile 4

identified, namely, elevated level of SII associated with a significantly increased risk of respiratory diseases mortality in asthma participants. The HR (95% CI) for the Q2, Q3, and Q4 groups were 1.26 (1.22–1.42), 1.41 (1.27–1.74), 1.67 (1.54–3.13), respectively (P trend < 0.001). Nevertheless, the fully adjusted model did not show a significant association between SII and cancer mortality. The trend of a consistent rise in HR was not observed in cancer mortality, as indicated in Table 2. The HR (95% CI) for the Q2, Q3, and Q4 groups were 2.18 (1.16–4.11), 0.82 (0.53–2.85), 1.94 (0.75–5.03), with no significant trend observed across the groups (P for trend = 0.51).

Assessing the dynamic changes of SII is crucial for the prognosis of asthma patients. An increase of 100 units in SII was associated with a 3% higher risk of all cause mortality, a 4% higher risk of cardiovascular diseases mortality, and a 8% higher risk of respiratory diseases mortality, after adjusting for all covariates. The detailed results were presented in Table 2.

Non-linear relationships

After adjusting for all covariates (Model 3), the RCS analysis was used to visualize the relationship between SII and all-cause and cause-specific mortality among adults with asthma. The overall curve indicates a non-linear relationship between SII and deaths from all causes, with inflection point of 326 (p for nonlinearity = 0.0021)(Fig. 3A). The same J-shaped relationship was found in cardiovascular and respiratory diseases mortality, with inflection points of 350 (p for nonlinearity = 0.0121) and 355 (p for

Table 2 Relationships of SII with all-cause and cause-specific mortality in patients with asthma from the NHANES 1999–2018 cohort

	All-cause mortality							
	crude model		**Model 1**		**Model 2**		**Model 3**	
SII	HR, 95%CI	P	HR, 95%CI	P	HR, 95%CI	P	HR, 95%CI	P
Q1	ref		ref		ref		ref	
Q2	0.99(0.73,1.34)	0.95	1.08(0.80,1.45)	0.62	1.14(1.04,1.53)	0.04	1.15(1.12,1.50)	< 0.0001
Q3	1.30(1.05,1.68)	0.04	1.26(1.17,1.64)	0.03	1.23(1.13,1.64)	0.01	1.52(1.36,1.72)	0.01
Q4	1.95(1.51,2.53)	< 0.0001	1.77(1.40,2.24)	< 0.0001	1.66(1.29,2.13)	< 0.0001	2.24(1.91,2.71)	0.02
Per 100 U increment	1.06(1.04,1.08)	< 0.0001	1.04(1.03,1.05)	< 0.0001	1.04(1.03,1.05)	< 0.0001	1.03(1.02,1.08)	0.01
p for trend		< 0.0001		< 0.0001		< 0.0001		0.01
	Cardiavascular disease mortality							
	crude model		**Model 1**		**Model 2**		**Model 3**	
SII	HR, 95%CI	P	HR, 95%CI	P	HR, 95%CI	P	HR, 95%CI	P
Q1	ref		ref		ref		ref	
Q2	1.31(0.77,2.22)	0.32	1.47(0.87,2.46)	0.15	1.61(0.95,2.72)	0.08	1.60(1.30,2.84)	0.01
Q3	1.56(1.06,2.41)	0.02	1.66(1.20,2.76)	0.01	1.67(1.22,2.75)	0.04	1.70(1.31,3.19)	0.01
Q4	2.34(1.51,3.62)	< 0.001	2.15(1.39,3.33)	< 0.001	2.04(1.32,3.15)	0.001	1.75(1.29,2.86)	< 0.001
Per 100 U increment	1.06(1.04,1.08)	< 0.0001	1.05(1.02,1.07)	< 0.001	1.05(1.02,1.08)	< 0.001	1.04(1.02,1.06)	0.01
p for trend		< 0.0001		< 0.001		0.004		0.02
	Cancer mortality							
	crude model		**Model 1**		**Model 2**		**Model 3**	
SII	HR, 95%CI	P	HR, 95%CI	P	HR, 95%CI	P	HR, 95%CI	P
Q1	ref		ref		ref		ref	
Q2	1.70(0.99,2.94)	0.06	1.83(1.09,3.07)	0.02	1.94(1.12,3.34)	0.02	2.18(1.16,4.11)	0.02
Q3	1.08(0.60,1.94)	0.79	1.04(0.57,1.89)	0.90	1.03(0.55,1.93)	0.93	0.82(0.53,2.85)	0.64
Q4	1.78(1.03,3.08)	0.04	1.68(1.00,2.83)	0.07	1.63(0.98,2.68)	0.06	1.94(0.75,5.03)	0.17
Per 100 U increment	1.04(1.01,1.07)	0.02	1.03(0.99,1.07)	0.12	1.03(0.99,1.07)	0.16	0.90(0.74,1.08)	0.25
p for trend		0.17		0.30		0.39		0.51
	Respiratory disease mortality							
	crude model		**Model 1**		**Model 2**		**Model 3**	
SII	HR, 95%CI	P	HR, 95%CI	P	HR, 95%CI	P	HR, 95%CI	P
Q1	ref		ref		ref		ref	
Q2	0.48(0.22,1.05)	0.07	0.57(0.25, 1.30)	0.18	0.64(0.27, 1.52)	0.31	1.26(1.22, 1.42)	0.01
Q3	1.97(0.93,4.17)	0.08	1.72(1.77, 3.84)	0.01	1.64(1.49, 2.87)	0.02	1.41(1.27, 1.74)	0.01
Q4	3.58(1.87,6.85)	< 0.001	3.23(1.71, 6.10)	< 0.001	2.90(1.42, 5.91)	0.003	1.67(1.54, 3.13)	< 0.001
Per 100 U increment	1.08(1.06,1.11)	< 0.0001	1.08(1.06, 1.09)	< 0.0001	1.08(1.06, 1.12)	< 0.0001	1.08(1.06, 1.10)	0.01
p for trend		< 0.0001		< 0.0001		< 0.0001		< 0.001

SII, systemic immune-inflammation index; Q1, Quartile 1; Q2, Quartile 2; Q3, Quartile 3; Q4, Quartile 4; ref, reference; HR, hazard ratios; CI, confidence interval

Crude model was not adjusted for any covariates

Model 1 was adjusted for race, age, sex, education level, marital status and PIR

Model 2 was adjusted for Model 1 plus BMI, alcohol user, smoking status, DM, CVD and hypertension

Model 3 was adjusted for Model 2 plus albumin, neutrophil counts, lymphocyte counts, platelet counts, NLR, PLR, ALT, AST, and serum creatinine

nonlinearity=0.0085) (Fig. 3B-C) respectively. However, the non-linear relationship was not observed with regard to cancer mortality (p for nonlinearity=0.0993) (Supplementary Figure S2).

When SII values were lower than 326, a 100-unit increase in SII was associated with an 8% decrease in the risk of all-cause mortality (HR: 0.92, 95% CI:0.85–0.96, Ptrend=0.001). However, if SII surpassed 326, a 100-unit increase in SII led to a 4% increase in the risk of all-cause mortality (HR: 1.04, 95% CI:1.01–1.06, Ptrend=0.03). When SII values were lower than 350, a 100-unit increase in SII was associated with a 11% decrease in the risk of cardiovascular diseases mortality (HR: 0.89, 95% CI:0.83–0.96, Ptrend=0.04). However, if SII surpassed 350, a 100-unit increase in SII led to a 4% increase in the risk of cardiovascular diseases mortality (HR: 1.04, 95% CI:1.02–1.07, Ptrend=0.03). Similarly, when SII values were lower than 355, a 100-unit increase in SII was associated with a 10% decrease in the risk of respiratory diseases mortality (HR: 0.90, 95% CI:0.85–0.97, Ptrend=0.01). Yet, if SII surpassed 355, a 100-unit increase in SII led to a 3% increase in the risk of respiratory diseases mortality (HR: 1.03, 95% CI:1.01–1.05, Ptrend=0.04). No inflection point was found for cancer mortality, hence, additional

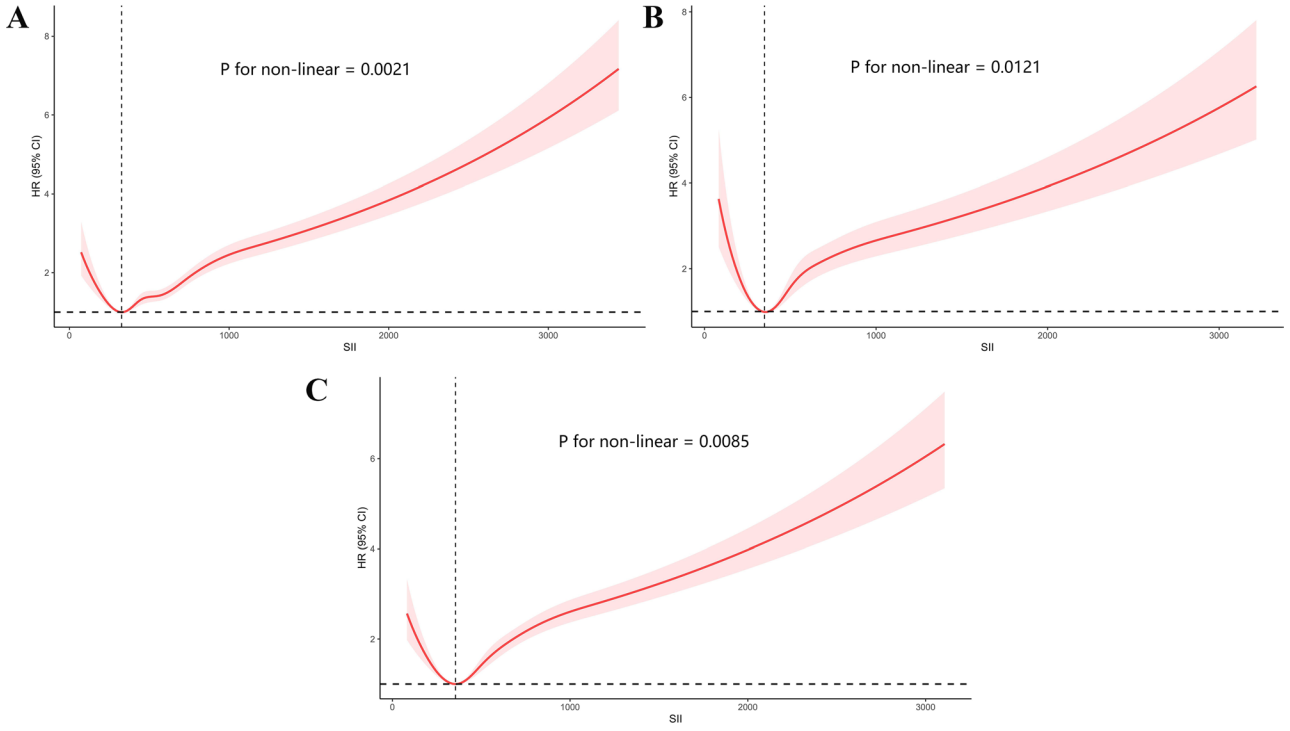

Fig. 3 Restricted cubic spline fitting for the association between SII and mortality from all-cause (**A**), cardiovascular diseases (**B**) and respiratory diseases mortality (**C**) in asthma patients. Adjusted for various demographic and health factors, including race, age, sex, education level, marital status, PIR, BMI, alcohol use, smoking status, diabetes mellitus (DM), cardiovascular disease (CVD), hypertension, albumin, neutrophil counts, lymphocyte counts, platelet counts, NLR (neutrophil-to-lymphocyte ratio), PLR (platelet-to-lymphocyte ratio), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine (Cr)

Table 3 Threshold effect analysis of SII on all-cause and cause-specific mortality in patients with asthma from the NHANES 1999–2018 cohort

	All-cause mortality	
SII	Per 100U increment	P
< 326	0.92(0.85–0.96)	0.001
>326	1.04(1.01–1.06)	0.03
	Cardiovascular disease mortality	
SII	Per 100U increment	P
< 350	0.89(0.83–0.96)	0.04
>350	1.04(1.02–1.07)	0.03
	Respiratory disease mortality	
SII	Per 100U increment	P
< 355	0.90(0.85–0.97)	0.01
>355	1.03(1.01–1.05)	0.04

analysis was not performed. Table 3 exhibited a summary of the details.

Subgroup and sensitivity analyses

The results presented in Table 4 show that the SII is significantly linked to the all cause mortality in various subgroups. Specifically, this association was observed in individuals aged 40–59 years (HR, 1.74; 95% CI, 1.46–3.12) and those aged 60 years and older (HR, 1.76; 95% CI, 1.37–2.27), as well as in males, females, individuals with a BMI of 30 or higher, non-Hispanic whites, current or former smokers, married/living with partner or widowed/divorced status, those without DM or with hypertension. However, no significant association was found in younger participants, those with a BMI under 30, non-smokers, individuals with diabetes, those without hypertension, with or without CVD and other specific demographic groups. Additional details on cause-specific mortality subgroup analyses can be found in Supplementary Tables S1A-C.

In our study, when we excluded participants with pre-existing cardiovascular disease, we also discovered significant associations between higher SII levels and increased risks of all-cause mortality, as well as cardiovascular or respiratory diseases mortality in patients with asthma(Supplementary Tables S2A-B). We conducted sensitivity analyses by excluding participants who passed away within 2 years of follow-up and performing Cox regression analysis again. This reevaluation confirmed the presence of the previously identified relationship (Supplementary Tables S3A-B). Interestingly, when we excluded participants under 45 years old, our study's conclusions remained consistent (Supplementary Tables S4A-B). After excluding patients with other chronic respiratory diseases, the associations between higher SII levels and increased risks of cause mortality in

Table 4 Subgroup of Relationship between systemic immune-inflammation index (SII) and all cause mortality

	Q1	Q2	Q3	Q4	*p* for trend	*p* for interaction
Age						0.39
20–39	ref	2.09(0.62, 7.04)	3.79(1.39,10.31)	2.29(0.64, 8.17)	0.32	
40–59	ref	0.94(0.49,1.79)	1.14(1.03,2.04)	1.74(1.46,3.12)	0.02	
≥ 60	ref	1.06(0.77,1.45)	1.05(0.78,1.43)	1.76(1.37,2.27)	< 0.0001	
Sex						0.56
Female	ref	0.95(0.61,1.46)	1.10(0.78,1.56)	1.75(1.25,2.44)	< 0.0001	
Male	ref	1.18(0.74,1.91)	1.65(1.14,2.37)	2.40(1.68,3.42)	< 0.0001	
BMI						0.06
<30	ref	0.62(0.23,1.67)	1.01(0.43,2.37)	0.56(0.24,1.29)	0.32	
≥30	ref	0.86(0.45,1.65)	1.35(1.17,1.72)	1.91(1.37,2.60)	0.01	
Race						0.74
non-Hispanic white	ref	0.99(0.62,1.56)	1.29(0.90,1.85)	2.07(1.44,2.99)	< 0.0001	
non-Hispanic black	ref	1.20(0.76,1.87)	1.35(0.87,2.10)	1.69(0.98,2.90)	0.06	
Mexican American	ref	0.92(0.30, 2.81)	1.16(0.47, 2.90)	0.87(0.28, 2.68)	0.82	
Others	ref	0.92(0.37,2.25)	0.99(0.42,2.32)	1.22(0.48,3.11)	0.59	
Smoking status						0.18
Now	ref	0.80(0.40, 1.58)	1.77(1.04, 3.00)	2.02(1.22, 3.32)	< 0.001	
Former	ref	1.16(0.72,1.88)	1.02(0.63,1.68)	2.04(1.32,3.16)	< 0.001	
Never	ref	1.04(0.63,1.72)	1.21(0.74,1.97)	1.37(1.13,2.76)	0.40	
Marital status						0.15
Married/living with partner	ref	1.37(0.85,2.19)	1.29(0.85,1.96)	2.24(1.45,3.46)	< 0.0001	
Widowed/divorced	ref	0.62(0.40,0.95)	1.04(0.71,1.52)	1.57(1.11,2.21)	< 0.0001	
Never married	ref	1.29(0.40, 4.19)	2.43(1.01, 5.86)	1.73(0.78, 3.84)	0.20	
DM						0.71
No	ref	1.26(0.75,2.11)	1.25(0.80,1.95)	1.94(1.22,3.07)	< 0.001	
Yes	ref	0.99(0.68,1.43)	1.33(0.96,1.85)	1.21(1.17,2.68)	0.10	
CVD						0.18
No	ref	0.96(0.65,1.43)	1.44(1.02,2.05)	1.28(1.08,1.49)	0.15	
Yes	ref	1.07(0.66,1.72)	1.02(0.64,1.62)	0.90(0.34,2.68)	0.20	
Hypertension						0.12
No	ref	0.81(0.44, 1.46)	1.17(0.67, 2.04)	1.22(0.76, 1.96)	0.17	
Yes	ref	1.20(0.85,1.71)	1.28(0.94,1.75)	2.22(1.60,3.06)	< 0.0001	

SII, systemic immune-inflammation index; BMI, body mass index; DM, diabetes mellitus; CVD, cardiovascular disease; Q1, Quartile 1; Q2, Quartile 2; Q3, Quartile 3; Q4, Quartile 4

patients with asthma also existed (Supplementary Tables S5A-B). It's worth noting that we did not find connection between SII levels and the risk of cancer mortality. In the Kaplan-Meier analysis, variations in survival rates were noted among different quartiles of SII for various disease mortalities in multiple sensitivity analyses we conducted (Supplementary Figures S3A-D, S4A-D, S5A-D).

Discussion

This study is the first to investigate the relationship between the Systemic Immune-Inflammation Index (SII) and mortality of asthma patients due to all causes, cardiovascular diseases, cancer, and respiratory diseases in Cox analyses, utilizing data from the NHANES project. According to our findings, SII is remarkably associated with increased mortality from all causes, as well as cardiovascular and respiratory diseases, yet unrelated to cancer mortality in asthma patients after multivariate adjustments. A J-shaped correlation exists between SII and all cause, cardiovascular or respiratory diseases mortality in participants with asthma. The risk of all cause, cardiovascular or respiratory diseases mortality was observed to be higher when the SII deviated from the inflection point, either by being too low or too high. Furthermore, the associations were consistent between sociodemographic and prior diseases related subgroups and stable in sensitivity analyses. These findings suggest that SII, a biomarker derived from complete blood count (CBC) data, may be a valuable tool for assessing mortality risk in asthma patients. In general, our research emphasizes the significance of taking into account the level of inflammation indicated by SII as an independent factor for the risk of death from all cause and specific causes among people with asthma. Moreover, the inflection point in the J-shaped relationship represents the SII value with the lowest risk of death, which can help us to

accurately identify the death risk from all cause and cardiovascular or respiratory diseases in asthma patients and further develop personalized treatment plan in clinical practice.

Asthma is a long-lasting inflammatory condition of the airways, which is affected by various types of cells, including eosinophils, neutrophils, lymphocytes, platelets and cellular components [31]. Previous research has mainly examined the significance of eosinophils in the blood as indicators of asthma [32]. More recently, other complete blood count (CBC) parameters have been suggested as additional biomarkers for assessing asthma outcomes [33]. Neutrophils are known to worsen airway injury primarily by secreting inflammatory mediators, including IL-8 and TNF-α, which play a major role in cases of severe or treatment-resistant asthma [34, 35]. Meanwhile, lymphocytes, particularly Th2 cells, have a significant role in regulating immune responses and stimulating other immune cells by producing cytokines that contribute to exacerbate ongoing inflammation in the airways [36]. Platelets are also involved in the progression of asthma by promoting airway inflammation and hyperreactivity through involvement in blood clotting and exacerbating inflammatory reactions [37]. The composite index SII offers various benefits over individual cell counts in terms of predictive accuracy. Single blood cell measurements can be easily affected by factors that impact cell volume, while the ratios of the SII promote consistency. Moreover, by combining three different types of inflammatory cells, the SII captures their interconnected effects and cumulative impact. This could result in a better representation of the overall inflammatory condition. In our study, we meticulously examined how SII levels are associated with all cause and specific causes of mortality in asthma patients, highlighting the importance of neutrophils, platelets, and lymphocytes in the development and prognosis of asthma. Our results show that heightened SII levels effectively reflect the measurable changes in these immune cells, leading to a higher likelihood of mortality in individuals with asthma.

In this investigation, we revealed that the relationship between the SII and mortality rates in individuals with asthma varied across different subgroups. Notably, the link between a high SII and increased mortality was most evident in adults over 60 years old. This divergent age effect suggests that the SII may reflect distinct aspects of immune system dysfunction that impact mortality risk. As people aged, they often experience chronic, low-level inflammation that can lead to tissue injury and degeneration [38], which is closely tied to increased morbidity and mortality [39]. Furthermore, we found that a high SII was more strongly associated with mortality in subgroups with a BMI of 30 or higher and those with a history of smoking. Both excess body fat and smoking can trigger the production of inflammatory chemicals and oxidative stress [40], which likely interact with SII-related immune impairment to exacerbate the negative effects on overall health.

Previous studies have noted a connection between elevated SII levels and a higher chance of death in both the general population and the individuals with conditions marked by significant inflammation [13, 41, 42]. Individuals with higher SII levels in the general population have shown a remarkable increase in all-cause (HR 1.29) and cardiovascular (HR 1.33) mortality compared to those with lower SII levels [43]. In the context of acute ischemic stroke in intensive care units, one study found a positive, though not-linear, correlation between SII levels and in-hospital mortality [14], as well as in individuals with stroke-related pneumonia [44]. Additionally, research has demonstrated that SII is linked to an elevated risk of death in individuals with COPD [24]. In the field of oncology, studies have identified SII as an independent predictor of overall mortality, highlighting its potential as a prognostic indicator [10, 45]. A meta-analysis about cardiac surgery enrolled over 3245 participants demonstrated that a high preoperative SII was strongly linked to a higher risk of developing atrial fibrillation after surgery, indicating its potential as a useful indicator for predicting this complication [9]. Although numerous studies have identified a connection between the SII and increased mortality rates in various diseases, its ability to predict survival outcomes in asthma patients has received relatively little attention. Our study addresses this gap, providing new insights that demonstrate the SII's potential as a reliable predictor of both all-cause and cardiovascular or respiratory diseases mortality in asthma patients.

Several notable advantages are worth mentioning. Initially, this study is a comprehensive, nationwide survey of over a lengthy period of time, with a large and representative sample, and takes into account the majority of factors that could potentially influence the results. Next, we conducted a thorough analysis to assess the prognostic value of the systemic inflammatory indicator, SII, in predicting all cause and specific causes of death in individuals with asthma. It provides novel insights into the crucial role of SII in asthma management. Additionally, SII can be readily calculated from standard complete blood count results, without incurring extra expenses. At last, we performed various subgroup and sensitivity analyses to validate the identified relationships, enhancing the reliability and stability of our conclusions.

Nevertheless, some limitations should be acknowledged. One major constraint is that the research being observational limits our ability to make causal conclusions. Although we have identified connections between the SII and different outcomes, establishing a clear cause-and-effect link is still out of our reach. Additionally, even

though we have made attempts to adjust for multiple factors that could affect the results, there is a chance that some unidentified variables could still impact the relationships we have observed. This may be because certain variables, potentially affecting the outcomes we studied, were not measured adequately or were not accounted for. Furthermore, the assessment of SII was done at a single point in time, without considering possible changes that may occur over time or as a result of therapeutic interventions. Conducting multiple SII measurements at different time points could provide a more nuanced insight into the dynamics of inflammation. Finally, the research used participants' self-reported medical histories to diagnose asthma cases, which may lead to errors or biased recollections that could impact the reliability and coherence of the findings. To build on these results, further research should verify our conclusions in different populations, explore the underlying causes, and investigate whether reducing the SII can lead to improved survival rates among individuals with asthma.

Conclusion

This study using extensive cohort data from the NHANES project demonstrated that elevated Systemic Immune-Inflammation Index (SII) were independently linked to a higher risk of all cause and cardiovascular or respiratory diseases mortality in individuals with asthma, even after accounting for relevant covariates. Moreover, there is a distinct non-linear association between SII and mortality from all cause, cardiovascular, or respiratory diseases, displaying a J-shaped pattern with inflection points identified at 326, 350, and 355. The findings were further validated through sensitivity analysis. All of these emphasize the standalone predictive importance of SII in individuals with asthma. Considering the significant link between SII and mortality in different groups among asthma patients, it may be advantageous to investigate strategies focused on decreasing inflammation. Such interventions could involve medication, exercise, and dietary changes, all of which could potentially improve the prognosis of individuals with asthma.

Supplementary Information

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Supplementary Material 1

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Author contributions
Z-BL: Formal analysis, Methodology, Software, Writing-original draft. S-YC: Formal analysis, Methodology, Software, Writing-original draft. NZ: Writing-review & editing, Methodology, Visualization. FQ: Writing-review & editing, Methodology, Visualization. W-NH: Conceptualization, Formal analysis, Supervision, Validation, Writing-review & editing. CC: Conceptualization, Formal analysis, Supervision, Validation, Writing-review & editing. All authors reviewed the manuscript.

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Data availability
All NHANES data and information are publicly available at https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate
This study was approved by the NCHS Research Ethics Review Board (ERB) and followed the ethical standards for human research. The details of the NCHS Research Ethics Review Board Approval can be found on the NHANES website (https://www.cdc.gov/nchs/nhanes/irba98.htm). No written informed consent was needed for this study according to the national and institutional regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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