Research article

Association between systemic inflammatory markers and chronic obstructive pulmonary disease: A population-based study

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ABSTRACT

Objective: To investigate whether inflammatory indices, including the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), product of platelet and neutrophil count (PPN), and lymphocyte-to-monocyte ratio (LMR), correlate with chronic obstructive pulmonary disease (COPD).
Methods: This was a cross-sectional study from the National Health and Nutrition Examination Survey (NHANES) database 2007–2018. The SII, NLR, PLR, PPN and LMR were calculated based on blood cell counts and were log2-transformed. COPD was diagnosed via a questionnaire or spirometry examination. Multivariate logistic regression, sensitivity analysis, subgroup analyses, and interaction tests were performed to evaluate the relationships.
Results: 23,875 participants, including 1000 COPD patients (453 diagnosed via spirometry examination, 547 diagnosed via a questionnaire), were enrolled in this study. Positive associations were observed between SII (OR 1.231, 95 % CI 1.081,1.401), NLR (OR 1.223, 95 % CI 1.064,1.405), PLR (OR 1.325, 95 % CI 1.086,1.617), PPN (OR 1.157, 95 % CI 1.031,1.298) and COPD, while a negative association was obtained between LMR and COPD (OR 0.794, 95 % CI 0.666,0.948) after covariate adjustments. When divided COPD patients into spirometry-based and questionnaire-based, only SII (OR 1.310, 95%CI 1.122,1.529), PLR (OR 1.669, 95%CI 1.272,2.191) and PPN (OR 1.218, 95%CI 1.050,1.412) significantly correlated with spirometry-based COPD, while only NLR (OR 1.303, 95%CI 1.055,1.609) and LMR (OR 0.524, 95%CI 0.406,0.677) significantly correlated with questionnaire-based COPD after covariate adjustments.
Conclusion: Significant associations are observed between different inflammation indices and COPD. Heterogeneity exists between spirometry-based and questionnaire-based COPD patients. Future studies are needed to verify the results.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition characterized by airway and alveolar abnormalities

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leading to respiratory symptoms and decreased lung function, with a prevalence of 10.3 % (95 % CI 8.2,12.8) globally and 8.6 % (95 % CI 7.5,9.9) in China [1–3]. Inflammatory responses play an essential role in the pathogenesis of COPD, which may be attributed to cigarette smoking, air pollutants, and other reasons [4]. Inflammation in patients with COPD mainly localizes in peripheral airways, causing metaplasia of epithelial cells, mucus hyperplasia and small airway loss [5]. The inflammatory response is also associated with disease progression and mortality in COPD patients [6]. Therefore, exploring appropriate inflammatory indicators may promote COPD evaluation and management.

Derived from routine blood examination, several inflammatory indices, including the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), product of platelet and neutrophil count (PPN) and lymphocyte-to-monocyte ratio (LMR), are proposed to evaluate systemic inflammatory status, therefore reflecting disease status and progression. Systemic inflammation is reported to be associated with several diseases, including hypertension [7], acute ischemic stroke [8], rheumatoid arthritis [9] and depression [10]. Moreover, systemic inflammatory markers may also be closely related to COPD pathogenesis. Increases in the NLR and PLR were observed in patients with COPD, especially during exacerbation [11], which are also related to adverse clinical outcomes [12]. However, studies focusing on the association between different inflammatory indices and COPD are still limited with small sample sizes.

Therefore, based on the National Health and Nutrition Examination Survey (NHANES) database 2007–2018 [9,13], this study aimed to evaluate the potential association between multiple inflammatory indices (SII, NLR, PLR, PPI and LMR) and COPD.

2. Methods

2.1. Study design

The design of this study follows The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [14].

2.2. Data and sample source

Conducted by the National Center for Health Statistics (NCHS), the NHANES program is designed to assess the health status of the American population via a nationally representative sample of 5000 persons annually, which was approved by NCHS Ethics Review Board (ERB)(Protocol number: Protocol #2005-06 and Protocol #2011-17) [9,13]. Both health interviews at home and health measurements in mobile centers are conducted to collect their health status and laboratory data. Six NHANES cycles from 2007 to 2018 were enrolled to evaluate the relationship between different systemic inflammation indices and COPD. The exclusion criteria of this research were (1) incomplete data of COPD diagnosis and complete blood counts, (2) pregnant participants and (3) age less than 20 or other incomplete data.

2.3. Assessment of different systemic inflammatory indices

Whole blood specimens from eligible participants were collected in the NHANES Mobile Examination Center. Inflammatory index calculations were based on the number of different types of white blood cells. The calculation was as follows: (1) SII = (neutrophils*platelets)/lymphocytes. (2) NLR = neutrophils/lymphocytes. (3) PLR = platelets/lymphocytes. (4) PPN = platelets*neutrophils. (5) LMR = lymphocytes/monocytes. The number of neutrophils, lymphocytes, platelets and monocytes was assessed with a complete blood count with a 5-part differential in laboratory data, which was calculated via the Beckman Coulter DxH 800 instrument and presented as 1000 cells/μl. Counting and sizing of complete blood count parameters were performed according to Beckman Coulter methodology. All inflammatory indices were $\log_2$-transformed to ensure their normal distribution.

2.4. Diagnostic criteria of COPD

The diagnosis of COPD was established via the questionnaire "Ever told you had COPD?" (Yes) in 2013–2018 cycles or post-bronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) < 70 % according to spirometry examination in 2007–2012 cycles. When performing spirometry examination, eligible participants firstly conducted an initial spirometry examination. Those whose FEV1/FVC ratio below 70 % or below the lower limit of normal in the initial test were selected to perform the 2nd test with bronchodilator medication. If no or little improvement was observed in FEV1/FVC ratio in the 2nd test, a diagnosis of COPD can be made. As COPD patients in this study were diagnosed with spirometry examination or a questionnaire, they were divided into spirometry-based COPD and questionnaire-based COPD in further analysis.

2.5. Covariate

Covariates that may affect the relationship between different systemic inflammatory indices and COPD were selected referring to previous studies and data availability of NHANES database [15,16], which include age (<60 or ≥60), sex (male or female), race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black or other race), marital status (With partner, Widowed, divorced or separated or Never married), education (Under high school, High school or equivalent or College graduate or above), poverty-to-income ratio (PIR) (<1.3, 1.3≤PIR<3.5 or≥3.5), body mass index (BMI) (<20, 20≤BMI<25, 25≤BMI<30 and ≥ 30), red

blood cell (RBC) counts, diabetes (Yes, No or Borderline), hypertension (Yes or No), asthma (Yes or No) and smoking status (Never smoker, Former smoker and Current smoker). The diagnosis of diabetes (Doctor told you have diabetes? Yes, No or Borderline), hypertension (Ever told you had high blood pressure? Yes or No) and asthma (Ever been told you have asthma? Yes or No) was obtained through "questionnaire data" in NHANES 2007–2018. Never smokers were defined as smoking less than 100 cigarettes in life.

2.6. Statistical analysis

Due to the complex, multistage, probability sampling design of the NHANES survey, appropriate weight, sample units and strata were applied for statistical analysis. Continuous variables are presented as the means with standard deviations (SDs) and were evaluated by Student's *t*-test, while categorical variables are summarized as proportions and were evaluated by the chi-square test. Multivariate logistic regression with three differently adjusted models was applied to explore the relationship between different inflammatory indices and COPD. In model 1, no covariates were adjusted. In model 2, age, sex and race were adjusted. In model 3, all covariates mentioned above were adjusted. The results are presented as odds ratios (ORs) with 95 % confidence intervals (CIs). Inflammatory indices were also divided into quartiles for sensitivity analysis to investigate the stability of the correlation. Additionally, subgroup and interaction analyses were also performed by age, sex, race, marital status, education status, PIR, diabetes, hypertension, asthma and smoking status for different indices. All analyses were performed using R (version 4.0.4) and Empowerstats software (EmpowerStats | Data Analysis for Biostatistics & Epidemiology), and $p < 0.05$ was considered statistically significant.
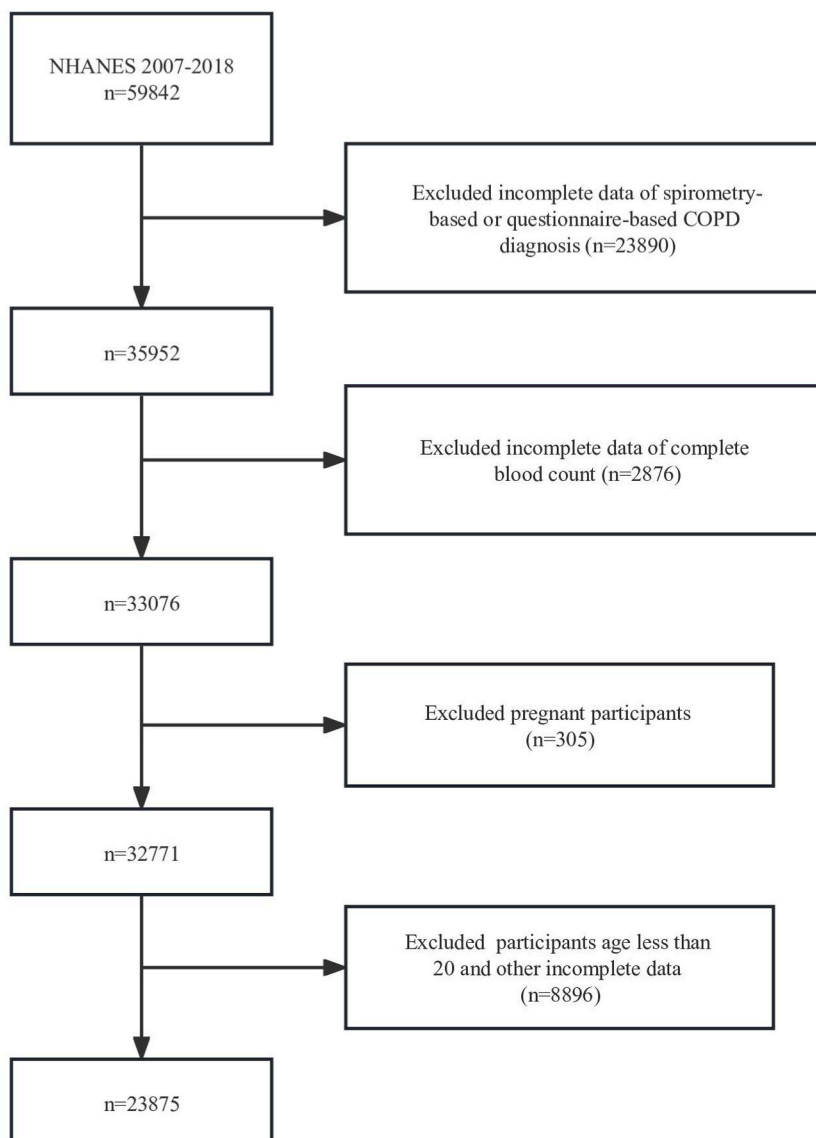
Fig. 1. Flowchart of participants selection from NHANES 2007–2018.

Table 1
Weighted baseline characteristics of participants enrolled in this study.

Variables	Non-COPD	COPD				P (COPD vs non-COPD)
		Total COPD	Based on spirometry	Based on questionnaire	p (between COPD)	
WBC	7.226 ± 2.680	7.723 ± 2.254	7.244 ± 2.058	8.151 ± 2.333	<0.001	<0.001
RBC	4.708 ± 0.469	4.686 ± 0.508	4.712 ± 0.486	4.663 ± 0.527	0.126	0.153
Lymphocyte	2.160 ± 1.649	2.095 ± 0.780	2.031 ± 0.683	2.153 ± 0.853	0.014	0.222
Neutrophil	4.260 ± 1.688	4.715 ± 1.783	4.385 ± 1.587	5.010 ± 1.893	<0.001	<0.001
Platelet	243.214 ± 61.431	243.406 ± 65.719	248.369 ± 61.634	238.975 ± 68.860	0.024	0.924
Monocyte	0.562 ± 0.198	0.624 ± 0.246	0.554 ± 0.185	0.686 ± 0.276	<0.001	<0.001
Log2SII	8.841 ± 0.733	9.044 ± 0.800	9.014 ± 0.693	9.071 ± 0.884	0.254	<0.001
Log2NLR	0.960 ± 0.625	1.169 ± 0.681	1.102 ± 0.589	1.230 ± 0.749	0.003	<0.001
Log2PLR	6.853 ± 0.514	6.906 ± 0.599	6.972 ± 0.534	6.847 ± 0.645	0.001	0.002
Log2PPN	9.867 ± 0.742	10.013 ± 0.749	9.953 ± 0.702	10.065 ± 0.786	0.018	<0.001
Log2LMR	1.935 ± 0.535	1.739 ± 0.636	1.872 ± 0.566	1.620 ± 0.671	<0.001	<0.001
Sex (%)					<0.001	<0.001
Male	48.492	58.311	70.907	47.067		
Female	51.508	41.689	29.093	52.933		
Age (%)					<0.001	<0.001
<60	77.567	47.204	60.848	35.026		
≥60	22.433	52.796	39.152	64.974		
Race (%)					0.318	<0.001
Mexican American	8.734	1.433	1.194	1.647		
Other Hispanic	5.88	1.689	1.231	2.099		
Non-Hispanic White	66.404	84.13	85.966	82.49		
Non-Hispanic Black	10.855	6.267	6.547	6.017		
Other race	8.127	6.481	5.062	7.747		
Marital status (%)					<0.001	<0.001
With partner	63.756	65.479	74.02	57.855		
Widowed, divorced or separated	17.074	27.567	19.77	34.527		
Never married	19.17	6.954	6.21	7.618		
Education (%)					<0.001	<0.001
Under high school	13.919	19.112	16.722	21.245		
High school or equivalent	22.247	31.235	26.68	35.302		
College graduate or above	63.834	49.653	56.598	43.454		
PIR (%)					<0.001	<0.001
PIR<1.3	20.799	28.106	14.669	40.1		
1.3≤PIR<3.5	35.088	34.222	30.588	37.466		
PIR≥3.5	44.113	37.672	54.743	22.434		
BMI (%)					<0.001	0.018
BMI<20	4.371	6.337	3.865	8.543		
20≤BMI<25	24.215	23.404	30.179	17.357		
25≤BMI<30	32.753	33.864	39.638	28.711		
BMI≥30	38.661	36.395	26.318	45.389		
Diabetes (%)					<0.001	<0.001
Yes	9.012	18.523	6.836	28.956		
No	88.764	79.059	91.329	68.107		
Borderline	2.224	2.417	1.835	2.937		
Hypertension (%)					<0.001	<0.001
Yes	29.861	50.405	36.282	63.011		
No	70.139	49.595	63.718	36.989		
Asthma (%)					<0.001	<0.001
Yes	13.611	30.523	17.163	42.448		
No	86.389	69.477	82.837	57.552		
Smoking (%)					<0.001	<0.001
Never smoker	58.778	17.489	23.422	12.194		
Former smoker	23.312	38.909	36.624	40.949		
Current smoker	17.910	43.601	39.954	46.857		

Continuous variables are presented as the means with SDs. Categorical variables are summarized as proportions.

SII: systemic immune-inflammation index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PPN: product of platelet and neutrophil count, LMR: lymphocyte-to-monocyte ratio; WBC: white blood cells, RBC: red blood cells, PIR: poverty-to-income ratio, BMI: body mass index.

Table 2

Association between inflammatory indicators and COPD.

Inflammation index	Crude model	Minimally adjusted	Fully adjusted
SII			
Continuous	**1.458(1.285,1.654)**	**1.404(1.234,1.597)**	**1.231(1.081,1.401)**
	<0.001	**<0.001**	**0.002**
Q1	Ref	Ref	Ref
Q2	1.129(0.834,1.530)	1.118(0.822,1.522)	1.121(0.815,1.544)
	0.435	0.479	0.485
Q3	1.198(0.913,1.573)	1.163(0.883,1.531)	1.061(0.812,1.386)
	0.196	0.285	0.666
Q4	**1.198(1.506,2.548)**	**1.856(1.413,2.437)**	**1.524(1.147,2.024)**
	<0.001	**<0.001**	**0.005**
p for trend	**<0.001**	**<0.001**	**0.004**
NLR			
Continuous	**1.683(1.475,1.920)**	**1.383(1.205,1.586)**	**1.223(1.064,1.405)**
	<0.001	**<0.001**	**0.005**
Q1	Ref	Ref	Ref
Q2	1.101(0.813,1.491)	0.998(0.734,1.350)	0.987(0.721,1.352)
	0.534	0.989	0.934
Q3	**1.493(1.199,1.859)**	**1.306(1.046,1.631)**	1.234(0.976,1.560)
	<0.001	**0.021**	0.078
Q4	**2.058(1.638,2.584)**	**1.511(1.198,1.907)**	1.281(0.999,1.642)
	<0.001	**<0.001**	0.051
p for trend	**<0.001**	**<0.001**	**0.028**
PLR			
Continuous	1.221(0.983,1.516)	1.122(0.913,1.378)	**1.325(1.086,1.617)**
	0.074	0.276	**0.007**
Q1	Ref	Ref	Ref
Q2	0.774(0.568,1.054)	0.761(0.558,1.038)	0.883(0.657,1.186)
	0.107	0.088	0.411
Q3	0.850(0.609,1.185)	0.825(0.585,1.163)	1.102(0.786,1.546)
	0.339	0.275	0.574
Q4	1.283(0.978,1.683)	1.135(0.849,1.517)	**1.508(1.126,2.020)**
	0.076	0.394	**0.008**
p for trend	**0.042**	0.251	**0.003**
PPN			
Continuous	**1.306(1.179,1.447)**	**1.501(1.346,1.673)**	**1.157(1.031,1.298)**
	<0.001	**<0.001**	**0.016**
Q1	Ref	Ref	Ref
Q2	**1.419(1.040,1.937)**	**1.503(1.100,2.053)**	**1.365(1.006,1.851)**
	0.030	**0.012**	**0.049**
Q3	**1.439(1.084,1.910)**	**1.623(1.224,2.152)**	1.297(0.975,1.726)
	0.014	**0.001**	0.078
Q4	**1.843(1.438,2.363)**	**2.408(1.871,3.100)**	**1.500(1.135,1.982)**
	<0.001	**<0.001**	**0.006**
p for trend	**<0.001**	**<0.001**	**0.010**
LMR			
Continuous	**0.522(0.439,0.622)**	**0.788(0.653,0.950)**	**0.794(0.666,0.948)**
	<0.001	**0.015**	**0.013**
Q1	Ref	Ref	Ref
Q2	**0.491(0.386,0.623)**	**0.646(0.506,0.823)**	**0.716(0.558,0.919)**
	<0.001	**<0.001**	**0.011**
Q3	**0.392(0.296,0.518)**	**0.598(0.441,0.809)**	**0.640(0.466,0.878)**
	<0.001	**0.001**	**0.007**
Q4	**0.480(0.362,0.635)**	0.877(0.646,1.191)	0.863(0.639,1.165)
	<0.001	0.403	0.339
p for trend	**<0.001**	0.179	0.164

Crude model: No covariates were adjusted.

Minimally adjusted: Adjusted for age, sex and race.

Fully adjusted: Adjusted for age, sex, race, marital status, education, poverty-to-income ratio, body mass index, red blood cell counts, diabetes, hypertension, asthma and smoking status.

SII: systemic immune-inflammation index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PPN: product of platelet and neutrophil count, LMR: lymphocyte-to-monocyte ratio.

Number of COPD: 1000 before weighted, 7072675 after weighted.

Table 3

Association between inflammatory indices and COPD diagnosed via spirometry or questionnaire.

Spirometry-based COPD				Questionnaire-based COPD			
Inflammatory index	Crude model	Minimally adjusted	Fully adjusted	Inflammatory index	Crude model	Minimally adjusted	Fully adjusted
SII				**SII**			
Continuous	**1.383**	**1.383**	**1.310**	**Continuous**	**1.530**	**1.435**	1.190
	(1.175,1.628)	**(1.168,1.638)**	**(1.122,1.529)**		**(1.272,1.841)**	**(1.193,1.727)**	(0.974,1.454)
	<0.001	**<0.001**	**0.001**		**<0.001**	**<0.001**	0.092
Q1	Ref	Ref	Ref	**Q1**	Ref	Ref	Ref
Q2	1.477	1.476	1.528	**Q2**	0.875	0.851	0.834
	(0.995,2.193)	(0.987,2.206)	(0.992,2.354)		(0.552,1.387)	(0.538,1.345)	(0.519,1.339)
	0.056	0.061	0.054		0.572	0.491	0.454
Q3	**1.463**	**1.469**	1.478	**Q3**	1.026	0.968	0.830
	(1.027,2.083)	**(1.024,2.107)**	(0.999,2.186)		(0.687,1.531)	(0.648,1.447)	(0.567,1.216)
	0.038	**0.040**	0.051		0.902	0.875	0.343
Q4	**1.861**	**1.873**	**1.766**	**Q4**	**2.026**	**1.842**	1.390
	(1.290,2.684)	**(1.284,2.731)**	**(1.206,2.585)**		**(1.426,2.879)**	**(1.282,2.644)**	(0.924,2.092)
	0.001	**0.002**	**0.004**		**<0.001**	**0.001**	0.118
p for trend	**0.005**	**0.005**	**0.012**	**p for trend**	**<0.001**	**<0.001**	**0.046**
NLR				**NLR**			
Continuous	**1.431**	**1.209**	1.167	**Continuous**	**1.932**	**1.563**	**1.303**
	(1.202,1.705)	**(1.004,1.456)**	(0.978,1.392)		**(1.602,2.331)**	**(1.288,1.897)**	**(1.055,1.609)**
	<0.001	**0.049**	0.090		**<0.001**	**<0.001**	**0.015**
Q1	Ref	Ref	Ref	**Q1**	Ref	Ref	Ref
Q2	1.265	1.148	1.164	**Q2**	1.069	0.962	0.981
	(0.891,1.797)	(0.801,1.643)	(0.798,1.697)		(0.670,1.708)	(0.599,1.544)	(0.602,1.598)
	0.192	0.455	0.434		0.780	0.871	0.938
Q3	**1.733**	**1.521**	**1.584**	**Q3**	**1.356**	1.187	1.058
	(1.219,2.464)	**(1.049,2.206)**	**(1.080,2.323)**		**(1.012,1.816)**	(0.884,1.593)	(0.759,1.474)
	0.003	**0.029**	**0.021**		**0.044**	0.258	0.741
Q4	**1.912**	1.463	1.428	**Q4**	**2.299**	**1.651**	1.305
	(1.318,2.775)	(0.987,2.169)	(0.957,2.129)		**(1.747,3.025)**	**(1.245,2.189)**	(0.935,1.822)
	<0.001	0.062	0.085		**<0.001**	**<0.001**	0.122
p for trend	**<0.001**	**0.045**	0.055	**p for trend**	**<0.001**	**0.001**	0.116
PLR				**PLR**			
Continuous	**1.579**	**1.547**	**1.669**	**Continuous**	0.977	0.878	1.105
	(1.210,2.061)	**(1.182,2.024)**	**(1.272,2.191)**		(0.714,1.338)	(0.677,1.140)	(0.842,1.450)
	0.001	**0.002**	**<0.001**		0.886	0.332	0.473
Q1	Ref	Ref	Ref	**Q1**	Ref	Ref	Ref
Q2	0.913	0.925	1.031	**Q2**	0.674	0.645	0.775
	(0.671,1.242)	(0.675,1.269)	(0.746,1.423)		(0.418,1.087)	(0.403,1.033)	(0.484,1.242)
	0.563	0.631	0.855		0.109	0.072	0.293
Q3	0.965	0.989	1.165	**Q3**	0.792	0.733	1.109
	(0.628,1.482)	(0.640,1.528)	(0.741,1.832)		(0.495,1.267)	(0.456,1.178)	(0.697,1.765)
	0.871	0.960	0.510		0.333	0.203	0.663
Q4	**1.815**	**1.808**	**2.077**	**Q4**	0.924	0.742	1.104
	(1.332,2.473)	**(1.306,2.503)**	**(1.489,2.897)**		(0.627,1.364)	(0.495,1.112)	(0.720,1.692)
	<0.001	**<0.001**	**<0.001**		0.693	0.152	0.651
p for trend	**<0.001**	**<0.001**	**<0.001**	**p for trend**	0.902	0.277	0.400
PPN				**PPN**			
Continuous	**1.172**	**1.347**	**1.218**	**Continuous**	**1.440**	**1.665**	1.132
	(1.008,1.362)	**(1.142,1.588)**	**(1.050,1.412)**		**(1.265,1.639)**	**(1.452,1.910)**	(0.949,1.352)
	0.042	**<0.001**	**0.011**		**<0.001**	**<0.001**	0.173
Q1	Ref	Ref	Ref	**Q1**	Ref	Ref	Ref
Q2	1.461	**1.533**	**1.533**	**Q2**	1.349	1.410	1.202
	(0.976,2.186)	**(1.029,2.286)**	**(1.023,2.298)**		(0.846,2.151)	(0.878,2.265)	(0.744,1.943)
	0.069	**0.039**	**0.042**		0.212	0.159	0.455
Q3	1.312	1.490	1.435	**Q3**	**1.539**	**1.725**	1.198
	(0.861,1.997)	(0.988,2.245)	(0.952,2.163)		**(1.051,2.254)**	**(1.182,2.516)**	(0.816,1.761)
	0.209	0.060	0.089		**0.029**	**0.006**	0.360
Q4	**1.602**	**2.105**	**1.798**	**Q4**	**2.090**	**2.724**	1.341
	(1.108,2.318)	**(1.451,3.054)**	**(1.257,2.573)**		**(1.509,2.895)**	**(1.943,3.819)**	(0.871,2.065)
	0.014	**<0.001**	**0.002**		**<0.001**	**<0.001**	0.187
p for trend	**0.025**	**<0.001**	**0.003**	**p for trend**	**<0.001**	**<0.001**	0.188
LMR				**LMR**			
Continuous	**0.803**	1.255	1.211	**Continuous**	**0.367**	**0.533**	**0.524**
	(0.651,0.990)	(0.986,1.598)	(0.962,1.523)		**(0.279,0.482)**	**(0.404,0.703)**	**(0.406,0.677)**
	0.043	0.069	0.107		**<0.001**	**<0.001**	**<0.001**
Q1	Ref	Ref	Ref	**Q1**	Ref	Ref	Ref

Table 3 (*continued*)

Q2	0.809	1.016	1.081	Q2	**0.336**	**0.447**	**0.491**
	(0.570,1.148)	(0.704,1.464)	(0.746,1.566)		**(0.247,0.457)**	**(0.330,0.607)**	**(0.355,0.680)**
	0.238	0.934	0.682		**<0.001**	**<0.001**	**<0.001**
Q3	**0.557**	0.826	0.831	Q3	**0.313**	**0.473**	**0.506**
	(0.387,0.801)	(0.545,1.253)	(0.552,1.251)		**(0.207,0.474)**	**(0.311,0.721)**	**(0.320,0.801)**
	0.002	0.371	0.379		**<0.001**	**<0.001**	**0.005**
Q4	0.789	**1.486**	1.426	Q4	**0.326**	**0.561**	**0.506**
	(0.584,1.065)	**(1.032,2.139)**	(0.991,2.054)		**(0.205,0.518)**	**(0.349,0.903)**	**(0.318,0.806)**
	0.124	**0.036**	0.060		**<0.001**	**0.020**	**0.005**
p for trend	**0.037**	0.173	0.236	p for trend	**<0.001**	**0.011**	**0.004**

Crude model: No covariates were adjusted.
Minimally adjusted: Adjusted for age, sex and race.
Fully adjusted: Adjusted for age, sex, race, marital status, education, poverty-to-income ratio, body mass index, red blood cell counts, diabetes, hypertension, asthma and smoking status.
SII: systemic immune-inflammation index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PPN: product of platelet and neutrophil count, LMR: lymphocyte-to-monocyte ratio.
Number of spirometry-based COPD: 453 before weighted, 3335644 after weighted.
Number of questionnaire-based COPD: 547 before weighted, 3737031 after weighted.
Number of total COPD: 1000 before weighted, 7072675 after weighted.

2.7. Patients and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

3. Results

3.1. Participant selection and baseline characteristics

A total of 23,875 participants, including 1000 COPD patients, were enrolled in this study after the selection and exclusion process (Fig. 1). Among all COPD patients, 453 were diagnosed via spirometry examination, while 547 were diagnosed via questionnaire. The weighted baseline characteristics of the enrolled participants are presented in Table 1. Overall, significant differences were observed in baseline characteristics between the non-COPD group and the COPD group, except for RBC (p = 0.153), lymphocyte (p = 0.222) and platelet (p = 0.924). Significant differences were also observed between spirometry-based and questionnaire-based COPD patients, except for RBC (p = 0.126), $\log_2$SII (p = 0.254) and race (p = 0.318).

3.2. Association between inflammatory biomarkers and COPD

The results from multivariate logistic regression investigating the relationships between inflammatory indices and total COPD are presented in Table 2. Elevated SII, NLR and PPN were positively associated with total COPD, while elevated LMR was negatively associated with total COPD in the three models. Interestingly, although no significant association was observed between PLR and total COPD in crude model (OR 1.221, 95%CI 0.983,1.516) and minimally adjusted model (OR 1.122, 95%CI 0.913,1.378), the positive relationship was observed in fully adjusted model (OR 1.325, 95%CI 1.086,1.617). When SII, NLR, PLR, PPN and LMR were treated as categorial variables in quartiles, significant results were observed in SII quartile 4 (OR 1.524, 95%CI 1.147,2.024), PLR quartile 4 (OR 1.508, 95%CI 1.126,2.020), PPN quartile 2 (OR 1.365, 95%CI 1.006,1.851) and quartile 4 (OR 1.500, 95%CI 1.135,1.982) and LMR quartile 2 (OR 0.716, 95%CI 0.558,0.919) and quartile 3 (OR 0.640, 95%CI 0.466,0.878) in fully adjusted model.

Table 3 shows the relationship between different inflammatory indices and COPD in the two diagnostic criteria among the three models. All five indices showed a significant correlation with spirometry-based COPD in the crude model. After fully adjustments, relationships between SII (OR 1.310, 95%CI 1.122,1.529), PLR (OR 1.669, 95%CI 1.272,2.191), PPN (OR 1.218, 95%CI 1.050,1.412) and spirometry-based COPD remained significant, while insignificant relationships between NLR (OR 1.167, 95%CI 0.978,1.392), LMR (OR 1.211, 95%CI 0.962,1.523) and spirometry-based COPD was observed. Sensitivity analysis showed that the relationships remained significant in SII quartile 4 (OR 1.766, 95 % CI 1.206, 2.585), PLR quartile 4 (OR 2.077, 95 % CI 1.489, 2.897), PPN quartile 2 (OR 1.218, 95 % CI 1.050, 1.412) and PPN quartile 4 (OR 1.798, 95 % CI 1.257, 2.573). Additionally, SII (OR 1.530, 95 % CI 1.272, 1.841), NLR (OR 1.932, 95 % CI 1.602, 2.331), PPN (OR 1.440, 95 % CI 1.265, 1.639) and LMR (OR 0.367, 95 % CI 0.279, 0.482) showed significant relationships with questionnaire-based COPD in the crude model. After covariate adjustments, only NLR (OR 1.303, 95%CI 1.055,1.609) and LMR (OR 0.524, 95%CI 0.406,0.677) showed significant relationships with questionnaire-based COPD, while SII (OR 1.190, 95%CI 0.974,1.454), PLR (OR 1.105 95%CI 0.842,1.450) and PPN (OR1.132, 95%CI 0.949,1.352) presented insignificant relationships with questionnaire-based COPD. The results of the sensitivity analysis showed that no NLR quartile obtained a significant relationship, while all LMR quartiles obtained significant relationships in the fully adjusted model.

3.3. Subgroup analysis and interaction tests in the overall population

The results of the subgroup analysis are presented in Figs. S1–S5, indicating that the significant associations between the SII, NLR, PLR, PPN, LMR and total COPD were not stable in some subgroups. For participants characterized as female, other Hispanic, non-Hispanic black, with partner, PIR≥3.5, BMI≥30, never smoker or current smoker, the significant associations were not significant among the five inflammatory indices. Moreover, for patients characterized as age≥60, high school or equivalent or suffering from diabetes or borderline diabetes, the positive association between the SII, NLR, PLR, and PPN and total COPD vanished, while a negative association between the LMR and total COPD still existed. The interaction tests showed that race significantly affected the SII-COPD (p = 0.037) and PPN-COPD (p = 0.005) relationships, BMI significantly affected the PLR-COPD (p = 0.045) and PPN-COPD (p = 0.007) relationships, and asthma significantly affected the LMR-COPD (p = 0.020) relationship.

4. Discussion

In this cross-sectional, population-based study, we observed significant associations between all five inflammatory indices and total COPD in a fully adjusted model. However, only the SII, PLR and PPN showed significant relationships with spirometry-based COPD, while only the NLR and LMR showed significant relationships with questionnaire-based COPD. Our results indicated that certain inflammatory indices may serve as biomarkers of COPD, and heterogeneity can be observed between spirometry-based COPD and questionnaire-based COPD in the NHANES database, which deserves further investigations.

The potential mechanisms of the positive relationships between inflammatory indices and COPD have not been fully revealed. Growing evidence suggests that stimulants, including cigarette smoke, bacteria, and viruses, may trigger neutrophilic inflammation by promoting airway epithelial cells to release neutrophilic mediators [17]. Activated neutrophils may secrete serine proteases and generate oxidative stress, leading to mucus hypersecretion, alveolar destruction and corticosteroid resistance, which is further aggravated in hypoxic COPD patients [17–19]. Platelets may also play a role in COPD pathogenesis via alveolar integrity loss, pulmonary vascular remodeling and dysregulation of hypoxia [20]. Moreover, chemokines released by epithelial cells and macrophages activate T lymphocytes, which exert cytotoxic effects and contribute to alveolar cell apoptosis [17]. These cells and their derived ratios may serve as potential biomarkers for COPD during clinical practice.

Previous studies have reported the value of inflammatory indices in COPD management. A population-based study with 4482 participants indicated that elevated SII levels were associated with a higher risk of mortality in COPD patients without sarcopenia (HR 1.59, 95 % CI 1.02, 2.48) [21]. A meta-analysis pointed out a positive association between the NLR and adverse outcomes (including ICU transfer, mortality, and others) in patients with acute exacerbation of COPD (OR = 1.054, 95 % CI 1.016,1.093, p = 0.005) [22]. A retrospective study found a significant increase in the PLR in patients with stable COPD (p = 0.006), which is related to COPD severity [23]. Another study based on COPD patients showed elevated NLRs (p < 0.001) and PLRs (p = 0.001), along with decreased LMRs (p = 0.001), in patients with higher malnutrition risk compared with those with lower malnutrition risk [24]. Inflammatory indices may also serve as possible indicators in comorbidity prediction of COPD patients. There was evidence showing that NLR and PLR can be regarded as indicators for lung cancer development in COPD patients [25]. Another study pointed out that PLR >216.82 may be considered as an optimal cutoff value differentiating COPD patients with pulmonary tuberculosis from those suffered from COPD alone [26]. Consistent with other studies, our study demonstrated positive relationships between the SII, NLR, PLR, and PPN and COPD, along with a negative relationship between the LMR and COPD, suggesting that systemic inflammation may play a role in COPD occurrence and development.

Moreover, the heterogeneity caused by different diagnostic criteria of COPD cannot be ignored. Postbronchodilator FEV$_1$/FVC<0.7 was regarded as the recommended criterion of COPD diagnosis according to COPD guideline from global initiative for chronic obstructive lung disease [27]. As COPD is characterized by inconspicuous early symptoms and a low awareness rate, the diagnostic value of self-report questionnaires is limited, leading to many cases of underdiagnosis [4,28]. In this study, compared with spirometry-based COPD patients, questionnaire-based COPD patients were associated with a higher prevalence of hypertension (p < 0.001), diabetes (p < 0.001) and asthma (p < 0.001) (Table 1). These results indicated that questionnaire-based COPD patients are associated with poor health status. The results of this study also suggested that the SII, PLR and PPN may serve as better indicators for spirometry-based COPD, while the NLR and LMR may serve as better indicators for questionnaire-based COPD. This may be attributed to the heterogeneity between spirometry-based COPD and questionnaire-based COPD. Since questionnaire-based COPD cannot reflect the real disease status, further studies based on spirometry examination should be conducted to investigate the real association between these inflammatory indices and COPD.

Additionally, interaction tests showed that race, BMI and asthma may exert a significant impact on the relationships. Different levels of inflammatory indices or COPD susceptibility in a particular group of participants may lead to different results compared with the overall population. A study based on the Lovelace Smokers' cohort demonstrated that Hispanic ethnicity was associated with lower COPD prevalence (OR 0.49, p = 0.007) and slower FEV$_1$ decline (OR 0.48, p = 0.003) compared with non-Hispanic white individuals [29]. Our results showed that the relationships remained significant in non-Hispanic white individuals among the five indices, while all significant relationships vanished in other Hispanic individuals among the five indices. As for BMI, a meta-analysis indicated that the underweight group (OR 1.96, 95 % CI: 1.78,2.17) was associated with higher COPD risk, while the overweight (OR 0.80, 95 % CI: 0.73, 0.87) and obesity groups (OR 0.77, 95 % CI: 0.68–0.86) were associated with lower COPD risk [30]. A retrospective study showed that BMI decrease during follow up was correlated with higher mortality rate in COPD patients after covariate adjustment (HR 3.106, 95% CI 1.439,6.704) [31]. In our results, no significant relationship between the five inflammatory indices and COPD was observed in those with BMI≥30, which may be attributed to the low susceptibility to COPD in obese participants. As for asthma history, a meta-analysis

summarized that having a history of asthma may serve as a risk factor for COPD [32]. Another study over 524 Hispanic/Latino individuals also showed that having a history of asthma may be regarded as one of the most essential risk factors in COPD (OR 3.37 95 % CI, 2.57,4.41) [33]. Consistently, our results suggested that a significant LMR-COPD relationship was enhanced in those with a history of asthma but vanished in those without.

There are still some limitations in our study that are worth mentioning. (1) Regarding its cross-sectional design, no causal relationship can be determined in this work. Further prospective cohort studies with large sample sizes are needed to verify the results. (2) Due to incomplete postbronchodilator spirometry examination results in the NHANES database, only 453 participants with confirmed postbronchodilator FEV1/FVC<70 % were enrolled as spirometry-based COPD patients, which was relatively too small to draw a final conclusion. (3) Although some covariates were adjusted in our work, potential covariates that are unavailable in NHANES database may still affect our results to some extent. (4)A self-reported questionnaire was applied to identify COPD patients in NHANES 2013–2018, which may be less accurate and increase potential bias. Promoting application of spirometry examination may be beneficial for management of COPD.

5. Conclusion

Taken together, this study demonstrated that the SII, NLR, PLR, and PPN are positively associated with total COPD, while the LMR is significantly negatively associated with total COPD. Heterogeneity can be observed between spirometry-based and questionnaire-based COPD and further prospective cohort studies are needed to verify the results.

Ethical Approval

Population of this study was enrolled form NHANES database, which is approved by the Ethics Review Board of National Center for Health Statistics (Protocol number: Protocol #2005-06 and Protocol #2011-17) (NHANES - NCHS Research Ethics Review Board Approval (cdc.gov)). Written informed consent of all participants were obtained in this survey.

Data availability statement

All data were available on NHANES website (NHANES - NCHS Research Ethics Review Board Approval (cdc.gov)).

CRediT authorship contribution statement

Dongru Du: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Guangyue Zhang:** Software, Data curation, Conceptualization. **Dan Xu:** Visualization, Resources. **Lian Liu:** Software, Methodology. **Xueru Hu:** Software, Methodology. **Tingting Zeng:** Software, Methodology. **Yongchun Shen:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Fengming Luo:** Writing – review & editing, Supervision, Resources, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31524.

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