Prospective Study

Association Between Systemic Inflammation Response Index and All-Cause Mortality in Individuals with Chronic Pain: Evidence from NHANES 1999-2004

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Background: Chronic pain is a common condition that has been linked to systemic inflammation. In recent years, the system inflammation response index (SIRI) has aroused researchers' interest as a novel inflammatory biomarker. The association between SIRI and mortality in individuals with chronic pain remains unclear.

Objectives: To explore the association between SIRI and all-cause mortality in individuals with chronic pain, and to assess the index's potential as a tool for risk stratification in this population.

Study Design: A population-based prospective cohort study.

Setting: The National Health and Nutrition Examination Survey (NHANES) 1999–2004, with mortality follow-up through December 31, 2019.

Methods: Cox proportional hazards regression models were employed to evaluate the association between log10-transformed SIRI and all-cause mortality in the chronic pain population, adjusting for demographic and health-related factors. To handle missing data, multiple imputation by chained equations was performed, generating 5 imputed datasets. Nonlinear relationships were examined using restricted cubic spline (RCS) regression and piecewise models to explore potential threshold effects.

Results: The study included 1,938 patients with chronic pain, of whom 647 died during follow-up. Higher log10(SIRI) was associated with higher all-cause mortality in fully adjusted models (hazard ratio [HR] per one-unit increase, 2.56; 95% confidence interval [CI], 1.67–3.94; $P < 0.001$). Compared to patients in the lowest SIRI tertile, those in the highest tertile had a higher mortality risk (HR, 1.45; 95% CI, 1.11–1.90; $P < 0.001$). RCS analyses further suggested a nonlinear association between SIRI and mortality, with a steeper increase in risk at higher SIRI levels. The association appeared stronger among adults aged ≥ 52 years.

Limitations: Chronic pain status was self-reported using a duration-based definition (≥ 3 months) and lacked detailed clinical characterization and treatment data.

Conclusions: In adults with chronic pain, higher SIRI was associated with a higher risk of all-cause mortality, with a more pronounced association in older adults. SIRI may be useful for mortality risk stratification in this population.

Key words: Systemic inflammation response index, chronic pain, all-cause mortality, threshold effect, NHANES

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Chronic pain has been defined as pain that persists or recurs for longer than 3 months, in accordance with the International Association for the Study of Pain (IASP) classification for the International Classification of Diseases, 11th Revision (ICD-11) (1). Affecting approximately 20% of the global population, chronic pain—particularly high-impact chronic pain—compromises a patient's quality of life substantially and imposes a significant burden on health care systems (2). Chronic pain is frequently associated with comorbid conditions such as depression, anxiety, and cardiovascular disease, making it one of the leading contributors to disability worldwide (3-6). Additionally, the long-term use of analgesics, especially opioids, raises concerns about dependency and misuse, further complicating management strategies (7). These challenges underscore the need for early identification of risk markers and improved clinical tools to inform patient stratification and long-term care planning.

Accumulating evidence suggests that inflammation may contribute to the development and persistence of chronic pain. Low-grade systemic inflammation has been reported in pain-related conditions such as osteoarthritis, fibromyalgia, and neuropathic pain (8-10). Pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), have been implicated in the modulation of nociceptive signaling pathways (11,12). Moreover, neuroinflammatory processes involving glial cell activation may promote central sensitization, which is thought to underlie the transition from acute to chronic pain (13). In turn, chronic pain may exacerbate systemic immune dysregulation, perpetuating inflammatory responses and increasing susceptibility to a range of comorbidities, including depression and cardiovascular events (14,15).

The systemic inflammation response index (SIRI)—a composite marker derived from peripheral neutrophil, monocyte, and lymphocyte counts—has been proposed as a robust indicator of systemic immune-inflammation status (16). Elevated SIRI values have been associated with adverse outcomes, including increased all-cause and cardiovascular mortality in populations with metabolic and cardiovascular disorders (17-19). Because SIRI can be calculated from routine complete blood counts, it represents a low-cost and widely accessible inflammation-based marker with potential utility for risk stratification (20,21).

However, whether SIRI is associated with mortality risk among adults who have chronic pain remains unclear. Therefore, we used NHANES 1999–2004 data linked to the National Death Index (NDI) to examine the association between SIRI and all-cause mortality among adults reporting chronic pain.

Methods

Study Design and Population

We conducted a population-based prospective cohort study using data from NHANES 1999-2004. Baseline SIRI and covariates were obtained at the examination, and patients were linked to the National Death Index to ascertain all-cause mortality through December 31, 2019. Ethical approval for NHANES was obtained from the National Center for Health Statistics Research Ethics Review Board, and written informed consent was acquired from all patients.

A total of 31,126 NHANES patients were eligible at baseline. We excluded individuals aged < 20 years (n = 15,794). Chronic pain was defined as self-reported pain lasting ≥ 3 months at baseline, based on variable MPQ110 from the NHANES Miscellaneous Pain Questionnaire ("How long have you experienced this pain?"). Patients who selected "at least 3 months but <1 year" or ">1 year" were classified as having chronic pain; those who did not meet this definition or had invalid responses were excluded (n = 13,159). We further excluded patients with missing data required to calculate SIRI (n = 231) and individuals without mortality follow-up information (n = 4). The final analytic cohort included 1,938 adults with chronic pain. A patient flow diagram is provided in Fig. 1.

Exposure: SIRI

SIRI was calculated by dividing the product of the neutrophil and monocyte counts by the lymphocyte count (22). Those counts were obtained through complete blood cell analyses performed using the Beckman Coulter MAXM instrument at the mobile examination centers (MECs), following the detailed specimen collection and processing procedures outlined in the National Health and Nutrition Examination Survey (NHANES) Laboratory Procedures Manual. Due to the skewed distribution of SIRI, a base-10 logarithmic transformation was applied, and log10(SIRI) was used as the primary exposure variable in all regression analyses.

Outcome and Follow-Up

The outcome of this study was all-cause mortality, defined as death from any cause. Mortality status

was determined by linkage to the NDI and the publicly available Linked Mortality Files (LMF). The LMF, which included a limited set of mortality variables for adult patients, was linked to NHANES data using public identifiers provided by the National Center for Health Statistics (NCHS). Follow-up time for each patient was recorded in months, with mortality data available from the date of NHANES participation through December 31, 2019.

Covariates

Several covariates that could have potentially confounded the relationship between SIRI and all-cause mortality were included in the analysis. These variables were grouped into demographic, lifestyle, and clinical factors.

The demographic category included age, gender, and race. The poverty-income ratio (PIR) was stratified into 3 categories: less than 1.00, 1.00 to 2.00, 2.00 to 3.9, and 4.00 or greater. Body mass index (BMI) was divided into categories of less than 30 kg/m² and greater than or equal to 30 kg/m² to distinguish between nonobese and obese patients. Education level was also split into 3 categories: less than high school, high school or equivalent, and above high school. Patients' marital status was classified as either living alone or not living alone.

The lifestyle category included smoking status, alcohol consumption, and physical activity (PA). Smoking status was defined dichotomously as "yes" for smokers and "no" for patients who had never smoked, based on responses to the NHANES Tobacco Use Questionnaire. Alcohol use was classified as "yes" if patients reported any alcohol consumption and "no" if they did not. PA was assessed using metabolic equivalent task minutes per week (MET-min/week), derived from self-reported PA data. Patients were classified into 3 PA categories based on WHO guidelines: low (< 600 MET-min/week), moderate (600–2999 MET-min/week), and high (≥ 3000 MET-min/week).

The clinical category included diabetes, hypertension, hyperlipidemia, coronary heart disease (CHD), stroke, and chronic kidney disease (CKD). Diabetes was defined by any of the following conditions: hemoglobin A1c (HbA1c) ≥ 6.5%, fasting plasma glucose ≥ 7.0 mmol/L, random plasma glucose ≥ 11.1 mmol/L, 2-hour plasma glucose ≥ 11.1 mmol/L during an oral glucose tolerance test (OGTT), current use of insulin or oral hypoglycemic agents, or a self-reported physician diagnosis of diabetes. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, self-reported diagnosis by a health care professional, or current use of antihypertensive medication. Hyperlipidemia was defined by any of the following: triglycerides ≥ 150 mg/dL, total cholesterol ≥ 200 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL, or current use of lipid-lowering medications. CKD was identified using either an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m², calculated using the CKD-EPI 2009 equation, or a random urine albumin-to-creatinine ratio (UACR) ≥ 30 mg/g. Pre-existing conditions were assessed via self-report. CHD was defined as a positive response to any of the following questions: "Ever told you had coronary heart disease?", "Ever told you had angina/angina pectoris?", or "Ever told you had a heart attack?" Stroke was defined as a positive response to the question: "Ever told you had a stroke?"

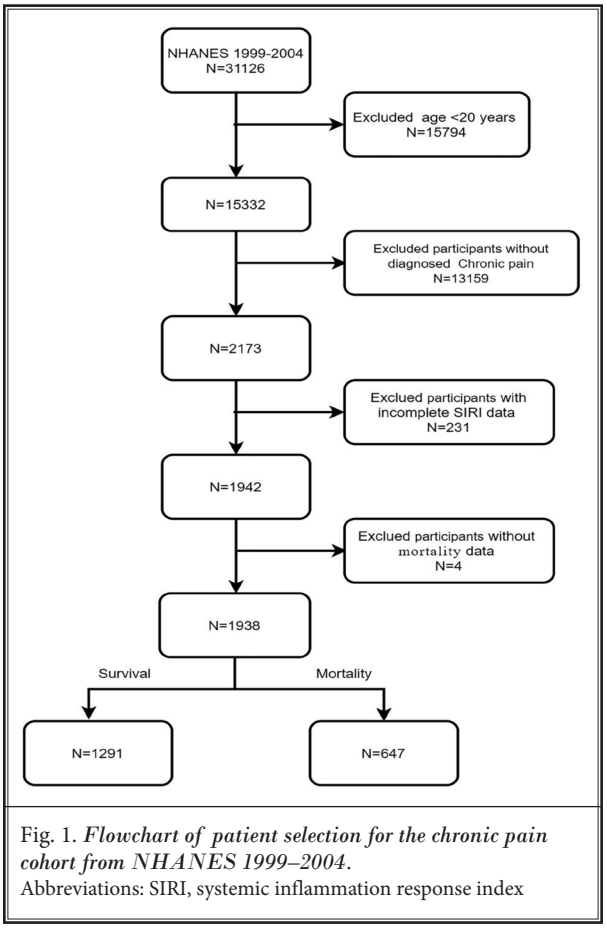


Fig. 1. *Flowchart of patient selection for the chronic pain cohort from NHANES 1999–2004.*
Abbreviations: SIRI, systemic inflammation response index

Statistical Analysis

All statistical analyses incorporated the complex,

multistage probability sampling design of the NHANES to yield nationally representative estimates. Survey weights, strata, and primary sampling units were applied in accordance with the analytical guidelines provided by the NCHS.

To handle missing data in covariates, multiple imputation using chained equations was performed. Five imputed datasets were created using predictive mean matching for continuous variables and logistic regression for categorical variables. The imputation model included all variables used in the primary analysis. Pooled estimates from the imputed datasets were obtained using Rubin's rules. Sensitivity analyses based on complete-case data were also planned to evaluate the robustness of the findings. Descriptive statistics were used to summarize the patients' baseline characteristics, stratified by survival status (survivors or deceased) at follow-up. For continuous variables, survey-weighted means and 95% confidence intervals (CIs) were calculated, with group differences assessed using survey-weighted linear regression. For categorical variables, survey-weighted proportions and 95% CIs were reported, and group differences were tested using survey-weighted chi-squared tests. Cox proportional hazards regression models were employed to examine the association between log10(SIRI) and all-cause mortality among individuals with chronic pain. Log10(SIRI) was evaluated both as a continuous variable and as a categorical variable based on tertile distribution. Hazard ratios (HRs) and 95% CIs were calculated. Three models were constructed: Model 1 was unadjusted; Model 2 was adjusted for age, gender, race, education level, PIR, and marital status; and Model 3 was further adjusted for obesity, smoking status, alcohol consumption, PA, diabetes, hypertension, hyperlipidemia, CKD, CHD, and stroke. To assess potential nonlinear associations between log10(SIRI) and all-cause mortality, restricted cubic spline (RCS) analysis with 3 knots was applied. When evidence of nonlinearity was observed, a 2-piecewise Cox regression model was fitted to identify threshold effects. The inflection point was determined using a recursive partitioning method, and model fit was compared using the log-likelihood ratio test. Subgroup analyses were conducted to explore the consistency of the association across various strata, including age, education level, obesity status, PA, and comorbid conditions. Interaction terms between log10(SIRI) and subgroup variables were included in the fully adjusted models to test for effect modification.

All statistical tests were 2-sided, and a *P*-value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using EmpowerStats software (www.empowerstats.com, X&Y Solutions, Inc.) and R software version 4.2.3 (www.r-project.org).

Results

Characteristics of the Study Population

Among 1,938 adults with chronic pain, 647 died during follow-up. Compared to survivors, decedents were older and had higher log10(SIRI) (both $P < 0.0001$). In addition, deceased individuals were more likely to have lived alone, reached lower educational attainment, fallen into the lowest PIR category, and reported low levels of physical activity. Significant differences between the deceased and surviving groups were also observed in several clinical and behavioral characteristics, including obesity, alcohol consumption, smoking, diabetes, CKD, hyperlipidemia, CHD, and stroke (all $P < 0.05$). By contrast, no significant differences were observed between the groups in terms of gender, race, or hypertension status ($P > 0.05$) (Table 1).

The Association Between log10(SIRI) And All-Cause Mortality

In survey-weighted Cox models, higher log10(SIRI) was associated with higher all-cause mortality (Table 2). In the unadjusted model, each one-unit increase in log10(SIRI) corresponded to a higher hazard of death (HR: 3.53, 95% CI: 2.38-5.23; $P < 0.001$). This association remained significant after adjustment for demographic characteristics (HR: 3.17, 95% CI: 2.10-4.78) and all covariates (HR: 2.56, 95% CI: 1.67-3.94). When SIRI was analyzed as a categorical variable, patients in the highest tertile showed a greater hazard of mortality than did those in the lowest tertile (HR: 1.45, 95% CI: 1.11-1.90; $P < 0.001$). A significant linear trend across tertiles was observed in all models (P for trend < 0.001).

RCS analysis suggested a nonlinear association between log10(SIRI) and all-cause mortality (Fig. 2). In the linear Cox model, higher log10(SIRI) was significantly associated with increased mortality (HR: 2.44, 95% CI: 1.76-3.38; $P < 0.0001$). A 2-piecewise Cox model identified an inflection point at approximately log10(SIRI) $\approx$ -0.23. Below this value, the association was not statistically significant (HR: 1.25, 95% CI: 0.80-1.96; $P = 0.3221$), whereas above this inflection point, mortality risk increased more steeply (HR: 8.72, 95% CI: 4.47-17.01; $P < 0.0001$). The piecewise model fit the data

better than the linear model (log-likelihood ratio test P = 0.001) (Table 3).

Subgroup Analysis

Across most subgroups, the association between log10(SIRI) and mortality was directionally consistent, with no evidence of effect modification (all P for interaction > 0.05), except by age (P for interaction = 0.0045). The association appeared stronger among patients aged ≥ 52 years (Fig. 3).

Sensitivity Analyses

In complete-case analyses, higher log10(SIRI) remained significantly associated with higher mortality risk, consistent with the primary (multiply imputed) analyses (Suppl. Table 1). The nonlinear pattern observed in the primary analyses was also reproduced in the complete-case RCS analyses (Suppl. Fig. 1).

Discussion

In this nationally representative prospective cohort of U.S. adults with chronic pain linked to mortality from NHANES 1999-2004 through December 31, 2019, higher SIRI was associated with an increased risk of all-cause mortality. This association remained significant after multivariable adjustment and was consistent when SIRI was modeled both continuously and by tertile categories, with similar results in sensitivity analyses. To our knowledge, this study is the first to evaluate the prog-

Table 1. *Baseline characteristics of patients with chronic pain according to survival status.*

Characteristic	Survivors (n = 1291)	Deceased (n = 647)	*P*-value
log10(SIRI)	0.03 (0.01, 0.04)	0.12 (0.10, 0.14)	< 0.0001
Age (years)	43.90 (42.98, 44.82)	62.44 (60.99, 63.88)	< 0.0001
Gender (%)			0.2818
Male	41.79 (38.29, 45.29)	45.37 (39.87, 50.87)	
Female	58.21 (54.71, 61.71)	54.63 (49.13, 60.13)	
Race (%)			0.2791
Mexican American	4.82 (3.41, 6.23)	2.05 (1.18, 2.92)	
Non-Hispanic Black	9.01 (6.98, 11.04)	9.43 (6.95, 11.92)	
Non-Hispanic White	77.03 (73.20, 80.86)	79.77 (74.06, 85.48)	
Other Hispanic	4.86 (2.91, 6.81)	4.93 (1.68, 8.17)	
Other race	4.28 (2.84, 5.72)	3.83 (2.01, 5.65)	
Marital Status			< 0.0001
Individuals living alone	29.49 (25.79, 33.19)	42.05 (37.15, 46.94)	
Individuals not living alone	70.51 (66.81, 74.21)	57.95 (53.06, 62.84)	
Education Level			< 0.0001
Under high school	17.82 (15.50, 20.14)	37.17 (32.66, 41.68)	
High school or equivalent	29.62 (26.18, 33.06)	27.14 (23.29, 31.00)	
Above high school	52.55 (48.66, 56.44)	35.69 (31.19, 40.19)	
PIR			< 0.0001
<=1	15.56 (12.58, 18.54)	22.13 (18.30, 25.97)	
>1	21.98 (18.84, 25.12)	30.25 (25.92, 34.59)	
>2	31.34 (27.52, 35.16)	28.35 (24.27, 32.43)	
>4	30.98 (27.32, 34.64)	19.48 (15.27, 23.69)	
Obese			0.0128
NO	63.67 (60.30, 67.04)	56.05 (51.09, 61.01)	
YES	36.33 (32.96, 39.70)	43.95 (38.99, 48.91)	
CKD			< 0.0001
NO	92.22 (90.40, 94.03)	70.41 (66.52, 74.30)	
YES	7.78 (5.97, 9.60)	29.59 (25.70, 33.48)	
Alcohol Consumption			0.0002
NO	25.35 (21.62, 29.08)	37.10 (32.18, 42.02)	
YES	74.65 (70.92, 78.38)	62.90 (57.98, 67.82)	
Hypertension			0.6788
NO	2.17 (1.37, 2.97)	2.48 (1.26, 3.71)	
YES	97.83 (97.03, 98.63)	97.52 (96.29, 98.75)	
Hyperlipidemia			< 0.0001
NO	26.84 (24.04, 29.64)	16.73 (13.80, 19.67)	
YES	73.16 (70.36, 75.96)	83.27 (80.33, 86.20)	
CHD			< 0.0001
NO	93.91 (91.92, 95.90)	73.19 (68.54, 77.84)	
YES	6.09 (4.09, 8.09)	26.81 (22.16, 31.46)	
Stroke			< 0.0001
NO	98.02 (96.92, 99.12)	89.66 (86.28, 93.04)	
YES	1.98 (0.88, 3.08)	10.34 (7.32, 13.36)	

nostic association of SIRI with mortality in a chronic pain population.

Our findings align with prior evidence linking higher SIRI to adverse prognosis in other chronic disease settings. Elevated SIRI has been associated with increased mortality in patients undergoing peritoneal dialysis and in individuals with hyperuricemia, and similar associations have been reported in CKD cohorts (23-26). In addition, higher SIRI has been linked to worse prognosis and increased mortality risk in cardiometabolic and cardiovascular populations, including coronary artery disease (CAD) and metabolic dysfunction–associated steatotic liver disease (MASLD) (27,28). Collectively, these data support the broader prognostic relevance of SIRI as a systemic inflammation marker across chronic disease contexts.

The observed association is biologically plausible. SIRI integrates neutrophil and monocyte counts relative to lymphocytes and may reflect a shift toward innate immune activation and away from adaptive immune balance (29). Chronic pain has been associated with low-grade systemic inflammation and neuroimmune processes (e.g., glial activation) that may facilitate peripheral and central sensitization (30,31). Although we adjusted for a broad set of sociodemographic, lifestyle, and clinical covariates, SIRI and chronic pain status were assessed at baseline and might have been influenced by shared comorbidities and upstream determinants; therefore, this study cannot establish a causal pain–inflammation pathway.

We observed a nonlinear dose–response relationship between SIRI and all-cause

Table 1 cont. *Baseline characteristics of patients with chronic pain according to survival status.*

Characteristic	Survivors (n = 1291)	Deceased (n = 647)	*P*-value
Smoking Status			0.0118
NO	40.50 (37.09, 43.91)	32.87 (28.01, 37.73)	
YES	59.50 (56.09, 62.91)	67.13 (62.27, 71.99)	
Diabetes			< 0.0001
NO	91.91 (90.28, 93.54)	72.51 (67.80, 77.22)	
YES	8.09 (6.46, 9.72)	27.49 (22.78, 32.20)	
PA			0.0026
Low	30.72 (27.71, 33.73)	41.81 (37.47, 46.15)	
Moderate	48.75 (45.54, 51.97)	42.34 (38.18, 46.50)	
High	20.67 (18.06, 23.28)	16.67 (13.02, 20.32)	

Continuous variables are presented as survey-weighted means with 95% CI, and *P*-values were calculated using survey-weighted linear regression models (svyglm). Categorical variables are also presented as survey-weighted percentages with 95% CI, and P-values were calculated using survey-weighted chi-square tests. Bold *P*-values indicate variables with strong statistical evidence of differences between survivors and deceased patients ($P < 0.001$).

Abbreviations: CI, confidence interval; CHD, coronary heart disease; CKD, chronic kidney disease; PA, physical activity; PIR, poverty–income ratio; SIRI, systemic inflammation response index.

Table 2. *Survey-weighted Cox proportional hazards models for the association between log10(SIRI) and all-cause mortality among individuals with chronic pain.*

log10(SIRI)	Model One		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Continuous variables						
log10(SIRI) per unit	3.53 (2.38, 5.23)	< 0.001	3.17 (2.10, 4.78)	< 0.001	2.56 (1.67, 3.94)	< 0.001
Categorical variable						
T1 group	1.0		1.0		1.0	
T2 group	1.16 (0.88, 1.52)	0.28	1.22 (0.85, 1.76)	0.28	1.11 (0.79, 1.56)	0.55
T3 group	1.84 (1.43, 2.36)	< 0.001	1.68 (1.28, 2.20)	< 0.001	1.45 (1.11, 1.90)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001

HR and 95% CI are presented for SIRI, modeled as both a continuous variable (per single-unit increase) and categorical tertiles (T1–T3). Tertile One (T1) was used as the reference group.

Model One was unadjusted. Model 2 was adjusted for age, gender, race, education level, PIR, and marital status. Model 3 was further adjusted for obesity, smoking status, alcohol consumption, PA, diabetes, hypertension, hyperlipidemia, CKD, CHD, and stroke. *P*-values for trend were calculated by modeling SIRI tertiles as an ordinal variable.

Abbreviations: CI, confidence interval; CHD, coronary heart disease; CKD, chronic kidney disease; HR, hazard ratio; PA, physical activity; PIR, poverty–income ratio; SIRI, systemic inflammation response index.

mortality. Spline analyses indicated a steeper increase in risk at higher SIRI levels, and piecewise modeling suggested an inflection point, which should be interpreted as a model-derived feature rather than a biologically predefined threshold. Prior studies have similarly reported nonlinear SIRI–mortality relationships, including J-shaped patterns in hypertensive NHANES participants and in individuals with hyperuricemia (18, 24). These findings suggest that the prognostic impact of systemic inflammation may not increase uniformly across its full range. Potential explanations include greater immune dysregulation and comorbidity clustering at higher levels of inflammatory burden; however, these interpretations remain hypothesis-generating. The nonlinear pattern was also reproduced in complete-case analyses, supporting the robustness of our findings.

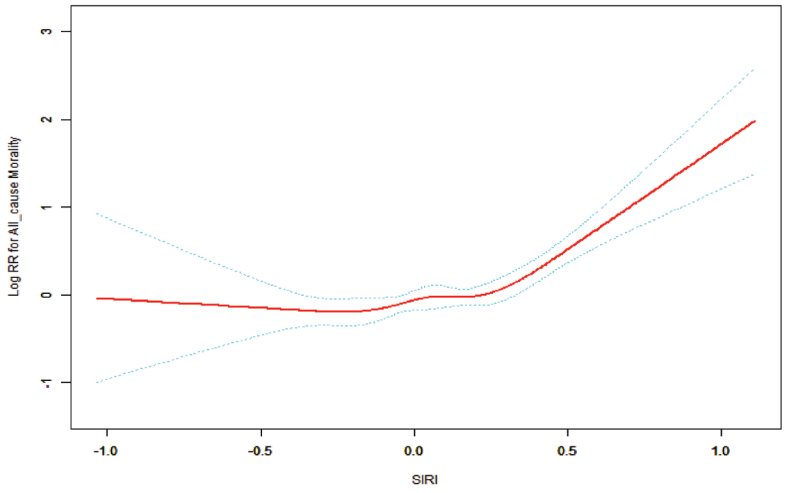


Fig. 2. *Restricted cubic spline analysis of the association between log10(SIRI) and all-cause mortality among individuals with chronic pain (multiply imputed dataset).*
The solid line represents the estimated log hazard ratio, and the dotted lines indicate the corresponding 95% CI. The analysis was conducted using the multiply imputed dataset and included 1,938 patients, among whom 647 deaths occurred during follow-up. A value of log(RR) = 0 corresponds to a hazard ratio of one, indicating no association. Models were adjusted for age, gender, race, education level, PIR, marital status, obesity, smoking status, alcohol consumption, PA, diabetes, hypertension, hyperlipidemia, CKD, CHD, and stroke. Abbreviations: CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; PA, physical activity; PIR, poverty–income ratio; SIRI, systemic inflammation response index.

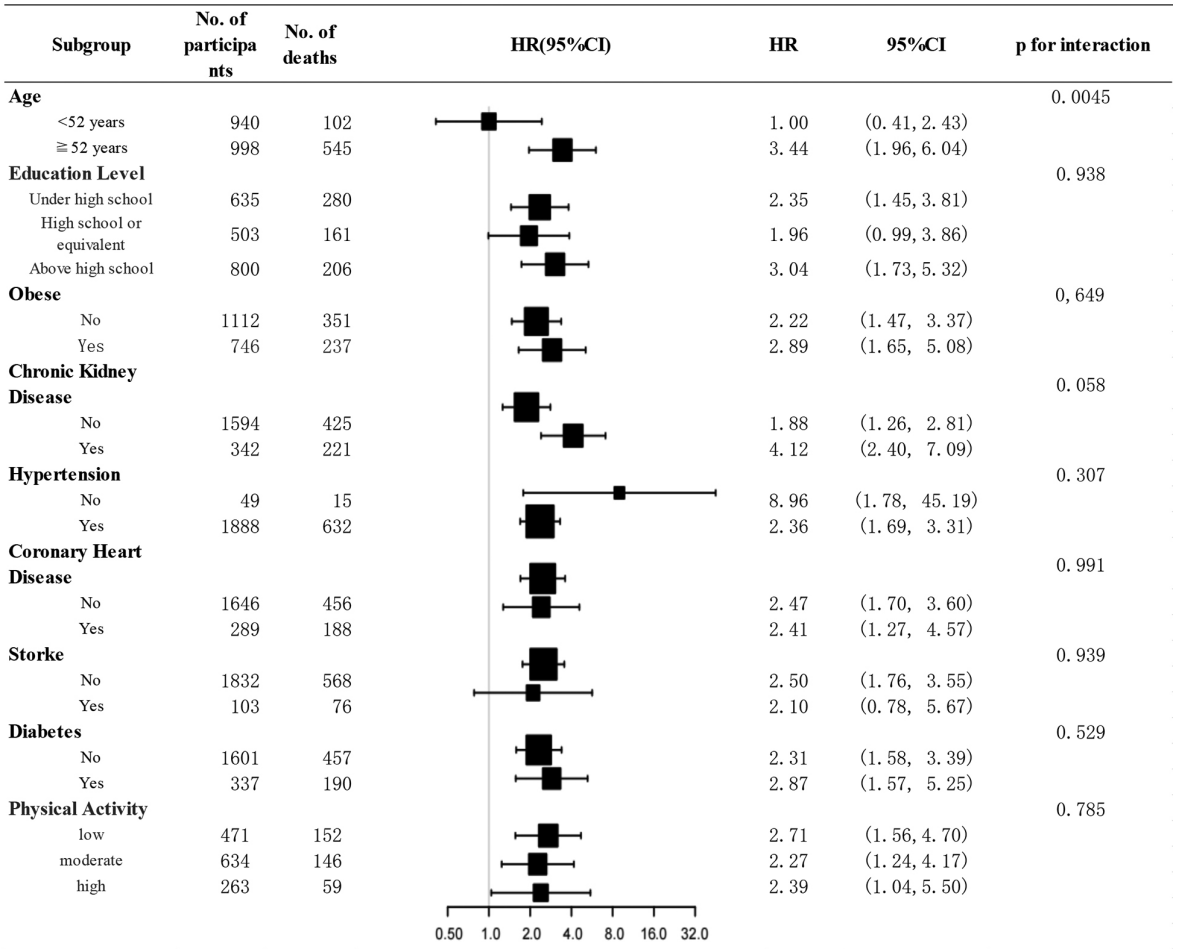
Subgroup analyses suggested potential effect modification by age (*P* for interaction = 0.0045), whereas we did not detect statistically significant interactions for other subgroups. Prior SIRI studies have also highlighted age as a potential modifier of SIRI–outcome associations (32-35); however, the presence and pattern of effect modification may vary across study populations and analytic approaches. The association between SIRI and mortality was generally consistent across strata, and sensitivity analyses indicated that the findings were unlikely to be driven by missing data. The stronger association observed among older adults may reflect immunosenescence and a higher burden of cardiometabolic or renal comorbidities, which could amplify the prognostic impact of systemic inflammation (36-38).

Because SIRI is calculated from routinely reported complete blood counts, it offers a low-cost, readily available snapshot of systemic inflammatory burden. Prior work has suggested that composite inflammation indices can refine prognostic assessment in higher-risk groups (39,40). In adults with chronic pain, our results indicate that SIRI may be a useful add-on for mortality risk stratification and can potentially help guide how

Table 3. *Piecewise Cox proportional hazards regression analysis of the association between log10(SIRI) and all-cause mortality.*

	All-Cause Mortality	
	HR (95%CI)	***P*-value**
Model I		
Linear effect	2.44 (1.76, 3.38)	< 0.0001
Model II		
Turning point (K)	-0.23	
Effect 1 < K	1.25 (0.80, 1.96)	0.3221
Effect 2 > K	8.72 (4.47, 17.01)	< 0.0001
Difference in effect between 2 and 1	6.96 (2.73, 17.72)	< 0.0001
Log-likelihood ratio test		0.001

A linear model (Model I) was compared to a 2-segment piecewise model (Model II), allowing for a single data-driven inflection point. The estimated inflection point should be interpreted as a model-dependent statistical feature rather than a biologically predefined or clinically actionable threshold. HR and 95% CI are reported for SIRI values below and above the inflection point. The log-likelihood ratio test was used to compare model fit. All models were adjusted for age, gender, race, education level, PIR, marital status, obesity, smoking status, alcohol consumption, PA, diabetes, hypertension, hyperlipidemia, CKD, CHD, and stroke. Abbreviations: CI, confidence interval; CHD, coronary heart disease; CKD, chronic kidney disease; HR, hazard ratio; PA, physical activity; PIR, poverty–income ratio; SIRI, systemic inflammation response index.



Subgroup	No. of participants	No. of deaths	HR	95%CI	p for interaction
Age					0. 0045
<52 years	940	102	1. 00	(0. 41, 2. 43)	
≧52 years	998	545	3. 44	(1. 96, 6. 04)	
Education Level					0. 938
Under high school	635	280	2. 35	(1. 45, 3. 81)	
High school or equivalent	503	161	1. 96	(0. 99, 3. 86)	
Above high school	800	206	3. 04	(1. 73, 5. 32)	
Obese					0, 649
No	1112	351	2. 22	(1. 47, 3. 37)	
Yes	746	237	2. 89	(1. 65, 5. 08)	
Chronic Kidney Disease					0. 058
No	1594	425	1. 88	(1. 26, 2. 81)	
Yes	342	221	4. 12	(2. 40, 7. 09)	
Hypertension					0. 307
No	49	15	8. 96	(1. 78, 45. 19)	
Yes	1888	632	2. 36	(1. 69, 3. 31)	
Coronary Heart Disease					0. 991
No	1646	456	2. 47	(1. 70, 3. 60)	
Yes	289	188	2. 41	(1. 27, 4. 57)	
Storke					0. 939
No	1832	568	2. 50	(1. 76, 3. 55)	
Yes	103	76	2. 10	(0. 78, 5. 67)	
Diabetes					0. 529
No	1601	457	2. 31	(1. 58, 3. 39)	
Yes	337	190	2. 87	(1. 57, 5. 25)	
Physical Activity					0. 785
low	471	152	2. 71	(1. 56, 4. 70)	
moderate	634	146	2. 27	(1. 24, 4. 17)	
high	263	59	2. 39	(1. 04, 5. 50)	

Fig. 3. *Forest plot of subgroup analyses for the association between log10(SIRI) and all-cause mortality.*
All models were adjusted for age, gender, race, education level, PIR, marital status, obesity, smoking status, alcohol consumption, PA, diabetes, hypertension, hyperlipidemia, CKD, CHD, and stroke, except for the stratification variable itself. *P*-values for interaction indicate effect modification across subgroups.
Abbreviations: CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; PA, physical activity; PIR, poverty–income ratio; SIRI, systemic inflammation response index.

closely patients are followed. In practice, an elevated SIRI may prompt more careful clinical review of older adults—particularly a focused evaluation for common coexisting conditions that often appear with chronic pain. Our subgroup analyses also suggested a stronger SIRI–mortality association in older age groups; however, this age-related pattern should be interpreted cautiously and confirmed in external cohorts. Compared to biomarkers that typically require ordering additional tests beyond a standard blood count (e.g., CRP or IL-6), SIRI can be generated from information that is already in hand for many outpatient visits and routine follow-up labs, which may make it easier to adopt without changing workflow. Still, SIRI should be viewed as complementary to, not a substitute for, a comprehensive clinical assessment that also considers pain characteristics, psychological comorbidity, and social determinants of health. Future studies should compare SIRI to CRP/IL-6 directly, quantify any incremental value beyond established risk factors, and test whether adding SIRI meaningfully improves risk classification in chronic pain populations.

However, our study has several limitations. Firstly, it was a population-based prospective observational cohort study with baseline exposure assessment; therefore, causal inference cannot be established, and

residual confounding and reverse causation cannot be excluded. Secondly, chronic pain status in NHANES was defined using a self-reported duration-based measure (≥ 3 months) and lacked detailed clinical characterization of the pain phenotype, including pain severity/intensity, specific etiology, anatomical sites, and comprehensive information on pain management, which might have introduced heterogeneity and misclassification within the chronic pain group. Thirdly, because chronic pain often co-occurs with cardiometabolic, renal, and other inflammatory conditions that may not be fully captured in NHANES, SIRI should be interpreted as an indicator of overall systemic inflammatory burden within a chronic pain cohort rather than inflammation attributable to chronic pain per se. Fourthly, unmeasured or incompletely measured factors—particularly medication use (e.g., opioids, NSAIDs, antidepressants), psychosocial stress, and other inflammatory conditions—could have influenced SIRI and/or mortality risks. Accordingly, these associations should be interpreted as prognostic rather than causal. Fifth, although the NHANES chronic pain sample is representative of noninstitutionalized adults in the U.S., the findings may not generalize to populations in other countries or to clinical cohorts. Finally, the number of deaths in some subgroups was modest, and the estimated inflection point could differ in other datasets or prospective settings. Future studies should validate these findings in independent cohorts and evaluate the clinical utility and incremental prognostic value of SIRI for risk stratification in chronic pain populations.

Conclusions

In this cohort of adults with chronic pain, higher SIRI was independently associated with a higher risk of all-cause mortality. SIRI may be a useful adjunct for mortality risk stratification, particularly in older adults, and warrants further evaluation in clinical and external validation studies.

Authors' Contributions

LWL, JY, and LS conceptualized the project, developed the methodology, and curated the data; LWL, YJC, and CYZ contributed to software development; LWL and YJC conducted the validation; and LWL and LS prepared the original draft of the manuscript, which JY and LS reviewed and edited. All authors have read and agreed to the published version of the manuscript.

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Disclaimer

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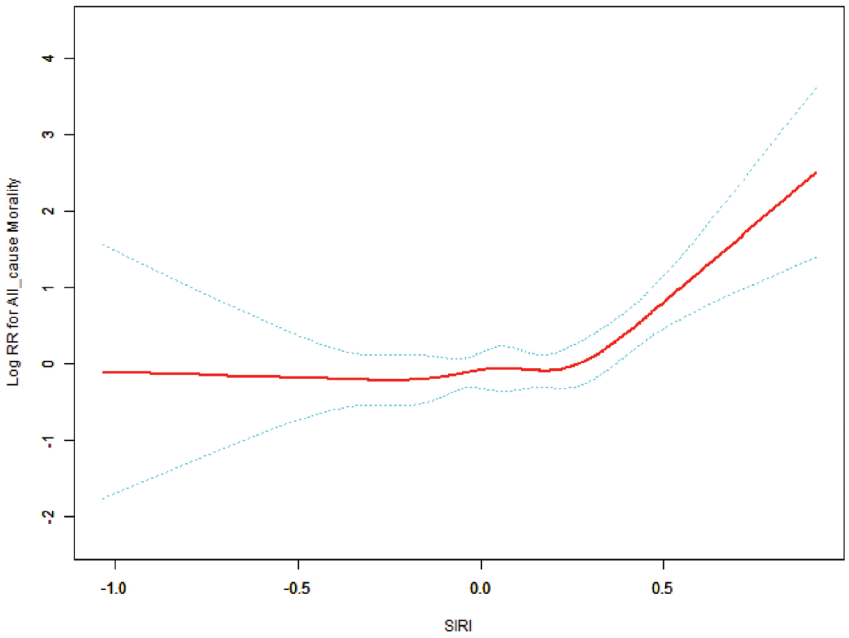
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Supplementary Fig. 1. ***Restricted cubic spline analysis of the association between log10(SIRI) and all-cause mortality among individuals with chronic pain (complete-case dataset).***
Restricted cubic spline analysis illustrating the association between log10(SIRI) and all-cause mortality among individuals with chronic pain based on the complete-case dataset. The solid line represents the estimated log hazard ratio, and the dotted lines indicate the corresponding 95% CI. The complete-case analysis included 585 patients, among whom 156 deaths occurred during follow-up. A value of log(RR) = 0 corresponds to a hazard ratio of one, indicating no association. Models were adjusted for age, gender, race, education level, PIR, marital status, obesity, smoking status, alcohol consumption, PA, diabetes, hypertension, hyperlipidemia, CKD, CHD, and stroke.