International Journal of Chronic Obstructive Pulmonary Disease

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ORIGINAL RESEARCH

# The Relationship Between Serum Inflammatory Markers and Chronic Obstructive Pulmonary Disease in Middle-Aged and Older Adults in the United States: A Cross-Sectional Study Based on NHANES 2013–2018

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**Objective:** Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease characterized by increased inflammation, persistent decline in lung function, and extensive lung damage. Research has shown that inflammation plays a crucial role in the formation and progression of COPD. The systemic inflammation response index (SIRI) is an emerging inflammatory biomarker whose clinical significance in COPD remains undetermined. This study aims to explore the potential association between serum inflammatory marker SIRI levels and the prevalence of COPD.

**Methods:** This cross-sectional study utilized data from the National Health and Nutrition Examination Survey (NHANES) database from 2013–2018. A total of 10,273 participants were analyzed and divided into two groups: COPD (n = 595) and non-COPD (n = 9678). Comparative analysis of demographic and clinical characteristics was performed between cohorts. The SIRI was calculated based on the counts of monocytes, neutrophils, and lymphocytes. Weighted logistic regression models were applied to assess the association between SIRI and COPD, while restricted cubic spline (RCS) curves were utilized to investigate potential non-linear relationships. Additionally, subgroup and interaction analyses were performed.

**Results:** Our study included 10,273 participants, of whom 595 were diagnosed with COPD, while 9678 were diagnosed with non-COPD. In the fully adjusted logistic regression model, SIRI was significantly positively correlated with COPD (OR = 1.96, 95% CI = 1.34–2.87). The analysis of the RCS curve revealed a non-linear relationship between SIRI and COPD *(P* < 0.05). Subgroup and interaction analyses further confirmed the robustness of our findings.

**Conclusion:** Serum inflammatory marker SIRI levels are positively correlated with the occurrence of COPD and exhibit a non-linear relationship.

**Keywords:** chronic obstructive pulmonary disease, SIRI, NHANES, inflammatory markers, cross-sectional study

## Background

Chronic obstructive pulmonary disease (COPD) is a multifactorial lung condition driven by various pathogenic mechanisms, characterized by persistent respiratory symptoms and airflow obstruction.[1,2] The clinical diagnostic criterion for COPD is a forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio of less than 0.7, reflecting the proportion of air forcefully exhaled in one second relative to the total volume exhaled after maximal inhalation. The key pathological features of COPD include chronic bronchitis and emphysema. Globally, COPD ranks among the top three causes of death. In 2012, it was responsible for over 3 million deaths, accounting for 6% of all global

Received: 15 April 2025
Accepted: 31 July 2025
Published: 13 August 2025

fatalities, imposing a substantial burden on clinical care and healthcare resources.[3–5] Although COPD remains a major public health challenge, it is both preventable and manageable with appropriate interventions.

The onset of COPD is often considered to be related to multiple factors. Studies have shown that abnormal inflammatory responses are strongly associated with the development of COPD, and these responses are often chronic and destructive. Over the past decade, research has increasingly highlighted the close link between COPD and inflammation.[6,7] Several factors associated with COPD, including dietary patterns, exposure to cigarette smoke, and infections, have been shown to significantly influence inflammation levels.[8,9] Chronic systemic inflammation is a nonspecific defense mechanism of the body in response to external stimuli or internal injury, involving the activation of various cellular and molecular processes. Prolonged inflammation can accelerate the progression of COPD.[10] The systemic inflammation response index (SIRI) is an emerging and promising inflammatory biomarker, calculated based on neutrophil, monocyte, and lymphocyte counts. It serves as an indicator of the body's systemic inflammatory status and offers a novel perspective for evaluating inflammatory responses. Increasing evidence has demonstrated associations between elevated SIRI levels and various inflammation-related diseases, including osteoarthritis, pancreatic cancer, esophageal cancer, and heart failure. Notably, higher SIRI levels have been linked to increased mortality in patients with heart failure and elevated all-cause mortality among individuals with diabetes. However, the relationship between SIRI and the development of COPD has not yet been fully elucidated.[11–15]

The National Health and Nutrition Examination Survey (NHANES) is a comprehensive survey conducted in the United States, utilizing complex, multi-stage, and probability sampling methods to collect nutritional and health information about the population. Through the NHANES database, an increasing number of factors related to human health and diseases have been identified. This cross-sectional study aims to investigate the potential association between COPD and the inflammatory marker SIRI in individuals aged over 40 within the US population. All participants were registered through the NHANES between 2013 and 2018.

# Materials and Methods

## Data Sources

This is a cross-sectional analysis utilizing data from the National Health and Nutrition Examination Survey (NHANES) (https://www.cdc.gov/nchs/nhanes). NHANES is a national survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). It combines interviews and physical examinations. NHANES uses a complex, multi-stage design to collect and analyze data that reflects the non-institutionalized US population. The execution of the study involves two key components: a comprehensive interview conducted at participants' homes and detailed health examinations carried out at mobile examination centers. Both components of the study are carefully conducted by skilled and certified researchers.

## Study Design and Participants

The detailed participant selection process is illustrated in Figure 1. This study analyzed publicly available NHANES data from the 2013–2018 cycles. Detailed information regarding the NHANES sampling design, study procedures, and survey protocols can be accessed on the official website of the National Center for Health Statistics (NCHS). The inclusion criteria for this study were as follows: 1) Age > 40 years; 2) Clear diagnosis of COPD; 3) Complete data on neutrophils, monocytes, and lymphocytes; 4) Exclusion of incomplete information on other essential data.

## Calculation of SIRI

Since inflammation levels have a significant impact on COPD, we used SIRI to comprehensively assess its effect on COPD. The calculation of SIRI is as follows: SIRI = N * M / L, where N, M, and L represent the counts of neutrophils, monocytes, and lymphocytes in the peripheral blood after preprocessing, respectively. Based on SIRI levels, participants were divided into three groups according to the 3rd quartiles: Quartile 1 (Q1), Quartile 2 (Q2), and Quartile 3 (Q3).

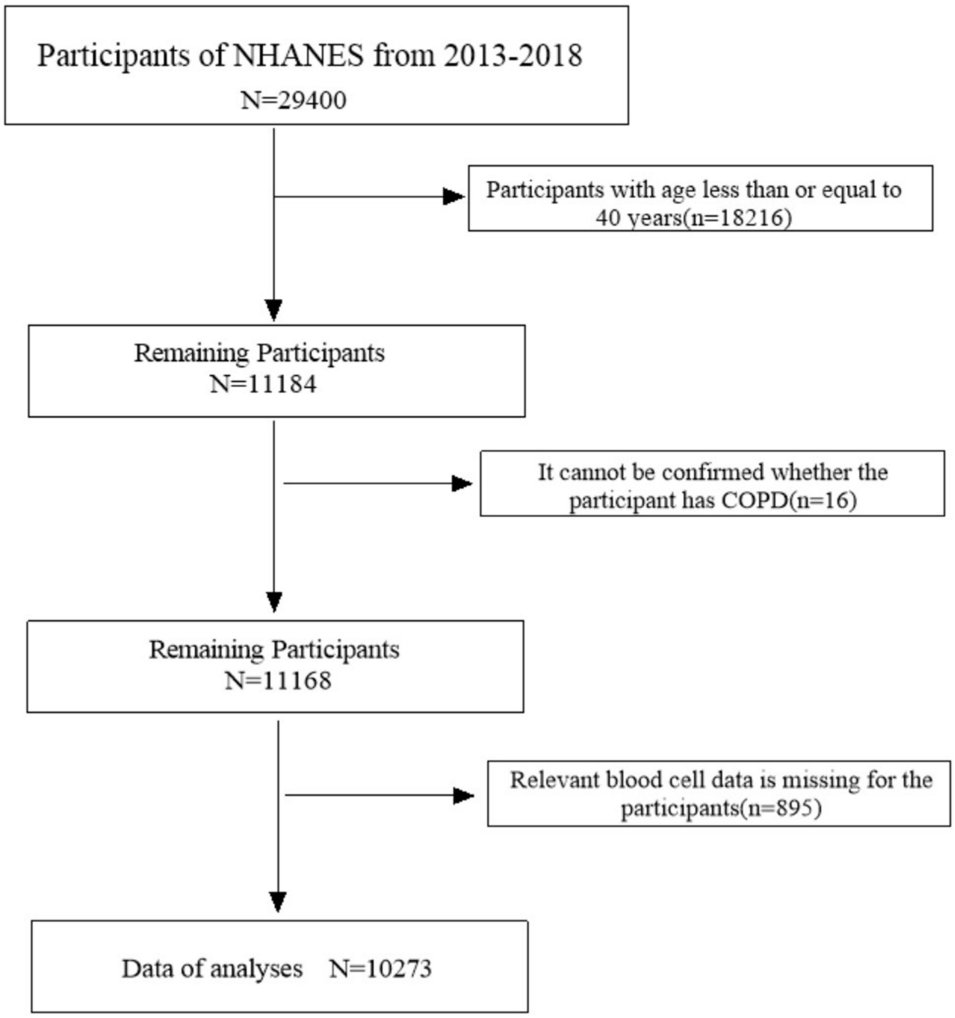


**Figure 1** Flowchart of Patient Inclusion and Exclusion in NHANES 2013–2018.

## Inclusion of Covariates

Based on standardized questionnaire surveys, we extracted participants' sociodemographic characteristics, including age, gender, race, education level, poverty-to-income ratio (PIR), smoking status, obesity, use of diabetic medications or insulin, and hypertension. Additionally, laboratory measurements such as monocyte count, neutrophil count, and lymphocyte count were collected. Missing data for these covariates were excluded from this study. Race/ethnicity was categorized as non-Hispanic White, non-Hispanic Black, Mexican American, and other races. Marital status was divided into married and unmarried. Education level was classified as less than high school and high school or higher. Household income was categorized based on the family PIR into two levels: poor and non-poor. Smoking status was classified as current smoker and non-smoker. Obesity status was categorized as obese and non-obese. Diabetes was categorized as diabetic and non-diabetic.

We obtained personal interview data on the history of COPD from participants aged over 40 in the NHANES, covering the period from 2013 to 2018. The questionnaire item used to determine the history of COPD was: "Has a doctor or other health professional ever told {you/SP} that {you/s/he} had COPD?" (MCQ160o).

## Statistical Analysis

In descriptive statistics, continuous variables are expressed as means (± SD), while categorical variables are presented as frequencies or percentages (n, %). When analyzing baseline characteristics, continuous variables with a normal

distribution were analyzed using independent sample *t*-tests, non-normally distributed continuous variables were analyzed using the Wilcoxon rank-sum test, and categorical variables were analyzed using the chi-square test. Additionally, appropriate weighted data were used in the analysis based on the specific situation.

We analyzed the association between SIRI and COPD using multivariable logistic regression. To control for confounding factors, we applied three multivariable logistic regression models: Model 1: Unadjusted; Model 2: Adjusted for age, sex, and race; Model 3: adjusted for all covariates. To investigate the potential non-linear relationship between SIRI and COPD, we performed restricted cubic spline (RCS) analysis. The reference point was set at 1.08, and adjustments were made for age, gender, race, education level, marital status, smoking status, body mass index, hypertension, diabetes, blood cell counts, and other factors. In addition, we conducted subgroup analyses by stratifying participants based on age, gender, race, marital status, smoking status, obesity, and history of hypertension. We also evaluated potential interactions across these subgroups. All analyses were conducted using the statistical software package R 4.4.2, and $p < 0.05$ was considered statistically significant.

# Results

## Baseline Analysis of Study Participants Based on COPD Status

The results show that patients with COPD have distinct clinical characteristics, including higher age, smoking rates, metabolic comorbidity burden, and systemic inflammation levels. These factors may collectively contribute to the progression and poor prognosis of COPD. A total of 10,273 participants were included in this study, 595 participants were diagnosed with COPD, and 9678 were diagnosed with non-COPD. In Table 1, there were 4940 males (47.0%) and 5333 females (53.0%). Among the participants, 6743 (70.4%) were aged 41–65 years, and 3530 (29.6%) were over 65 years old. The majority of participants were non-Hispanic White (4004 participants, 69.6%). Significant differences were observed in all baseline variables except for gender, lipids, and BMI ($p < 0.05$). Among participants diagnosed with COPD, the proportion of smokers was higher. Additionally, the prevalence of metabolic disorders such as hyperlipidemia and hypertension was also higher in this group. Furthermore, the proportion of participants with SIRI in the third quartile was significantly higher compared to those in the first quartile among those diagnosed with COPD.

## Correlation Between Serum SIRI Levels and COPD

Multivariate logistic regression analysis, adjusted for various confounding variables, showed a positive correlation between SIRI and the prevalence of COPD in all three models. Notably, participants in the highest third (Q3) of SIRI levels had a significantly higher risk of COPD compared to those in the lowest third (Q1). The trends observed in all three models were statistically significant ($p < 0.05$) (Table 2).

## RCS Analysis

We used RCS curves to investigate whether there is a linear relationship between SIRI and the prevalence of COPD. The results (Figure 2) showed a non-linear correlation between the two variables ($P < 0.05$). As SIRI levels increased, the risk of COPD gradually rose, suggesting a positive association between systemic inflammation and COPD risk. However, this risk did not continue to rise indefinitely at very high levels of SIRI.

## Subgroup Analysis

The results of the subgroup analysis (Figure 3) showed that when stratified by age, gender, race, marital status, smoking, obesity, and hypertension, SIRI remained positively correlated with COPD ($OR > 1$). The results indicated that the association between SIRI and COPD was more pronounced among individuals aged over 65 years. This association also appeared stronger in males compared to females, and was notably enhanced in individuals with elevated blood pressure. Furthermore, interaction tests revealed no significant interactions between SIRI and COPD across subgroups ($P > 0.05$), suggesting that the positive association remained consistent and did not differ significantly among the various subpopulations.

**Table 1** Baseline Characteristics of Study Population

| Character | Overall (N=10273) | With COPD (N=595) | Without COPD (N=9678) | P |
|---|---|---|---|---|
| **Age-new** | | | | <0.001 |
| 41–65 | 6743 (70.4%) | 296 (56.4%) | 6447 (71.2%) | |
| >65 | 3530 (29.6%) | 299 (43.6%) | 3231 (28.8%) | |
| **Gender** | | | | 0.769 |
| Male | 4940 (47.0%) | 322 (47.8%) | 4618 (47.0%) | |
| Female | 5333 (53.0%) | 273 (52.2%) | 5060 (53.0%) | |
| **Race** | | | | <0.001 |
| Mexican American | 1444 (6.8%) | 25 (1.8%) | 1419 (7.1%) | |
| Non-Hispanic White | 4004 (69.6%) | 393 (80.9%) | 3611 (68.9%) | |
| Non-Hispanic Black | 2180 (10.1%) | 100 (6.9%) | 2080 (10.3%) | |
| Other | 2645 (13.5%) | 77 (10.4%) | 2568 (13.7%) | |
| **Marital status** | | | | <0.001 |
| Yes | 6367 (67.5%) | 282 (56.9%) | 6085 (68.1%) | |
| No | 3906 (32.5%) | 313 (43.1%) | 3593 (31.9%) | |
| **Education_new** | | | | 0.001 |
| Below high school | 2480 (14.1%) | 171 (20.9%) | 2309 (13.7%) | |
| High School or above | 7793 (85.9%) | 424 (79.1%) | 7369 (86.3%) | |
| **Hypertension** | | | | <0.001 |
| Yes | 5992 (53.1%) | 421 (69.0%) | 5571 (52.1%) | |
| No | 4281 (46.9%) | 174 (31.0%) | 4107 (47.9%) | |
| **Lipids** | | | | 0.055 |
| No | 3320 (31.1%) | 220 (34.9%) | 3100 (30.8%) | |
| Yes | 6953 (68.9%) | 375 (65.1%) | 6578 (69.2%) | |
| **PIR_new** | | | | <0.001 |
| Poor | 1761 (10.5%) | 169 (24.4%) | 1592 (9.7%) | |
| Not poor | 8512 (89.5%) | 426 (75.6%) | 8086 (90.3%) | |
| **DM** | | | | <0.001 |
| Yes | 2804 (21.4%) | 222 (35.0%) | 2582 (20.6%) | |
| No | 7469 (78.6%) | 373 (65.0%) | 7096 (79.4%) | |
| **Obesity** | | | | 0.003 |
| Yes | 4213 (41.7%) | 255 (42.7%) | 3958 (41.7%) | |
| No | 5903 (57.1%) | 322 (54.3%) | 5581 (57.2%) | |
| Unknown | 157 (1.2%) | 18 (3.0%) | 139 (1.1%) | |
| **Smoke** | | | | <0.001 |
| Yes | 4726 (46.1%) | 512 (87.5%) | 4214 (43.6%) | |
| No | 5547 (53.9%) | 83 (12.5%) | 5464 (56.4%) | |
| **SIRI** | | | | <0.001 |
| Q1 | 3816 (32.8%) | 111 (17.4%) | 3705 (33.7%) | |
| Q2 | 3167 (33.2%) | 151 (31.2%) | 3016 (33.3%) | |
| Q3 | 3290 (34.1%) | 333 (51.5%) | 2957 (33.0%) | |
| **BMI** | 29.78 (±6.93) | 30.08 (±8.05) | 29.79 (±6.73) | 0.506 |
| **LBXWBCSI** | 7.27 (±4.67) | 8.08 (±2.25) | 7.24 (±3.30) | <0.001 |
| **Lymphocyte** | 2.20 (±3.90) | 2.13 (±0.83) | 2.12 (±2.47) | 0.793 |
| **Monocyte** | 0.59 (±0.21) | 0.68 (±0.26) | 0.59 (±0.19) | <0.001 |
| **Neutrophils** | 4.24 (±1.70) | 4.97 (±1.80) | 4.28 (±1.65) | <0.001 |

## Discussion

Until now, there has been a lack of research on the correlation between serum inflammatory marker SIRI and the incidence of COPD. In our current study, we observed a positive correlation between serum SIRI levels and the

**Table 2** Association Between the SIRI and COPD

| Character | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | β (95% CI) | p-value | β (95% CI) | p-value | β (95% CI) | p-value |
| **SIRI** | | | | | | |
| **Q1** | Ref | | Ref | | Ref | |
| **Q2** | 1.817 (1.406, 2.348) | <0.001 | 1.706 (1.315, 2.213) | <0.001 | 1.468 (1.092, 1.973) | 0.013 |
| **Q3** | 3.022 (2.138, 4.271) | <0.001 | 2.645 (1.886, 3.710) | <0.001 | 1.957 (1.337, 2.865) | 0.001 |
| P for trend | | <0.001 | | <0.001 | | 0.002 |

prevalence of COPD. Higher serum SIRI levels were associated with an increased risk of COPD, and this relationship remained consistent even after adjusting for covariates.

The pathogenesis of COPD remains unclear. Previous studies suggest that its pathogenesis primarily involves inflammation, oxidative stress, and an imbalance between proteases and antiproteases.[16] When the immune system is compromised and the body is unable to compensate, it eventually leads to small airway damage and emphysema. Inflammation is a key factor in the onset and progression of COPD. Airway inflammation in COPD is primarily characterized by the infiltration and proliferation of inflammatory cells, such as neutrophils, lymphocytes, and monocytes/macrophages, which migrate into the airways and lung tissues. These cells can be detected in sputum and bronchoalveolar lavage fluid. The increase in inflammatory cells is often triggered by the activation of cytokines and mediators released by airway epithelial cells in response to inhaled cigarette smoke and particulate matter. Numerous inflammatory mediators, including free radicals, chemokines, cytokines, and growth factors, contribute to the development and progression of COPD.[17–19] A study found[20] that the levels of the Neutrophil-to-Lymphocyte Ratio (NLR) in

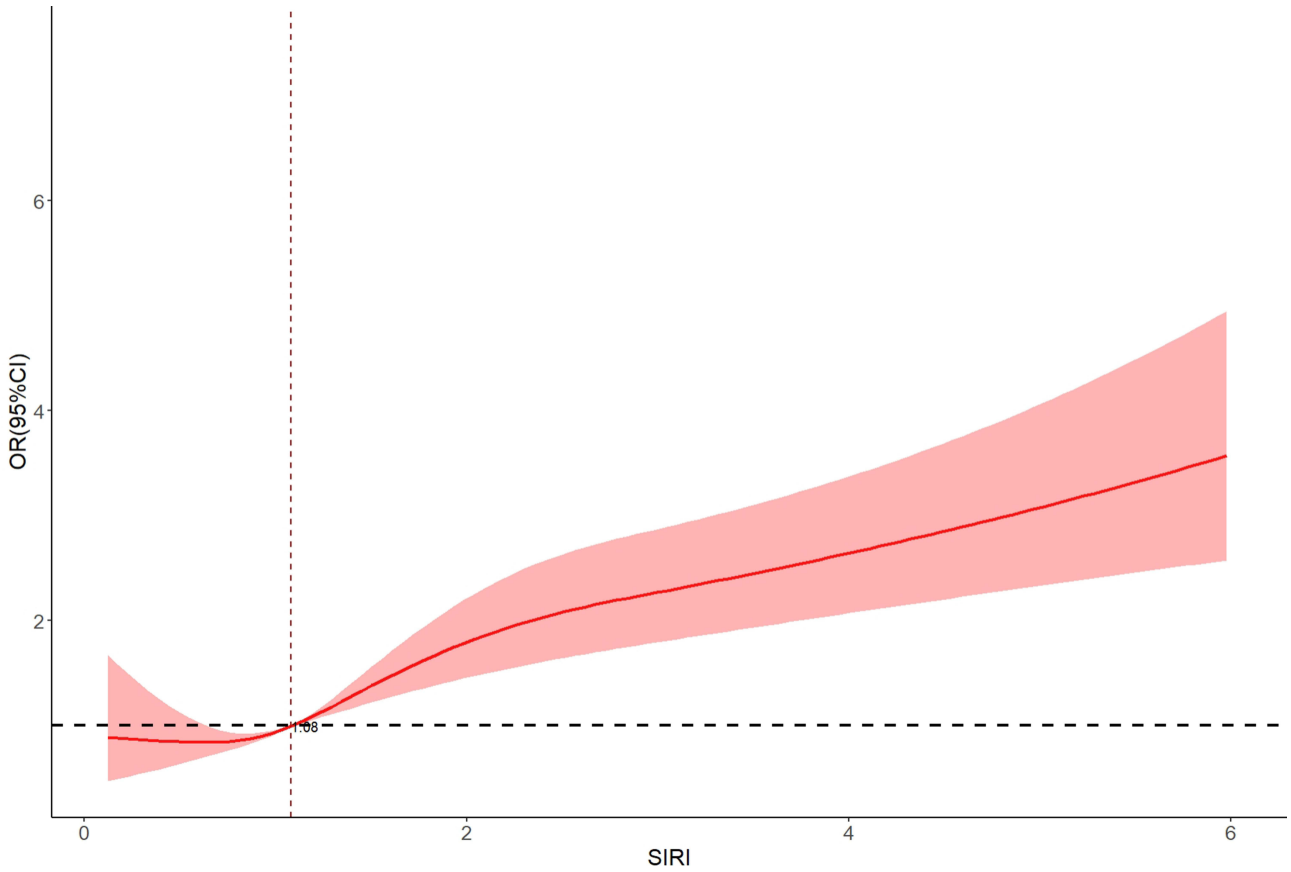


**Figure 2** The restricted cubic spline model revealed a significant dose–response relationship between SIRI and COPD ($P < 0.05$).

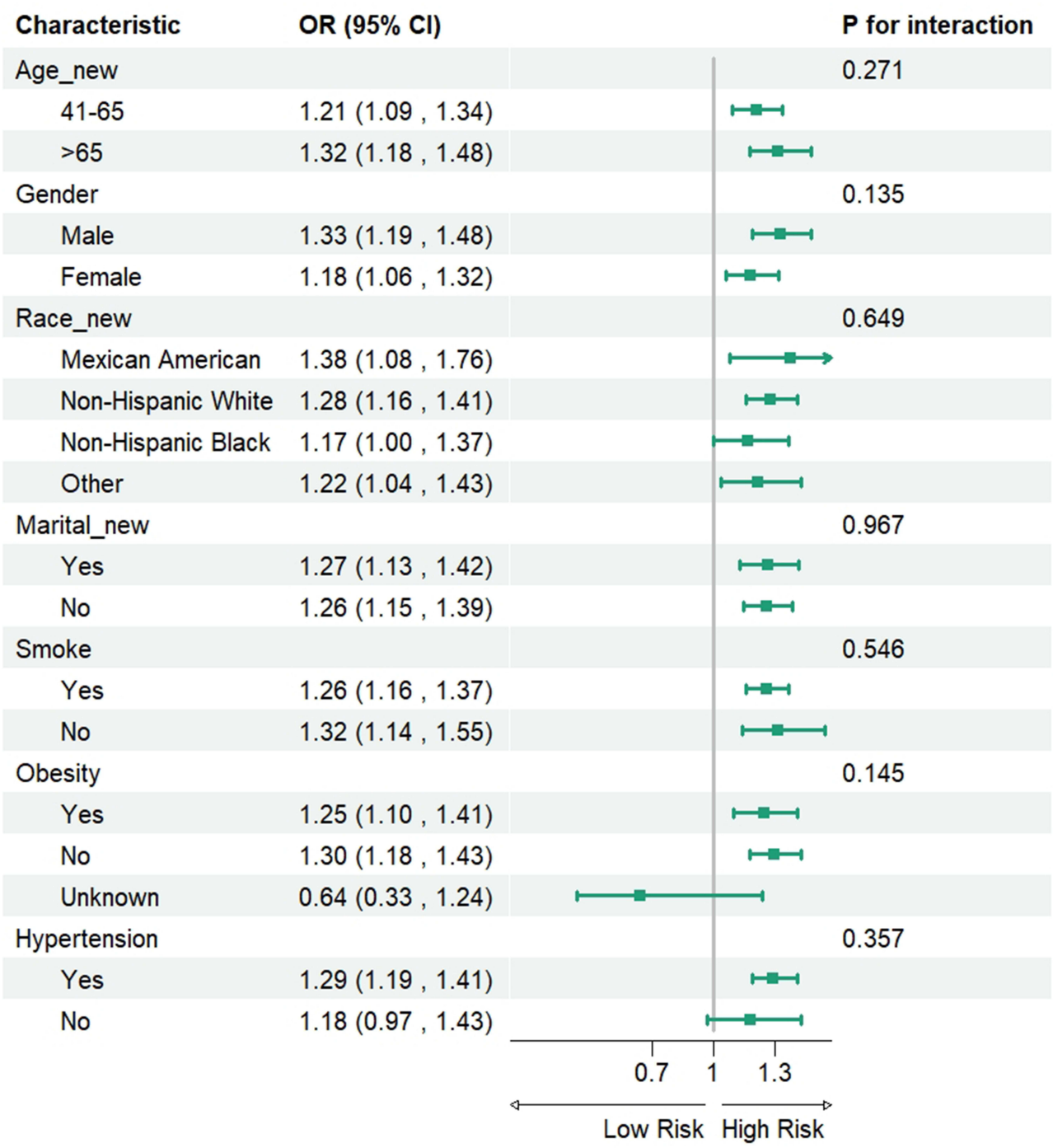


**Figure 3** Subgroup analysis for the association between SIRI and COPD.

patients with acute exacerbation of COPD were positively correlated with poor outcomes, including mortality, the need for mechanical ventilation, and transfer to the intensive care unit. Another cross-sectional study involving 10,364 participants found[21] that Systemic Immune-Inflammation Index (SII) was positively correlated with the risk of COPD and showed a non-linear relationship. Compared to composite inflammatory markers like NLR and SII, SIRI may offer distinct advantages in assessing COPD. By incorporating monocytic parameters, SIRI provides a more comprehensive reflection of the chronic inflammatory response and tissue remodeling processes characteristic of COPD. Unlike acute-phase inflammatory proteins such as C-reactive protein (CRP), SIRI, based on the ratio of neutrophils, monocytes, and


https://doi.org/10.2147/COPD.S534504

lymphocytes, is less affected by confounding factors like acute infections, offering better stability and reproducibility in the results. These features make SIRI a promising biomarker for evaluating the inflammatory status of COPD.

The SIRI is calculated based on the number of neutrophils, monocytes, and lymphocytes, reflecting the relative proportion of these three cell types. Neutrophils can be excessively activated in the airways of COPD patients, releasing inflammatory mediators such as interleukin-8, which attract more neutrophils to the affected areas and initiate oxidative stress by releasing oxygen free radicals.[22] Therefore, neutrophils are considered key cells in the pathogenesis of COPD. A reduction in lymphocytes is a marker of stress, which can lead to the destruction of alveoli in COPD patients. $CD8^+$ cells produce pro-inflammatory cytokines, including interleukin-2(IL-2), interferon-gamma, and TNF-alpha (TNF-α). These cytokines are increased in COPD patients and recruit other inflammatory cells.[23] When the counts of neutrophils and monocytes increase, or when the lymphocyte count decreases, SIRI typically rises. A 20-year comprehensive follow-up study involving 2656 rheumatoid arthritis (RA) patients found[24] that serum SIRI was non-linearly positively correlated with all-cause mortality and cardiovascular mortality in RA patients. This correlation was especially prominent in female patients and those with a high BMI. Another study on the relationship between SIRI and the risk of kidney stones found[25] a significant positive correlation between SIRI and kidney stones. As SIRI levels increased, the risk of kidney stones gradually rose. Based on the existing literature evidence, we can tentatively infer that SIRI may be an effective biomarker for predicting the development of inflammation-related diseases. It is worth noting that although SIRI has been the subject of research in many different fields, there is still limited research exploring its relationship with COPD.

This study found a significant positive correlation between serum SIRI levels and the prevalence of COPD. In this study, SIRI was divided into three groups: Q1, Q2, and Q3. In all three models adjusted for potential confounding factors, the Q3 group showed a higher prevalence compared to the Q1 group. Subgroup analysis results indicated that this association was consistent across different populations. The study also found a non-linear positive correlation between SIRI and COPD, suggesting that high SIRI levels may be an independent risk factor for COPD. This prospective cohort study involving 10,273 participants found that an increase in SIRI was significantly associated with a higher prevalence of COPD. Based on previous research, the potential mechanism behind this phenomenon may be that an increase in neutrophils in the blood triggers a higher probability of chronic inflammation in the lungs, while the decrease in lymphocytes leads to reduced lung immune function, ultimately resulting in a higher prevalence of COPD.

The findings of this study may provide some insights into the screening and management of COPD. First, SIRI can be derived from routine blood count data, eliminating the need for specialized equipment or additional costs, making it well-suited for primary healthcare settings. Second, for high-risk populations (smokers + age > 40), SIRI could be considered as part of routine screening, serving as an inflammatory monitoring tool for the comprehensive management of COPD. However, several limitations should be acknowledged. First, the NHANES population represents only the US population and may not be applicable to other populations. Second, our study focused on individuals above 40 years old, excluding children and adolescents. Third, due to the cross-sectional design of NHANES, inferring a causal relationship between SIRI and COPD is limited. Fourth, COPD diagnosis relies on self-report, and some important variables, such as lung function data (FEV1%, FVC%, FEV1/FVC), were not included in the analysis, which may introduce bias into the results. Fifth, due to the limitations of the dataset, we were unable to conduct parallel analyses involving NLR and SII. This represents an important area for future research.

## Conclusion

In this cross-sectional study based on the NHANES database, we observed that elevated serum SIRI levels were significantly associated with an increased risk of COPD, indicating that SIRI may serve as a potential novel inflammatory marker for predicting the development of COPD. However, due to the study's observational design, the causal relationship between SIRI and the onset or progression of COPD remains to be confirmed in future prospective studies.

## Abbreviations

COPD, Chronic obstructive pulmonary disease; SIRI, Systemic inflammation response index; NHANES, National Health and Nutrition Examination Survey; RCS, restricted cubic spline; FEV1, forced expiratory volume in 1 second; FVC,

forced vital capacity; PIR, poverty-to-income ratio; NCHS, National Center for Health Statistics; CDC, Centers for Disease Control and Prevention; 95% CI, 95% confidence interval; OR, Odds ratio.

## Data Sharing Statement

The data supporting the findings of this study were obtained from the National Health and Nutrition Examination Survey (NHANES), which is publicly available at https://www.cdc.gov/nchs/nhanes. In accordance with transparency standards, the corresponding author affirms their commitment to making all data supporting this study's conclusions available upon reasonable request.

## Ethics Approval and Consent to Participate

This study was based on publicly available data from the National Health and Nutrition Examination Survey (NHANES), which is conducted by the National Center for Health Statistics (NCHS). All NHANES participants provided written informed consent, and the survey protocol was approved by the NCHS Research Ethics Review Board. As this study involved only secondary analysis of de-identified data, it was exempt from further review by the Institutional Review Board of The Second Affiliated Hospital of Jiaxing University.

## Acknowledgments

The authors would like to express their sincere gratitude to all the participants and staff involved in the NHANES for their invaluable contributions and dedication.

## Author Contributions

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

## Funding

The study was supported by Zhejiang Provincial Medical and Health Technology Plan (Grant No. 2021PY029).

## Disclosure

The authors declare no competing interests.

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