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Relationship between systemic immune response index (SIRI) and COPD: a cross-sectional study based on NHANES 2007–2012

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Although the link between inflammation and chronic obstructive pulmonary disease (COPD) is increasingly recognized, the correlation between systemic immune response index (SIRI), a novel marker of inflammation, and COPD is unknown. This cross-sectional study used data from patients with complete lung function in NHANES 2007–2012 to explore the relationship between SIRI and COPD. We performed a series of statistical analyses on a total of 5056 participants, including multiple linear regression, smoothed curve fitting, ROC curve analysis, and subgroup analysis. In the fully corrected model, the logistic multiple regression showed that SIRI was associated with a high risk of COPD (OR1.350, 95% CI:1.220,1.493). The ROC curve showed that SIRI (AUC = 0.596) was significantly more efficient than other inflammatory factors in predicting COPD. Smoothed curve fit effect and threshold effect analyses showed a linear correlation between SIRI COPD prevalence, and subgroup analyses showed that the effect of SIRI on COPD was more pronounced in still smokers (OR 1.58, 95% CI: 1.34, 1.86) versus men (OR 1.62, 95% CI: 1.44, 1.83). The results of the interaction test provide evidence supporting SIRI as an independent risk factor for COPD.

Keywords System inflammation response index, Inflammation, COPD, NHANES, Cross-sectional study

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease characterized by progressive and irreversible airflow limitation[1]. Currently, COPD remains one of the major contributors to morbidity and mortality in the world's population, substantially impacting patients' well-being and increasing their medical expenses[2]. According to projections, COPD will rank as the third most common cause of mortality globally by 2030. The disorder is more common among men, yet the occurrence in women is rising, leading to a diminishing gender disparity. Additionally, COPD is more common in low-income countries, possibly because these areas are more exposed to more severe air pollutants[3]. The pathogenesis of COPD consists of many factors and the process is complex and varied[4], and although important advances have been made in the understanding of COPD, there is still a need for further research into the underlying mechanisms of COPD and the implementation of effective interventions to improve patient prognosis.

SIRI includes absolute numbers of neutrophils, monocytes, and lymphocytes[5]. According to recent research, SIRI is linked to the onset of CVD[6]; there is a positive correlation with psoriasis[7], high levels of SIRI are associated with a high mortality rate in sepsis[8], and SIRI can be used to predict the survival of patients with pancreatic cancer who are receiving chemotherapy[9], however, there are few data on the connection between SIRI and the prevalence of COPD.

COPD is characterized by persistent airway inflammation and immune dysfunction[10]. Research has demonstrated a correlation between inflammation and immunology in the onset and progression of COPD. Higher levels of oxidative stress and pro-inflammatory cytokines in the airways of patients with COPD suggest that inflammation persists[11,12]. Given how simple it is to get clinical data straight from SIRI, investigating its relationship to COPD is crucial for both diagnosing and treating the disease.

Therefore, the purpose of the research was to investigate the connection between SIRI and COPD, utilizing cross-sectional information obtained from the NHANES.

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Method

Study data and population

We analyzed data from the 2007–2012 NHANES in this cross-sectional investigation. For a thorough explanation of the NHANES and information on how data are collected, observe the National Center for Health Statistics. In summary, NHANES is a series of cross-sectional, complex, multistage surveys conducted by the Centers for Disease Control and Prevention (CDC) of a nationally representative U.S. noninstitutionalized population that provides data on the health and nutritional status of the populations surveyed.

We analyzed NHANES data collected during the period 2007–2012, totaling $N = 30,442$ subjects, and included a total of 5,056 (2,517 males and 2,539 females) subjects after excluding data on lack of demographics, smoking, alcohol consumption, whole blood counts, lipids, lung function, and comorbidities. Inclusion exclusion criteria are shown in Fig. 1.

NHANES has received ethical approval from the National Center for Health Statistics Research Ethics Review Board (National Center for Health Statistics Research Ethics Review). National Center for Health Statistics Research Ethics Review Board approval (National Center for Health Statistics, 2012).

Criteria for COPD

In this study, the COPD diagnostic standards were (1) FEV 1/FVC < 70% after inhalation of bronchodilators, (2) a history of chronic bronchitis or smoking and current need for COPD treatment, and (3) self-reported presence of emphysema[13].

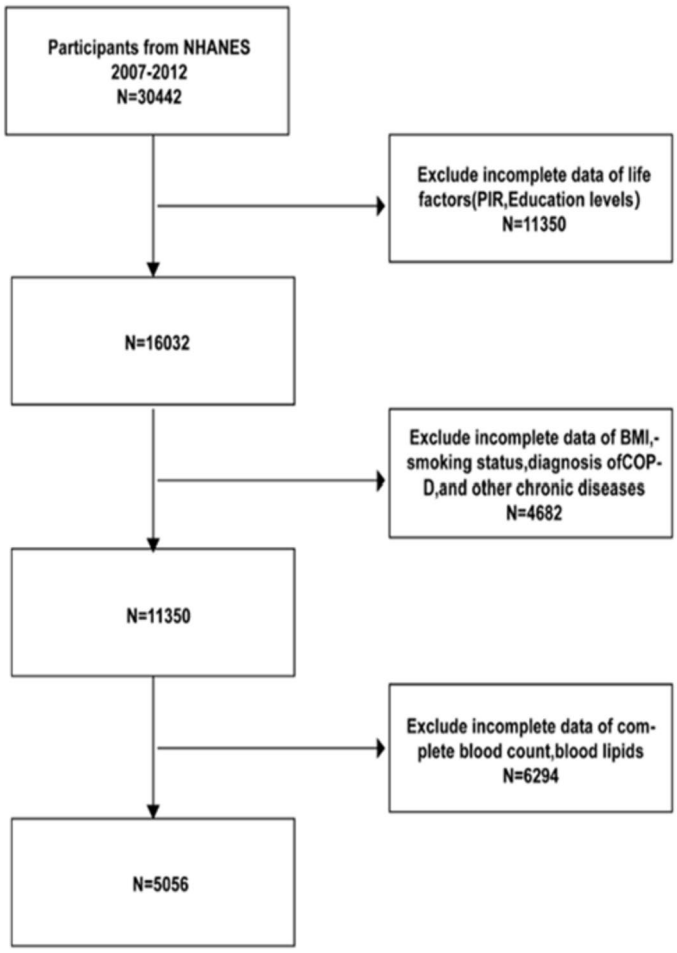

Fig. 1. Study flowchart illustrating the inclusion and exclusion of participants.

Calculation of different systemic inflammation indices

Patients were collected from eligible subjects at the NHANES mobile screening center. SIRI was defined as (N × M)/L, where N, M, and L represent peripheral neutrophil, monocyte, and lymphocyte counts, respectively. The calculation of other inflammatory factors is detailed in the accompanying table.

Covariates

Relevant or potential confounders were determined based on existing research literature and clinical knowledge. For this article, the following covariate information was collected. Participant demographic data and sociodemographic data: including age (continuous), sex (male/female), race (non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic, and other races), education level (< high school, high school, and > high school), and poverty-to-income ratio. Lifestyle and body measurements such as smoking situation (never, former, current), alcohol consumption, and body mass index (BMI) were also included. Criteria for categorizing smoking and alcohol use were consistent with previous reports. Information on concurrent cardiovascular diseases, including hypertension, diabetes, coronary heart disease, angina, stroke, and heart attack was also added as covariates through the questionnaire.

Statistical analysis

Since the NHANES survey employs a sophisticated, multi-phase, stratified probability sampling method, suitable weights, sampling units, and strata were utilized for the statistical analysis. Comparisons were done based on the normality and distribution of the data for continuous variables, which were displayed as the median with the first and third quartiles or the mean with its standard deviation (SD), utilizing either the Student's t-test or the Mann-Whitney U test. Meanwhile, categorical variables were reported as counts and percentages, and they were analyzed using either the chi-squared test or the Fisher's exact test. Multifactorial logistic regression analysis was used to analyze the relationship between different inflammatory indicators and COPD. Covariates were not taken into account in Model 1. Age, gender, race, and education were taken into account in model 2, and all of the aforementioned covariates were taken into account in model 3. 95% CI (confidence intervals) and odds ratios (OR) were used to express the results. The diagnostic value of novel inflammatory biomarkers screened by multivariate regression analysis was evaluated using subject work characteristics (ROC) curves. To determine whether there was a nonlinear association between COPD and SIRIs, smoothed curve fitting, threshold effect, and saturation effect studies were employed. Heterogeneity between subgroups is assessed by interactions. R (version 4.2.2) and EmpowerStats software were used for all analyses, and a p-value of less than 0.05 was deemed statistically significant.

Result

Baseline characteristics of the participant population

A total of 5056 participants were recruited for the study, and the sample included 4350 non-COPD participants as well as 706 COPD patients. The baseline characteristics of the participants are shown in Table 1. Patients with COPD were older than normal, and the difference was statistically significant ($P < 0.001$). The COPD group had higher age, gender, race, education, BMI, history of hypertension, diabetes, coronary heart disease, heart attack, history of stroke, smoking status, drinking status, FEV1 values, leukocyte count, lymphocyte count, neutrophil count, and indices such as SIRI, SII, NLR, and LMR, and the differences were statistically significant ($P < 0.001$).

Relationship between inflammatory markers and CODP

Table 2 displays the results of the multivariable logistic regression study investigating the connection between inflammatory indicators and COPD. An increase in SIRI, SII, NLR, and LLR was positively correlated with the overall occurrence of COPD, whereas a decrease in LMR was negatively related to COPD. When these inflammatory markers were analyzed as categorical variables in quartiles, in the fully adjusted model, SIRI was in quartile 3 (OR 1.344 95%CI 1.042,1.732) and quartile 4 (OR 1.836 95%CI 1.438,2.343), SII was in quartile 3 (OR 1.288 95%CI 1.010, 1.642) and quartile 4 (OR1.486 95%CI 1.173, 1.883), NLR in quartile 2 (OR1.313 95%1.016, 1.698), quartile 3 (OR1.611 95%CI 1.256, 2.067) and quartile 4 (OR1.745 95%CI 1.370, 2.222), and LLR in quartile 4 (OR1.342 95%CI1.060, 1.699) both showed significant.

Smooth curve fitting

Smoothed curve fitting showed in Fig. 2 that there was a linear relationship between the SIRI index and the incidence of COPD after adjusting for all covariate models. the risk of COPD incidence for each unit increase in the SIRI was a 16% increase from the previous level (OR = 1.166 95% CI (1.040,1.307)).

ROC curve analysis

ROC curve analysis was shown in Fig. 3 which used to evaluate the validity of inflammatory indicators. The results were shown in Fig. 3, and the AUCs of SIRI, LMR, NLR, SII, and LLR were 0.596, 0.583, 0.574, 0.555, and 0.521 indicating that SIRI was better than the other inflammatory indicators in predicting COPD.

Subgroup analysis and interactions

The results of subgroup analyses and interactions are shown in Fig. 4 which illustrates that there was no significant moderating effect of SIRI on the COPD association across age, race, and the presence or absence of diabetes, hypertension, coronary heart disease, heart attack, angina pectoris, stroke, and whether or not alcohol was consumed. In contrast, significant moderating effects were demonstrated in gender and whether or not they smoked, with the association of SIRI with COPD being stronger in men than in women, and the effect of SIRI on COPD being stronger in smokers, especially those who still smoked, whereas the association was not significant

Variables	Non-COPD *N* = 4350	COPD *N* = 706	*P*-value
Age (years)	45.07 ± 16.02	58.20 ± 13.98	< 0.001
Sex (n, %)			< 0.001
Male	2078 (47.77%)	439 (62.18%)	
Female	2272 (52.23%)	267 (37.82%)	
Race (n, %)			< 0.001
Non-Hispanic white	758 (17.43%)	41 (5.81%)	
Non-Hispanic Black	469 (10.78%)	52 (7.37%)	
Mexican American	1881 (43.24%)	460 (65.16%)	
Other Hispanic	878 (20.18%)	123 (17.42%)	
Other	364 (8.37%)	30 (4.24%)	
Education level (n, %)			< 0.001
Less than 9th	381 (8.76%)	66 (9.35%)	
9–11th	618 (14.21%)	136 (19.26%)	
High school	953 (21.91%)	186 (26.35%)	
Some college	1289 (29.63%)	167 (23.65%)	
College Graduate	1107 (25.45%)	151 (21.39%)	
PIR	2.57 ± 1.64	2.62 ± 1.66	0.387
BMI (kg/m^2)	29.07 ± 6.72	27.89 ± 6.09	< 0.001
Hypertension (n, %)			< 0.001
No	3035 (69.77%)	368 (52.12%)	
Yes	1315 (30.23%)	338 (47.88%)	
Diabetes (n, %)			0.002
No	3917 (90.05%)	608 (86.12%)	
Yes	433 (9.95%)	98 (13.88%)	
Coronary heart disease (n, %)			< 0.001
No	4260 (97.93%)	662 (93.77%)	
Yes	90 (2.07%)	44 (6.23%)	
Heart attack (n, %)			< 0.001
No	4276 (98.30%)	652 (92.35%)	
Yes	74 (1.70%)	54 (7.65%)	
Angina (n, %)			< 0.001
No	4290 (98.62%)	683 (96.74%)	
Yes	60 (1.38%)	23 (3.26%)	
Stroke (n, %)			< 0.001
No	4262 (97.98%)	677 (95.89%)	
Yes	88 (2.02%)	29 (4.11%)	
Smoke (n, %)			< 0.001
Never smoke	2573 (59.15%)	206 (29.18%)	
Ever smoke	933 (21.45%)	255 (36.12%)	
Still, smoke	844 (19.40%)	245 (34.70%)	
Drink (n, %)			< 0.001
No	3246 (74.62%)	573 (81.16%)	
Yes	1104 (25.38%)	133 (18.84%)	
FEV1 (ml)	3156.26 ± 875.45	2489.22 ± 826.73	< 0.001
FVC (ml)	3922.32 ± 1075.15	3901.26 ± 1185.98	0.576
Total cholesterol (mg/dL)	194.32 ± 39.49	195.07 ± 41.69	0.914
Triglycerides (mg/dL)	122.41 ± 66.64	124.72 ± 61.69	0.047
HDL cholesterol (mg/dL)	1.39 ± 0.40	1.40 ± 0.42	0.838
LDL cholesterol (mg/dL)	116.15 ± 34.71	116.12 ± 35.77	0.777
Red blood cell count (1000 cells/uL)	4.67 ± 0.48	4.69 ± 0.49	0.173
White blood cell count (1000 cells/uL)	6.62 ± 2.08	6.95 ± 2.08	< 0.001
Platelet (1000 cells/uL)	247.56 ± 65.81	245.80 ± 68.29	0.426
Lymphocyte number (1000 cells/uL)	2.03 ± 0.95	1.96 ± 0.63	0.028
Segmented neutrophils. Number (1000 cells/uL)	3.84 ± 1.56	4.18 ± 1.70	< 0.001
SIRI	1.03 ± 0.66	1.30 ± 0.93	< 0.001
Continued			

Variables	Non-COPD *N* = 4350	COPD *N* = 706	*P*-value
SII	504.89 ± 285.36	568.48 ± 332.66	< 0.001
NLR	2.03 ± 0.96	2.31 ± 1.15	< 0.001
LLR	62.75 ± 27.21	65.41 ± 29.48	0.078
LMR	4.38 ± 1.87	3.92 ± 1.61	< 0.001

Table 1. The means of continuous variables are displayed along with standard deviations. Proportions are used to summarize categorical variables. *SIRI* Systemic inflammatory response index, *SII* systemic immune-inflammation index, *NLR* neutrophil-to-lymphocyte ratio, *LLR* low-density-lipoprotein to lymphocyte ratio, *LMR* lymphocyte-to-monocyte ratio.

Inflammation index	Crude model	Minimally adjusted	Fully adjusted
SIRI			
Continuous	**1.516 (1.380, 1.665) < 0.001**	**1.259 (1.131, 1.401) < 0.001**	**1.350 (1.220, 1.493) < 0.001**
Q1	Ref	Ref	Ref
Q2	1.279 (0.994, 1.647) 0.062	1.143 (0.873, 1.497) 0.329	1.180 (0.908, 1.532) 0.216
Q3	**1.534 (1.201, 1.960) < 0.001**	1.209 (0.926, 1.579) 0.162	**1.344 (1.042, 1.732) 0.023**
Q4	**2.352 (1.865, 2.965) < 0.001**	**1.494 (1.154, 1.935) 0.002**	**1.836 (1.438, 2.343) < 0.001**
SII			
Continuous	**1.001 (1.000, 1.001) < 0.001**	**1.000 (1.000, 1.001) 0.008**	**1.000 (1.000, 1.001) 0.003**
Q1	Ref	Ref	Ref
Q2	1.094 (0.862, 1.388) 0.461	1.118 (0.865, 1.444) 0.394	1.169 (0.912, 1.499) 0.216
Q3	1.261 (0.999, 1.592) 0.051	1.254 (0.976, 1.611) 0.077	**1.288 (1.010, 1.642) 0.042**
Q4	**1.571 (1.255, 1.968) < 0.001**	**1.436 (1.123, 1.835) 0.004**	**1.486 (1.173, 1.883) 0.001**
NLR			
Continuous	**1.212 (1.132, 1.296) < 0.001**	1.057 (0.985, 1.134) 0.121	**1.130 (1.052, 1.213) < 0.001**
Q1	Ref	Ref	Ref
Q2	1.253 (0.978, 1.605) 0.075	1.134 (0.870, 1.477) 0.353	**1.313 (1.016, 1.698) 0.038**
Q3	**1.576 (1.241, 2.001) < 0.001**	**1.368 (1.057, 1.771) 0.017**	**1.611 (1.256, 2.067) < 0.001**
Q4	**1.988 (1.577, 2.506) < 0.001**	**1.350 (1.047, 1.741) 0.021**	**1.745 (1.370, 2.222) < 0.001**
LLR			
Continuous	**1.003 (1.006, 1.007) 0.017**	0.997 (0.994,1.000) 0.071	**1.005 (1.003, 1.008) < 0.001**
Q1	Ref	Ref	Ref
Q2	0.845 (0.670, 1.065) 0.153	0.862 (0.642, 1.061) 0.135	0.915 (0.717, 1.167) 0.473
Q3	1.008 (0.805, 1.261) 0.948	0.849 (0.665, 1.082) 0.186	1.202 (0.948, 1.524) 0.129
Q4	1.110 (0.891, 1.383) 0.353	**0.735 (0.577, 0.935) 0.012**	**1.342 (1.060, 1.699) 0.014**
LMR			
Continuous	**1.098 (1.051, 1.147) < 0.001**	**1.082 (1.030, 1.138) 0.002**	**1.047 (0.996, 1.100) 0.071**
Q1	Ref	Ref	Ref
Q2	**0.649 (0.522, 0.806) < 0.001**	0.897 (0.709, 1.134) 0.363	**0.714 (0.568, 0.896) 0.004**
Q3	**0.531 (0.426, 0.661) < 0.001**	0.908 (0.713, 1.156) 0.433	**0.6377 (0.506, 0.802) < 0.001**
Q4	**0.451 (0.361, 0.561) < 0.001**	0.904 (0.705, 1.160) 0.428	**0.525 (0.417, 0.663) < 0.001**

Table 2. Univariate and multivariate regression analysis of various inflammatory indicators and COPD. Significant values are in bold. Crude model: No covariates were adjusted. Minimally adjusted: Adjusted for age, sex, race, and education level. Fully adjusted: Adjusted for age, sex, race, education level, PIR, BMI, hypertension, diabetes, coronary heart disease, heart attack, angina, stroke, smoke status, and drinking status.

in never-smokers. Interestingly, although racial differences were not significant in the effect of SIRI on COPD, the effect of SIRI on COPD was strongest among Mexican Americans.

Discussion

This is the first article to examine the relationship between SIRI and COPD. We discovered that elevated levels of SIRI exhibited a linear correlation with a higher incidence of COPD. Meanwhile, the ROC curve showed that SIRI was superior to SII and other inflammatory indicators in distinguishing COPD from non-COPD. Subgroup analyses showed that the effect of SIRI on COPD was more pronounced in men as well as in those who still

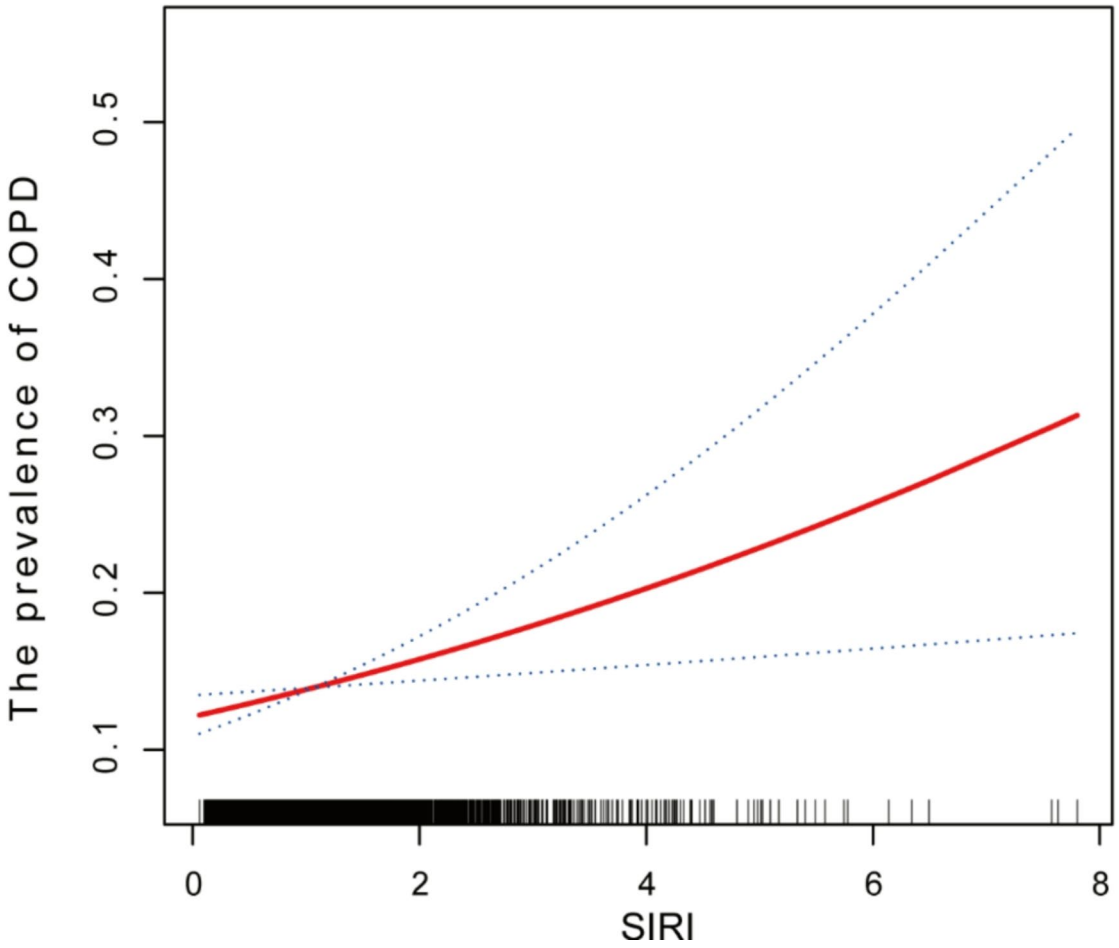

Fig. 2. X is the SIRI index, Y is the prevalence of COPD.

smoked. The present study suggests that the SIRI index can be used as a potential COPD biomarker for further studies.

The underlying mechanisms of COPD have not yet been fully characterized. Studies have shown that activated neutrophils in COPD patients can secrete serine proteases, which generate oxidative stress and increase alveolar destruction, thereby exacerbating hypoxia in COPD patients[11,12,14]. A variety of cytokines and proteases secreted by neutrophils have been associated with lung injury and lung remodeling in COPD.IL-1 and CXCL 8, neutrophil elastase (NE), matrix metalloproteinase (MMP), and high-mobility-group protein 1 (HMGB 1) were shown to be associated with COPD severity and frequency[15–17]. T cells activated by chemokines are also able to promote the process of alveolar cell apoptosis[11]. Lymphocytes play an important role in COPD airway remodeling by mediating acquired immunity as inflammatory mediators regulatory or protective functions. Current research focuses on the infiltration of T and B lymphocytes and the reduction of regulatory T cells in the airway[18–21]. It has also been shown that platelets can be involved in the development and progression of COPD through a variety of mechanisms, including the secretion of platelet factor 4 that disrupts pulmonary elasticity and induces a prethrombotic state and pulmonary vascular remodeling[22,23]. These cells and their derived ratios have been further investigated as potential inflammatory markers capable of guiding COPD prediction and prevention.

In previous literature, it has been shown that SII, NLR, LLR, PLR, etc. can be used as new inflammatory markers in COPD.NLR may be associated with COPD combined with pulmonary hypertension and mortality in COPD[24,25]. It may serve as an indicator of unfavorable outcomes and fatality during acute flare-ups of COPD[17,26,27]. According to one study, people with COPD who do not have sarcopenia have a greater chance of dying if their SII levels are raised[28]. It has also been shown that COPD patients at higher risk of malnutrition have elevated NLR and PLR and reduced LMR compared to COPD patients whose risk of malnutrition is accordingly lower[29]. LLR is an independent factor influencing severity in COPD patients[30]。 This is further confirmed by our experiments.

The strengths of this study are the design based on a large prospective population, which fills a gap in the relationship between SIRI and COPD prevalence, as well as revealing the quantitative and qualitative relationship between the SIRI index and COPD. Second, NHANES used a stratified multistage sampling design to obtain a sample representative of the institutionalized civilian population in the United States, which allows for broad applicability and generalizability of the study. Third, it controlled for many potential factors and used ROC curves to compare the efficiency of the effects of each indicator on COPD. In addition, the study had the following

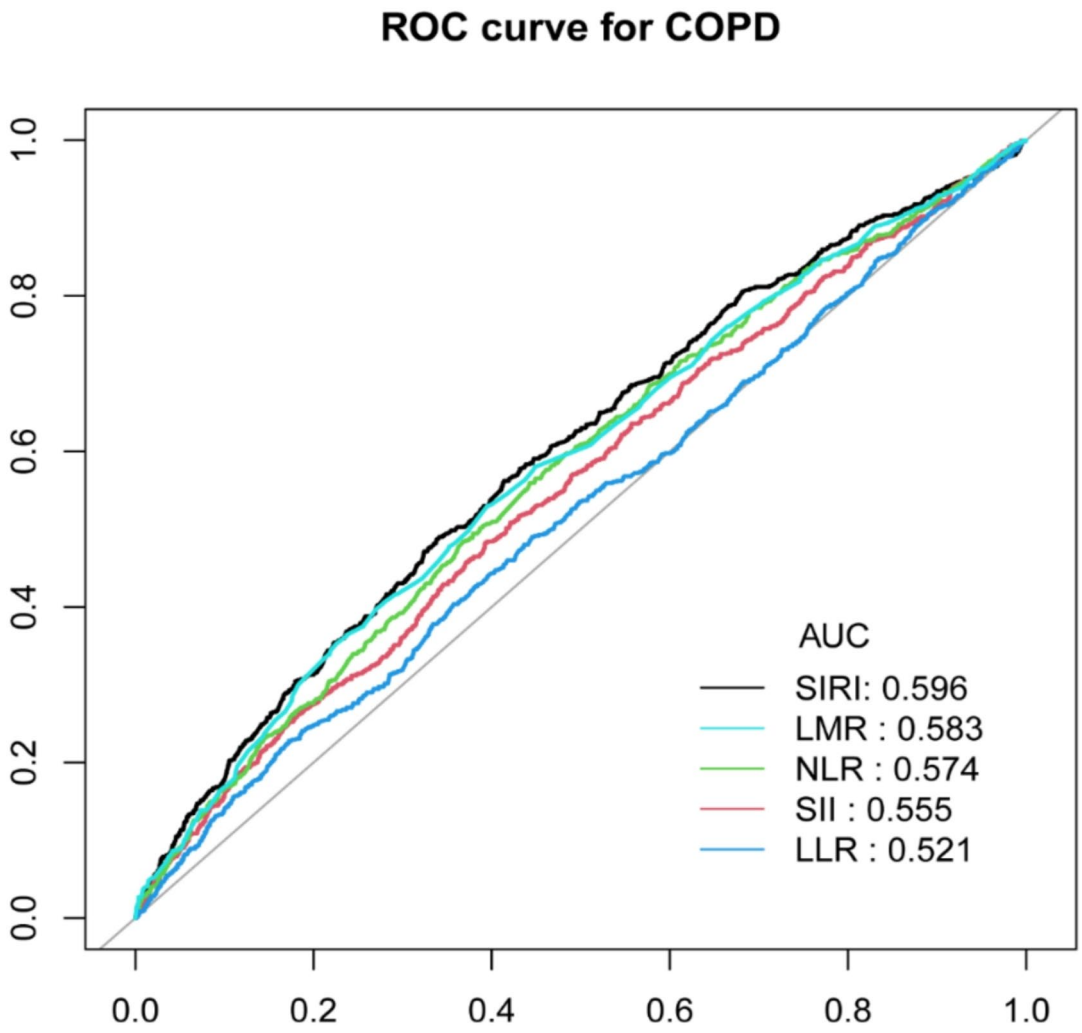

Fig. 3. ROC curve of inflammatory markers and COPD.

limitations; first, although we controlled for potential confounding factors, we were unable to eliminate some unknown other uncontrollable factors. Second, due to the nature of cross-sectional studies, it is difficult to infer causal relationships. Third, some of the survey data from the questionnaire may have been biased due to the effects of recall. Fourth, the study only looked at people in the United States; it needs to be verified in other countries. To further improve the utility of this marker, it is necessary to confirm the predictive value of SIRI for COPD in future studies with some longitudinal studies and RCTs.

Conclusion

Overall, this study showed that SIRI was positively associated with the prevalence of COPD, and for every 1-unit increase in SIRI, the prevalence of COPD increased by 16.6% compared with the previous one, meanwhile, the ROC curve showed that the SIRI index predicted COPD significantly better than the other indexes, which may play an important role for us in the routine clinical practice of diagnosing COPD.

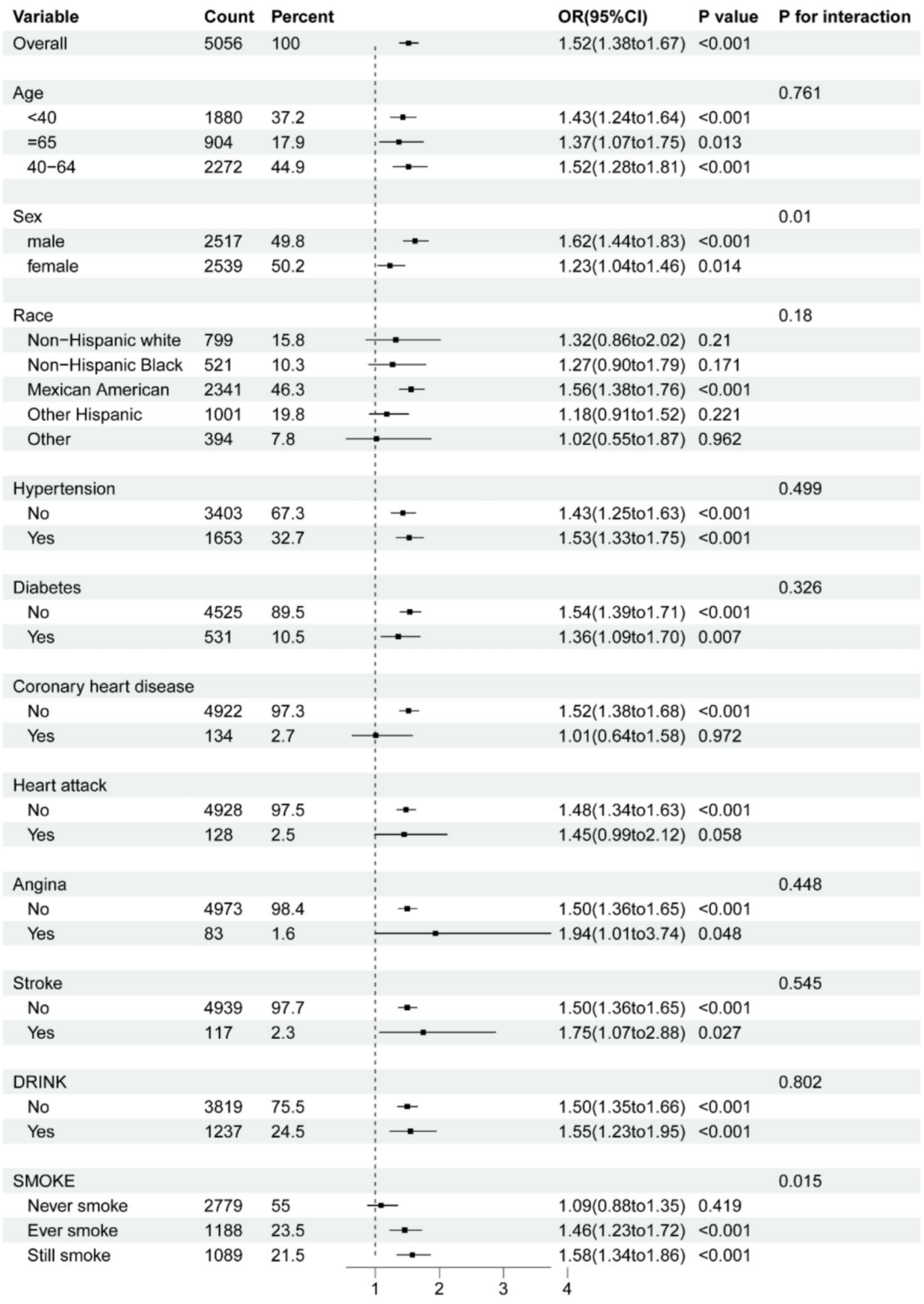

Fig. 4. The association between SIRI and COPD by different subgroups.

Data availability

The data used in this study were derived from the National Health and Nutrition Examination Survey (NHANES) 2007-2012 datasets, which are publicly available and can be accessed through the NHANES website at https://www.cdc.gov/nchs/nhanes/index.htm.

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Author contributions

Conceptualization: S.J.; Methodology: S.J.; Writing—original draft preparation: S.J. and W.H.; Writing—review and editing: S.J. and Q.C. All authors read and approved the final manuscript.

Declarations

Ethics approval and consent to participate

The protocols of NHANES were approved by the institutional review board of the National Center for Health Statistics, CDC. NHANES has obtained written informed consent from all participants.

Competing interests

The authors declare no competing interests.

Additional information

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