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The systemic inflammation response index as risks factor for all-cause and cardiovascular mortality among individuals with respiratory sarcopenia

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Abstract

Background Respiratory sarcopenia is associated with poor outcomes, yet effective biomarkers for risk stratification remain limited. This study investigates the associations between complete blood count (CBC)-derived inflammatory biomarkers, including neutrophil-to-lymphocyte ratio (NLR), neutrophil-monocyte-to-lymphocyte ratio (NMLR), and systemic inflammation response index (SIRI) and both all-cause and cardiovascular mortality in patients with respiratory sarcopenia.

Methods We conducted a cohort analysis of 1,673 adults with possible respiratory sarcopenia using data from the National Health and Nutrition Examination Survey (NHANES) from 2007 to 2012, with mortality follow-up through December 31, 2019. Possible respiratory sarcopenia was assessed via peak expiratory flow rate (PEFR). Multivariable Cox regression models evaluated associations between NLR, NMLR, SIRI, and mortality outcomes, adjusted for demographic, socioeconomic, and health-related covariates. Additional CBC-derived biomarkers (PLR, dNLR, MLR, SII) were analysed, and mediation analysis assessed albumin's role as a partial mediator of mortality.

Results Over a median follow-up of 116 months, 263 deaths occurred, including 68 from cardiovascular causes. Elevated NLR, NMLR, and SIRI were significantly associated with increased risks of all-cause and cardiovascular mortality. SIRI emerged as the strongest predictor, with adjusted hazard ratios (HRs) of 1.65 (95% CI, 1.23–2.22) for all-cause mortality and 3.18 (95% CI, 1.83–5.53) for cardiovascular mortality. Albumin partially mediated the relationship between SIRI and all-cause mortality (12.1%).

Conclusion Elevated NLR, NMLR, and SIRI are associated with increased mortality risks in respiratory sarcopenia, with SIRI demonstrating the highest predictive power. Integrating SIRI into clinical assessments may aid in identifying high-risk patients, allowing for targeted interventions.

Keywords All-cause mortality, Cardiovascular mortality, Neutrophil-to-lymphocyte ratio, Neutrophil-to-monocyte-to-lymphocyte ratio, Respiratory sarcopenia, Systemic inflammation response index

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Introduction

Respiratory sarcopenia, a form of sarcopenia characterized by weakness and atrophy of respiratory muscles, is increasingly recognized as a clinically significant condition linked to impaired respiratory function and systemic skeletal muscle degradation [1–3]. This condition commonly arises from a confluence of factors, including physical inactivity, chronic diseases, malnutrition, cachexia, and ageing-related inflammation. While respiratory sarcopenia involves reduced respiratory muscle strength, it does not always coincide with whole-body sarcopenia [4, 5], which is characterized by generalized skeletal muscle mass and strength loss. The concept of respiratory sarcopenia has emerged as a critical focus within sarcopenia research, given its potential to exacerbate respiratory compromise and elevate mortality risk, particularly among older adults and individuals with chronic illness [3, 6]. Reduced expiratory muscle strength, which compromises cough reflex and respiratory efficiency, has also been associated with higher susceptibility to pneumonia and poorer survival outcomes in critically ill patients [1, 7]. Consequently, respiratory sarcopenia may represent an underappreciated target for interventions aimed at reducing morbidity and mortality.

To address this, there is an urgent need for reliable, cost-effective biomarkers to assess mortality risk in respiratory sarcopenia, potentially guiding earlier clinical interventions. Inflammatory indices derived from routine complete blood counts (CBC), such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic inflammation response index (SIRI), have shown promise as indicators of systemic inflammation and immune activation in a range of chronic conditions [8–13]. Recent research has suggested that chronic inflammation is a major contributor to muscle catabolism, accelerating sarcopenia's progression by promoting nutrient depletion and oxidative stress [3, 13–15]. However, the relationship between these CBC-derived inflammatory markers and mortality risk in respiratory sarcopenia remains underexplored.

In this study, we aim to elucidate the associations between multiple CBC-derived inflammatory markers and both all-cause and cardiovascular mortality in individuals with respiratory sarcopenia using data from the National Health and Nutrition Examination Survey (NHANES). By investigating the prognostic value of these inflammatory markers, we seek to uncover the potential mechanisms underlying sarcopenia progression and to identify practical, readily available biomarkers that may improve risk stratification and guide preventive strategies in this high-risk population.

Methods

Study population

We used data from NHANES 2007–2012, a cross-sectional program that assesses the health and nutritional status of a nationally representative sample of U.S. residents [16, 17]. The initial sample included 16,486 individuals aged 20 to 79 years. Participants were eligible for inclusion if they completed both spirometry and CBC testing, with mortality status available through NHANES-linked National Death Index (NDI) records. Individuals without respiratory sarcopenia ($n=9,801$) were excluded. Additionally, we excluded participants with obstructive lung disease ($n=1,801$) to ensure that Peak Expiratory Flow Rate (PEFR) values reflected respiratory muscle function rather than airflow limitation. Individuals with missing mortality data ($n=1$), missing PEFR values ($n=3,099$), or missing CBC-derived inflammatory indices ($n=111$) were also excluded. The final analytic sample included 1,673 eligible participants (Fig. 1). NHANES protocols were approved by the National Center for Health Statistics Research Ethics Review Board, and all participants provided written informed consent. The NHANES dataset contains no identifiable patient characteristics.

Definition of possible respiratory sarcopenia and inflammatory biomarker measurements

Although maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) are considered the gold standards for assessing respiratory muscle strength, these key measures were not available in the NHANES. Following prior studies, PEFR was used as a substitute marker for respiratory muscle strength [1, 5, 18]. PEFR were derived from standardized spirometry assessments performed in accordance with the American Thoracic Society and European Respiratory Society guidelines. In this study, possible respiratory sarcopenia was defined as one standard deviation below the sex-specific mean PEFR derived from the NHANES population. Predicted values for FEV1 were calculated using the GLI 2012 equations [19]. Predicted value for PEF were calculated using the NHANES III equations [20].

CBCs were conducted using a Beckman Coulter automated analyzer. Inflammatory indices were calculated from leukocyte differentials as follows: NLR = neutrophil count / lymphocyte count; PLR = platelet count / lymphocyte count; derived NLR (dNLR) = neutrophil count / (white blood cell count-lymphocyte count); monocyte-to-lymphocyte ratio (MLR) = monocyte count / lymphocyte count; neutrophil-monocyte-to-lymphocyte ratio (NMLR) = (monocyte count + neutrophil count) / lymphocyte count; SIRI = neutrophil count × monocyte count / lymphocyte count; and systemic immune-inflammation

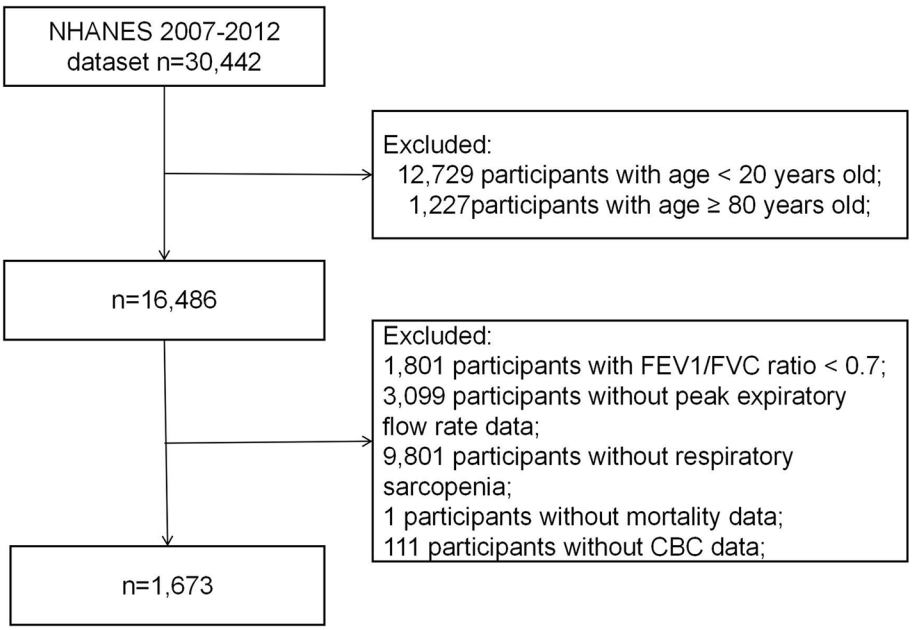

Fig. 1 Flowchart of the sample selection from National Health and Nutrition Examination Survey (NHANES) 2007–2012

index (SII) = platelet count × neutrophil count / lymphocyte count. All indices are expressed in 1,000 cells/μL.

Mortality ascertainment

Mortality data were obtained from NHANES-linked NDI public-use files, with follow-up available through December 31, 2019 [21]. Cause of death was determined based on International Classification of Diseases, Tenth Revision (ICD-10) codes, with cardiovascular mortality categorized by the National Center for Health Statistics (NCHS) as deaths due to heart disease (ICD-10 codes I00–I09, I11, I13, I20–I51).

Assessment of covariates

Demographic and health-related covariates included age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other), education level (below high school, high school, above high school), annual household income (less than $50,000, $50,000 or more), body mass index (BMI), smoking status, alcohol use, estimated glomerular filtration rate (eGFR), and history of diseases (diabetes, hypertension, cardiovascular disease, stroke, and cancer). Laboratory measurements included total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), creatinine, urine albumin-to-creatinine ratio (UACR), and serum albumin levels. Diabetes was defined by self-report, hemoglobin A1c levels ≥ 6.5%, or fasting blood glucose ≥ 126 mg/dl [22]. Hypertension was defined by a self-reported diagnosis of high blood pressure. Cardiovascular disease history was determined by self-reported diagnosis of congestive heart failure, coronary heart disease, or myocardial infarction. BMI was classified as normal (< 25 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥ 30 kg/m^2) [23]. Undernutrition was defined as a body mass index (BMI) < 18.5 kg/m^2. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, with chronic kidney disease (CKD) defined as eGFR < 60 ml/min/1.73 m^2 or UACR ≥ 30 mg/g [24].

Statistical analysis

Participants were categorized into lower and higher inflammatory biomarker groups based on cutoffs determined using maximally selected rank statistics, a method that identifies the threshold of a continuous variable that maximally separates survival outcomes. This approach, implemented through the 'maxstat' package in R, iteratively evaluates potential cutoff points to identify the one associated with the largest log-rank test statistic, thus optimizing the discriminatory ability of the variable for mortality outcomes. The statistical significance of the cutoff was validated through permutation tests to minimize the risk of overfitting. Baseline characteristics were compared between patients with and without respiratory sarcopenia using analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables.

Multiple Cox regressions were utilized to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cardiovascular mortality associated with inflammatory markers. Model 1 adjusted for age, sex, race/ethnicity, education level, annual household income, alcohol status, and smoking status. Model 2 included additional adjustments for BMI, eGFR, diabetes, hypertension, cardiovascular diseases, stroke, cancer, HDL, TG, TC and serum albumin levels. Kaplan–Meier survival curves and log-rank tests assessed mortality differences between higher and lower inflammatory biomarker groups. To evaluate robustness of the findings, sensitivity analyses and subgroup analyses were performed.

Restricted cubic spline (RCS) regressions with three knots were applied to assess potential nonlinear relationships between inflammatory biomarkers and mortality outcomes. Time-dependent receiver operating characteristic (ROC) curve analysis was performed to assess the predictive accuracy of NLR, NMLR, and SIRI for all-cause and cardiovascular mortality at 3, 5, and 10 years, with full covariate adjustment [25].

Mediation analysis was conducted to examine indirect effects of SIRI on mortality. The mediation model estimated the direct and indirect effects of SIRI on mortality, with indirect effects quantified as the proportion mediated by each factor. Results were presented with 95% confidence intervals.

All statistical analyses were performed using R software version 4.4.0. Statistical significance was set at a two-sided $P < 0.05$.

Results

Baseline characteristics of study population

Of the initial NHANES sample, 1,673 individuals (15.14%) met the criteria for possible respiratory sarcopenia. Baseline characteristics of those participants, compared to non-respiratory sarcopenia participants, are presented in Table 1. Participants with respiratory sarcopenia were generally older, had lower levels of educational and household income, and displayed higher BMI. Additionally, they exhibited lower levels of HDL, lower serum albumin, higher triglycerides, and a greater prevalence of comorbid chronic diseases. The prevalence of undernutrition among these participants was low, at only 1.57%. Lung function measures, including forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), FEV1/FVC ratio, FEV1%predicted and PEFR %predicted, were significantly lower in the respiratory sarcopenia group, consistent with impaired respiratory function.

Associations of the inflammatory markers with all-cause and cardiovascular mortality

During a median follow-up period of 116 months, 263 deaths occurred among participants with respiratory sarcopenia, with cardiovascular causes accounting for 4.06% of these deaths. In multivariable Cox regression models, elevated levels of NLR, NMLR, and SIRI were significantly associated with increased risks of all-cause mortality. However, PLR, MLR, SII, and dNLR did not show significant correlations (Table S1). In the fully adjusted Model 2, HRs for all-cause mortality were 1.13 (95% CI, 1.02–1.25) for NLR, 1.12 (95% CI, 1.02–1.24) for NMLR, and 1.18 (95% CI, 1.02–1.36) for SIRI (Table 2).

Cutoff values for NLR, NMLR, and SIRI were determined by maximally selected rank statistics, categorizing participants into higher and lower inflammatory biomarker groups (Fig. S1-3). The baseline characteristics of participants with higher and lower NLR, NMLR, and SIRI are presented in Tables S2-S4, respectively. In the higher groups, elevated risks of all-cause mortality remained robust across all covariate adjustments, with HRs of 1.45 (95% CI, 1.07–1.97) for NLR, 1.18 (95% CI, 1.02–1.36) for NMLR, and 1.65 (95% CI, 1.23–2.22) for SIRI in Model 2 (Table 2).

For cardiovascular mortality, a similar positive association was observed. The fully adjusted Model 2 indicated HRs of 1.24 (95% CI, 1.02–1.50) for NLR, 1.22 (95% CI, 1.02–1.46) for NMLR, and 1.42 (95% CI, 1.08–1.86) for SIRI. Participants in the higher biomarker groups exhibited significantly elevated risks of cardiovascular mortality, with HRs of 1.93 (95% CI, 1.09–3.42) for NLR, 2.10 (95% CI, 1.20–3.68) for NMLR, and 3.18 (95% CI, 1.83–5.53) for SIRI (Table 2).

Correlation and adjusted analysis with C-reactive protein

Among a subset of 1,127 participants with available C-reactive protein (CRP) data (NHANES 2007–2010), weak but statistically significant correlations were observed between CRP and the inflammatory markers (Pearson correlation coefficients of 0.18 to 0.22, all $P < 0.001$) (Fig. S4-6). Adjusting for CRP in the association models revealed that SIRI remained an independent predictor of both all-cause and cardiovascular mortality, while NLR and NMLR associations with all-cause mortality were not statistically significant after CRP adjustment (Table S5).

Survival analysis

Kaplan–Meier survival analysis revealed that participants in the higher NLR, NMLR, and SIRI groups had had significantly lower survival probabilities for both

Table 1 Baseline characteristics of the study participants

Characteristics	All participants (*N* = 11,053)	Respiratory sarcopenia		*p* value
		No (*N* = 9,380)	Yes (*N* = 1,673)	
Age, years	44.00 (31.00,58.00)	41.00 (30.00,54.00)	59.00 (45.00,68.00)	< 0.001
Male	5259 (47.58%)	4487 (47.84%)	772 (46.14%)	0.202
BMI, kg/m^2	28.21 (24.46,32.70)	28.02 (24.30,32.50)	29.23 (25.30,34.09)	< 0.001
Obesity, %	4256 (38.51%)	3504 (37.49%)	752 (45.41%)	< 0.001
Undernutrition, %	138 (1.25%)	112 (1.20%)	26 (1.57%)	0.210
Race, %				< 0.001
Non-Hispanic White	4484 (40.57%)	3986 (42.49%)	498 (29.77%)	
Non-Hispanic Black	2363 (21.38%)	1897 (20.22%)	466 (27.85%)	
Mexican American	1923 (17.40%)	1613 (17.20%)	310 (18.53%)	
Others	2283 (20.66%)	1884 (20.09%)	399 (23.85%)	
Household income, %				< 0.001
< $55,000	6554 (59.30%)	5334 (56.87%)	1220 (72.92%)	
≥ $55,000	4037 (36.52%)	3676 (39.19%)	361 (21.58%)	
Not recorded	462 (4.18%)	370 (3.94%)	92 (5.50%)	
Education levels, %				< 0.001
Below high school	2736 (24.75%)	2034 (21.68%)	702 (41.96%)	
High school	5733 (51.87%)	4959 (52.87%)	774 (46.26%)	
Above high school	2584 (23.38%)	2387 (25.45%)	197 (11.78%)	
Smoking status, %	4563 (41.28%)	3825 (40.78%)	738 (44.11%)	0.011
Drinking status, %	7590 (68.67%)	6633 (70.71%)	957 (57.20%)	< 0.001
Diabetes status, %	1335 (12.08%)	924 (9.85%)	411 (24.57%)	< 0.001
Cardiovascular diseases, %	502 (4.54%)	309 (3.29%)	193 (11.54%)	< 0.001
Hypertension, %	3245 (29.36%)	2450 (26.12%)	795 (47.52%)	< 0.001
Stroke, %	210 (1.90%)	113 (1.20%)	97 (5.80%)	< 0.001
Malignancy, %	680 (6.15%)	510 (5.44%)	170 (10.16%)	< 0.001
CKD, %	1031 (9.33%)	709 (7.66%)	322 (19.67%)	< 0.001
eGFR, mL/min/1.73 m^2	101.43 (86.32,115.93)	102.94 (88.14,116.92)	92.40 (75.82,108.28)	< 0.001
HDL, mmol/L	1.29 (1.06,1.58)	1.29 (1.06,1.58)	1.27 (1.06,1.53)	0.016
Albumin, g/L	43.00 (41.00,45.00)	43.00 (41.00,45.00)	42.00 (40.00,44.00)	< 0.001
TC, mmol/L	4.96 (4.32,5.71)	4.96 (4.32,5.69)	5.02 (4.29,5.77)	0.127
TG, mmol/L	1.37 (0.89,2.13)	1.34 (0.88,2.10)	1.52 (1.00,2.31)	< 0.001
White blood cell, × 10^9/L	6.80 (5.60,8.20)	6.80 (5.60,8.20)	6.90 (5.70,8.20)	0.288
Neutrophil, × 10^9/L	3.90 (3.00,5.00)	3.90 (3.00,5.00)	3.90 (3.00,5.00)	0.865
Lymphocyte, × 10^9/L	2.10 (1.70,2.50)	2.10 (1.70,2.50)	2.10 (1.70,2.60)	0.484
Monocyte, × 10^9/L	0.50 (0.40,0.60)	0.50 (0.40,0.60)	0.50 (0.40,0.60)	0.012
Platelet, × 10^9/L	243.00 (205.00,288.00)	240.00 (203.00,287.00)	258.00 (212.00,300.00)	0.006
NLR	1.88 (1.43,2.50)	1.88 (1.44,2.48)	1.87 (1.41,2.50)	0.546
PLR	117.78 (94.00,147.14)	117.89 (94.35,146.80)	115.93 (92.14,149.05)	0.448
MLR	0.24 (0.19,0.30)	0.24 (0.19,0.30)	0.24 (0.19,0.32)	0.062
SII	456.23 (330.00,639.40)	456.00 (331.55,637.15)	458.25 (317.78,651.20)	0.695
dNLR	0.84 (0.80,0.88)	0.84 (0.81,0.88)	0.84 (0.80,0.87)	< 0.001
NMLR	2.13 (1.65,2.76)	2.13 (1.67,2.76)	2.12 (1.64,2.80)	0.687
SIRI	0.93 (0.64,1.34)	0.93 (0.64,1.34)	0.95 (0.65,1.40)	0.233
FEV1, L	3.08 (2.50,3.71)	3.21 (2.67,3.83)	2.24 (1.83,2.80)	< 0.001
FVC, L	3.82 (3.12,4.61)	3.96 (3.29,4.74)	2.86 (2.32,3.60)	< 0.001
FEV1/FVC	0.80 (0.76,0.84)	0.81 (0.77,0.85)	0.78 (0.74,0.83)	< 0.001
FEV1%predicted	1.00 (0.94,1.00)	1.00 (0.96,1.00)	0.92 (0.81,1.00)	< 0.001
PEFR, L/s	8.02 (6.66,9.70)	8.46 (7.16,10.04)	5.25 (4.62,6.72)	< 0.001
PEFR %predicted	1.01 (0.87,1.16)	1.04 (0.91,1.19)	0.79 (0.67,0.91)	< 0.001

Table 1 (continued)

Continuous variables are presented as the mean and 95% confidence interval, category variables are described as the percentage and 95% confidence interval

BMI body mass index, *CKD* Chronic kidney disease, *HDL* High density lipoprotein cholesterol, *TC* Cholesterol, *TG* Triglycerides, eGFR, estimated glomerular filtration rate, *FVC* forced vital capacity, *FEV1* forced expiratory volume in 1 s, *PEFR* peak expiratory flow rate, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-lymphocyte ratio, *dNLR* neutrophil-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio, *NMLR* neutrophil-monocyte-to-lymphocyte ratio, *SII* systemic immune-inflammation index, *SIRI* systemic inflammatory response index

Table 2 The relationships between inflammatory markers and mortality in respiratory sarcopenia

Characteristic	Crude model		Model 1		Model 2	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
All-cause mortality						
NLR	1.20(1.11,1.31)	< 0.001	1.15(1.05,1.25)	0.002	1.13(1.02,1.25)	0.015
NLR category						
Lower NLR (*n* = 1415)	Ref		Ref		Ref	
Higher NLR (*n* = 258)	1.86(1.41,2.47)	< 0.001	1.64(1.23,2.19)	< 0.001	1.45(1.07,1.97)	0.017
NMLR	1.20(1.11,1.30)	< 0.001	1.14(1.05,1.24)	0.002	1.12(1.02,1.24)	0.016
NMLR category						
Lower NMLR (*n* = 1386)	Ref		Ref		Ref	
Higher NMLR (*n* = 287)	1.98(1.51,2.59)	< 0.001	1.75(1.33,2.32)	< 0.001	1.51(1.13,2.03)	0.005
SIRI	1.39(1.22,1.58)	< 0.001	1.24(1.09,1.42)	0.001	1.18(1.02,1.36)	0.024
SIRI category						
Lower SIRI (*n* = 1386)	Ref		Ref		Ref	
Higher SIRI (*n* = 287)	1.99(1.53,2.61)	< 0.001	1.78(1.35,2.36)	< 0.001	1.65(1.23,2.22)	< 0.001
Cardiovascular mortality						
NLR	1.26(1.09,1.47)	0.002	1.23(1.04,1.45)	0.016	1.24(1.02,1.50)	0.03
NLR category						
Lower NLR (*n* = 1263)	Ref		Ref		Ref	
Higher NLR (*n* = 215)	2.63(1.57,4.40)	< 0.001	2.31(1.36,3.93)	0.002	1.93(1.09,3.42)	0.024
NMLR	1.25(1.09,1.44)	0.002	1.21(1.03,1.43)	0.019	1.22(1.02,1.46)	0.033
NMLR category						
Lower NMLR (*n* = 1241)	Ref		Ref		Ref	
Higher NMLR (*n* = 237)	2.69(1.63,4.45)	< 0.001	1.46(1.46,4.14)	< 0.001	2.10(1.20,3.68)	0.01
SIRI	1.51(1.20,1.90)	< 0.001	1.41(1.10,1.80)	0.006	1.42(1.08,1.86)	0.013
SIRI category						
Lower SIRI (*n* = 1240)	Ref		Ref		Ref	
Higher SIRI (*n* = 238)	3.27(2.00,5.33)	< 0.001	3.13(1.87,5.24)	< 0.001	3.18(1.83,5.53)	< 0.001

Crude Model, unadjusted. Model 1, adjusted for age, sex, ethnicity, smoking status, drinking status, education level and annual household income. Model 2, adjusted for age, sex, ethnicity, smoking status, drinking status, education level, annual household income, BMI, diabetes, cardiovascular disease, stroke, hypertension, cancer history, eGFR, HDL, TG, TC and albumin. *NLR* neutrophil-to-lymphocyte ratio, *NMLR* neutrophil-monocyte-to-lymphocyte ratio, *SIRI* systemic inflammatory response index, *BMI* body mass index, *HDL* High density lipoprotein cholesterol, *TC* Cholesterol, *TG* Triglycerides, *eGFR* estimated glomerular filtration rate, *HRs* hazard ratios, *CI* confidence interval

all-cause and cardiovascular mortality compared to those in the lower groups (all $P < 0.001$) (Fig. 2 A-F).

Sensitivity and subgroup analyses

Sensitivity analyses confirmed the robustness of the main findings. In the sensitivity analyses, excluding participants younger than 45 years or those who died within the first 2 years of follow-up did not substantially alter the associations for SIRI, although NLR and NMLR associations with mortality were no longer statistically significant in some models (Tables S6 and S7). In participants without baseline cardiovascular disease or stroke, elevated SIRI levels remained a significant predictor of both all-cause and cardiovascular mortality (Table S8).

In subgroup analyses, we observed a significant interaction between elevated SIRI levels and smoking status with respect to all-cause mortality (HR = 2.49; 95% CI, 1.74–3.55, $P < 0.001$). However, no significant interactions

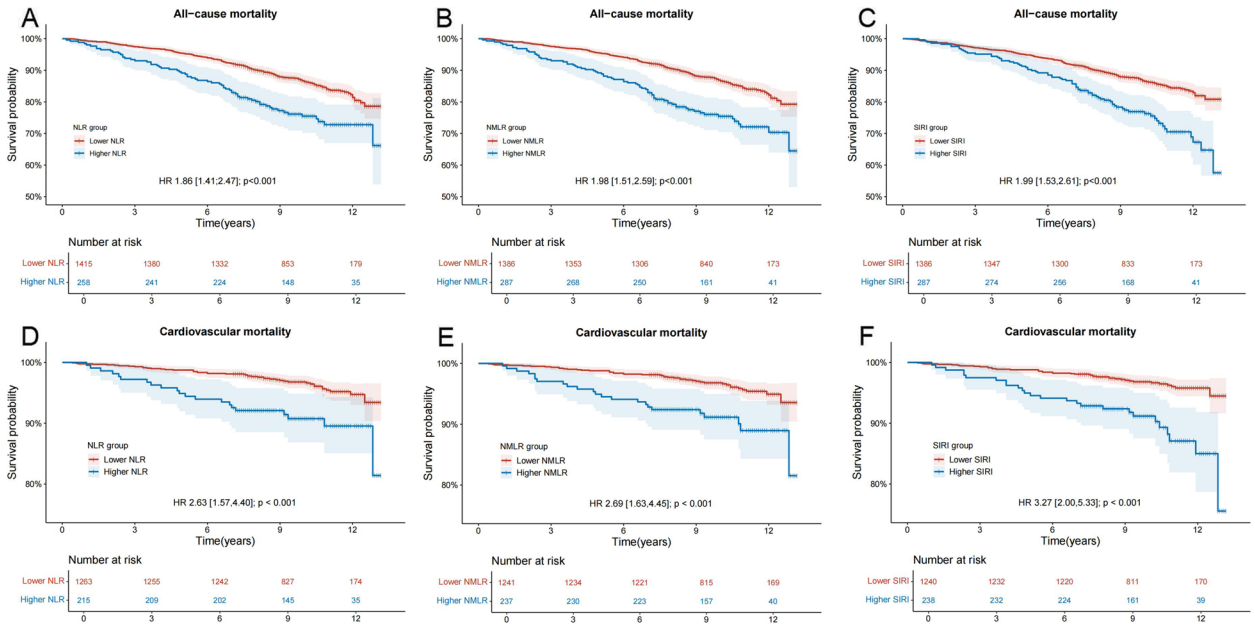

Fig. 2 Kaplan–Meier Survival Curves for Mortality Stratified by NLR, NMLR, and SIRI in Patients with possible Respiratory Sarcopenia. **A**-**C** All-cause mortality; **D**-**F** Cardiovascular mortality. NLR, Neutrophil-to-Lymphocyte Ratio; NMLR, Neutrophil-Monocyte-to-Lymphocyte ratio; SIRI, Systemic Inflammation Response Index

were detected among the subgroup variables for NLR and NMLR (all *P* for interaction > 0.05) (Tables S9–S11).

Dose–response association of the inflammatory markers with mortality

RCS analyses indicated no evidence of a nonlinear association between NLR, NMLR, and SIRI and increased risks of both all-cause and cardiovascular mortality (all $P > 0.05$ for nonlinearity) (Fig. 3A-F).

Prognostic accuracy of inflammatory markers

Time-dependent ROC curve analysis suggested comparable predictive efficacy for NLR, NMLR, and SIRI in predicting both all-cause and cardiovascular mortality over 3, 5, and 10-year intervals. SIRI demonstrated slightly superior predictive accuracy compared to NLR and NMLR, with area under the curve (AUC) values ranging from 0.713 to 0.785 for all-cause mortality and from 0.803 to 0.820 for cardiovascular mortality (Fig. S7-9).

Mediation analysis

Mediation analysis indicated that albumin partially mediated the association between SIRI and all-cause mortality, accounting for 12.1% of SIRI's effect on mortality (Fig. 4A). SIRI was negatively correlated with albumin ($\beta = -0.378$, $P < 0.001$), and albumin, in turn, was positively associated with survival ($\beta = 0.039$, $P = 0.002$). For cardiovascular mortality, no significant mediation effect of albumin on the relationship with SIRI was observed (Fig. 4B).

Discussion

In this large, nationally representative cohort study, we found that elevated levels of the CBC-derived inflammatory markers—NLR, NMLR, and SIRI—were independently associated with higher risks of all-cause and cardiovascular mortality among individuals with possible respiratory sarcopenia. SIRI emerged as the strongest predictor, with its association persisting across sensitivity and subgroup analyses. This study focuses on possible respiratory sarcopenia, a condition marked by respiratory muscle atrophy and systemic inflammation, distinguishing it from general sarcopenia [4, 5]. Our findings provide new insights into the prognostic value of routine inflammatory markers in this vulnerable population, offering a practical and accessible tool to identify high-risk patients for targeted interventions.

An increasing number of studies has established the prognostic value of CBC-derived inflammatory markers such as NLR and SIRI, in various chronic conditions, such as diabetes [26], hypertension [27], chronic obstructive pulmonary disease [28], and chronic heart failure [29]. Systemic low-grade inflammation is increasingly recognized as a central driver in the pathogenesis of sarcopenia, contributing to both muscle catabolism and functional decline [30]. Consistent with prior studies [9], our findings identify NLR, NMLR, and SIRI as

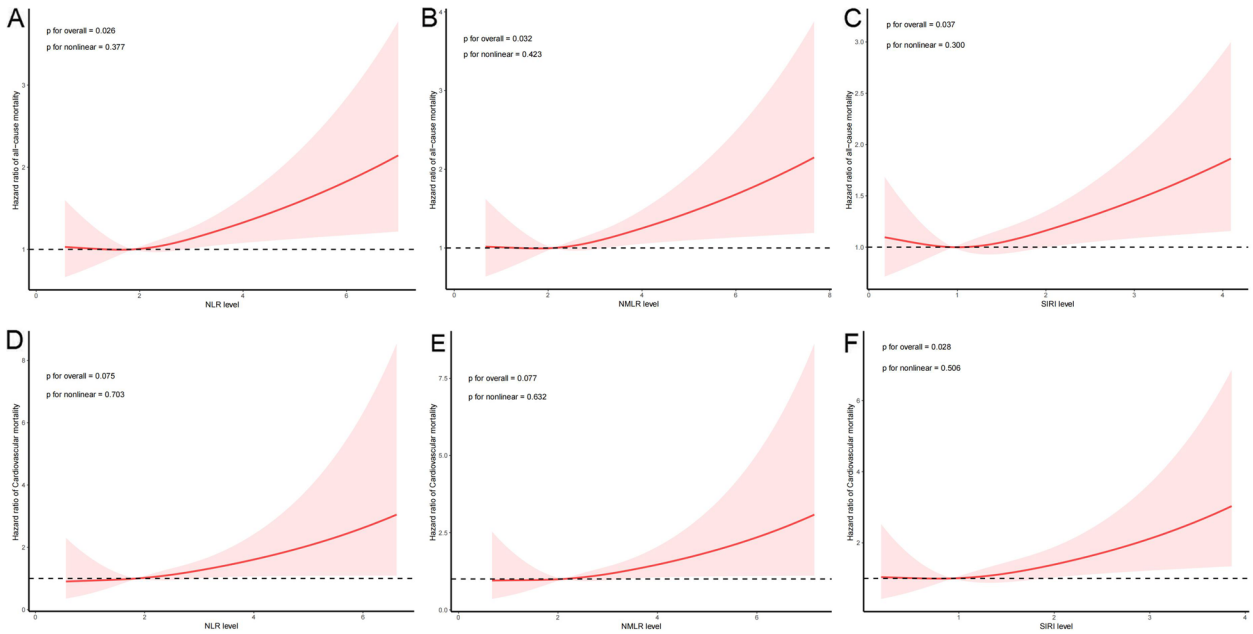

Fig. 3 Dose–Response Associations for the NLR, NMLR, and SIRI in relation to Mortality in Patients with possible Respiratory Sarcopenia. Adjusted for age, sex, ethnicity, smoking status, drinking status, education level, annual household income, BMI, diabetes, cardiovascular disease, stroke, hypertension, cancer history, eGFR, HDL, TG, TC and albumin. **A**-**C** All-cause mortality; **D**-**F** Cardiovascular mortality. BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, High density lipoprotein cholesterol; TC, Cholesterol; TG, Triglycerides; NLR, Neutrophil-to-Lymphocyte Ratio; NMLR, Neutrophil-Monocyte-to-Lymphocyte ratio; SIRI, Systemic Inflammation Response Index

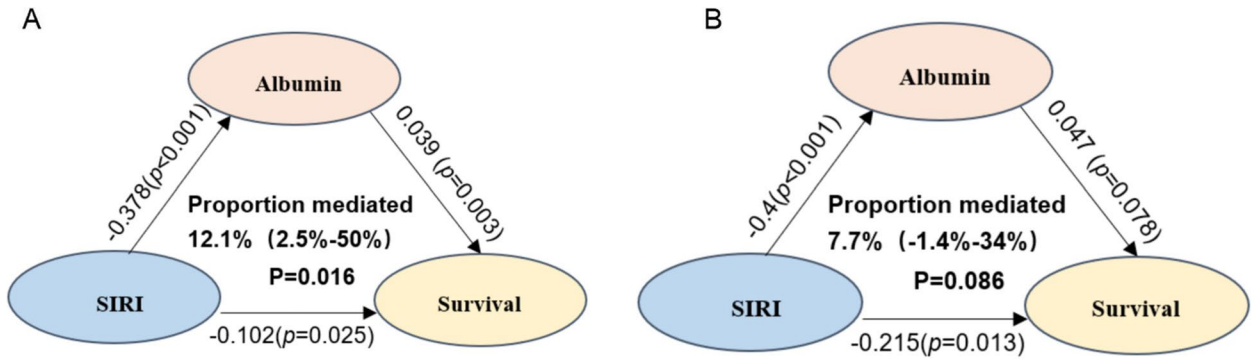

Fig. 4 The mediating effect of albumin on the relationship between SIRI and survival. Adjusted for age, sex, ethnicity, smoking status, drinking status, education level, annual household income, BMI, diabetes, cardiovascular disease, stroke, hypertension, cancer history, eGFR, HDL, TG, and TC. **A** All-cause mortality; **B** Cardiovascular mortality. BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, High density lipoprotein cholesterol; TC, Cholesterol; TG, Triglycerides; SIRI, Systemic Inflammation Response Index

significant predictors of all-cause and cardiovascular mortality in possible respiratory sarcopenia. Importantly, SIRI emerged as the most robust predictor in our cohort, demonstrating a strong association with mortality even after adjustment for CRP, a widely used marker of systemic inflammation. This independence from CRP suggests that SIRI may capture unique inflammatory dynamics particularly relevant to mortality risk in respiratory sarcopenia. Previous studies have highlighted SIRI's predictive value across conditions associated with heightened inflammation, such as hyperuricemia [31], sarcopenia [9], hypertension [32], COVID-19 [33], and even in the general populations, where higher SIRI levels consistently correlate with adverse outcomes [34]. The persistent association with elevated SIRI with poor prognosis across these diverse conditions suggests it may serve as a reliable marker of systemic inflammation severity and a direct link to the risk of mortality. By demonstrating SIRI's predictive utility in respiratory sarcopenia, our study extends these findings to a distinct

population characterized by respiratory muscle atrophy, underscoring SIRI's potential as a practical and accessible biomarker to identify individuals at high risk in clinical settings.

SIRI, as an integrated marker of inflammation and immune dysregulation, reflects the balance between pro-inflammatory and anti-inflammatory pathways by combining neutrophil, monocyte, and lymphocyte counts. Elevated SIRI levels indicate heightened systemic inflammation and immune imbalance [34], which may contribute to muscle atrophy and functional decline central to respiratory sarcopenia. The low-grade systemic inflammation observed in patients with respiratory sarcopenia is likely multifactorial, with aging, comorbidities, obesity, smoking, and physical inactivity as key contributors [30, 35–37]. Chronic conditions, such as cardiovascular disease, diabetes, and hypertension, are prevalent in this population and are known to drive inflammatory processes. Additionally, obesity, particularly visceral adiposity, promotes the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Smoking, a significant risk factor for both systemic inflammation and respiratory dysfunction, exacerbates inflammatory pathways through oxidative stress and immune activation. Furthermore, physical inactivity, which is common in individuals with sarcopenia, impairs muscle metabolism and contributes to the accumulation of inflammatory mediators. Together, these factors may create a pro-inflammatory milieu, compounding the risk of adverse outcomes in respiratory sarcopenia.

Our mediation analysis further suggested that serum albumin, a marker of nutritional status, partly mediated the relationship between SIRI and all-cause mortality, underscoring an interplay between systemic inflammation, nutritional depletion, and mortality risk in respiratory sarcopenia. While aging alone does not fully account for hypoalbuminemia, elevated IL-6 and TNF-α reduce albumin synthesis and accelerate its degradation [38, 39], leading to lower serum albumin levels often observed in frail or sarcopenic patients [40]. Low albumin levels, which are independently associated with increased frailty and sarcopenia risk, may thus compound the adverse effects of chronic inflammation on muscle integrity [39, 41]. These findings suggest that, for patients with respiratory sarcopenia and elevated SIRI, nutritional interventions targeting inflammation and supporting protein balance could be critical for preserving muscle mass and function, potentially mitigating the progression to disability.

Respiratory sarcopenia may develop independently of whole-body sarcopenia, particularly in its early stages, due to unique factors affecting respiratory muscle function. For example, chronic pulmonary conditions, aging-related declines in respiratory mechanics, and localized inflammation can disproportionately impact respiratory muscles. While we acknowledge the potential overlap between respiratory and whole-body sarcopenia, not all individuals with respiratory sarcopenia meet the diagnostic criteria for generalized sarcopenia, as supported by recent studies [4, 5]. To improve the specificity of PEFR for respiratory muscle function in this study, we also excluded individuals with obstructive lung disease (FEV1/FVC < 0.7), thereby reducing potential confounding from airway obstruction and strengthening the reliability of our respiratory muscle assessment. This comparison underscores the validity of using PEFR as a reliable marker of respiratory muscle function and its prognostic relevance in patients with respiratory sarcopenia.

However, several limitations of this study should be acknowledged. Firstly, the absence of MIP and MEP measurements in the NHANES dataset is a limitation of our study, as these are considered the standard methods for assessing respiratory muscle strength in the diagnosis of respiratory sarcopenia. While PEFR provides an accessible and feasible alternative, it does not capture all aspects of respiratory muscle function. As a surrogate, PEFR may not adequately reflect the complex nature of respiratory sarcopenia. Moreover, the reliance on PEFR as a proxy could have resulted in some misclassification of respiratory sarcopenia status, potentially affecting the generalizability of our findings to populations assessed using alternative diagnostic criteria. Future research should aim to incorporate direct measurements like MIP and MEP to enhance the accuracy of diagnosing respiratory sarcopenia. Secondly, despite extensive adjustment for a wide range of potential confounders, residual confounding by unmeasured factors such as comorbidities, environmental exposures, or genetic predispositions may still influence the observed associations. Thirdly, the study focused exclusively on CBC-derived indicators as biomarkers of systemic inflammation, but the inclusion of other inflammatory markers, such as TNF-α and IL-6, could provide additional insights into the inflammatory mechanisms underlying respiratory sarcopenia and its associated mortality risk. Lastly, the study population was limited to U.S. adults, and the findings may not be generalizable to populations in other countries with different healthcare systems, lifestyles, and genetic backgrounds. Further research in diverse populations is needed to confirm the applicability of these findings globally.

Conclusion

In conclusion, this study provides compelling evidence that elevated NLR, NMLR, and SIRI are significantly associated with increased risks of both all-cause and

cardiovascular mortality in patients with possible respiratory sarcopenia. Notably, SIRI emerged as the most robust predictor of all-cause and cardiovascular mortality, highlighting its potential as a prognostic biomarker in this population. Integrating SIRI into routine clinical assessments may enhance clinicians' ability to identify individuals at heightened risk, enabling more personalized interventions. These findings provide a foundation for further research to validate SIRI's predictive value across diverse populations and explore its integration with additional biomarkers to improve prognostic models. Future studies, especially longitudinal and interventional designs, are essential to refine clinical approaches in managing respiratory sarcopenia and mitigating associated mortality risks.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions
YL, XY and YG organized the data and wrote the manuscript. YL and XY contributed to the interpretation of the results. JX, RS and YK designed the study and revised the manuscript. All authors contributed to the critical revision of this manuscript.

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Data availability
The study utilized data obtained from the National Health and Nutrition Examination Survey (NHANES), accessible at https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate
Ethical clearance for the current study was granted by the National Center for Health Statistics Ethics Review Board, and all participants were required to provide written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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