

# Association Between C-Reactive Protein to Lymphocyte Ratio and Chronic Obstructive Pulmonary Disease: A Cross-Sectional Study

Ting Ao , Yingxiu Huang , Peng Zhen, Ming Hu 

Department of Infectious Diseases, Beijing Luhe Hospital, Capital Medical University, Beijing, People's Republic of China

Correspondence: Ming Hu, Department of Infectious Diseases, Beijing Luhe Hospital, Capital Medical University, No. 82, Xinhua South Road, Tongzhou District, Beijing, 101100, People's Republic of China, Tel +86 13651328259, Email hmyx2012@sina.com

**Background:** The inflammatory response plays a critical role in the progression and prognosis of Chronic Obstructive Pulmonary Disease (COPD). The C-reactive protein to lymphocyte ratio (CLR) has emerged as a potential novel biomarker of systemic inflammation. Nevertheless, the association between CLR and COPD remains unclear. The objective of this study was to explore the possible connection between CLR and COPD.

**Methods:** We conducted a retrospective study on 22,581 participants from the NHANES dataset (1999–2010). To evaluate the relationship between CLR and COPD, logistic regression analysis, restricted cubic spline analysis, and threshold effect analysis were utilized. Furthermore, subgroup and sensitivity analyses were conducted to assess the robustness of the identified association.

**Results:** Multivariate logistic regression models indicated that the ln-transformed CLR was significantly associated with an increased risk of COPD (OR: 1.14, 95% CI: 1.04–1.25;  $P = 0.005$ ). Compared to participants classified with the first tertile of ln-transformed CLR (T1), the risks of COPD for those in T2 and T3 were 1.03 and 1.33 times higher, respectively. An evident upward trend was noted with an increase in the ln-transformed CLR ( $P$  for trend = 0.032). Furthermore, an inverse L-shaped association was identified between the ln-transformed CLR and the risk of COPD. The robustness and consistency of these findings were further confirmed by subgroup and sensitivity analyses.

**Conclusion:** Increased CLR correlated with a heightened risk of developing COPD, exhibiting nonlinear patterns and threshold effects.

**Keywords:** C-reactive protein to lymphocyte ratio, chronic obstructive pulmonary disease, inflammation, national health and nutrition examination survey

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic respiratory condition marked by the gradual destruction of the pulmonary tissue, ultimately leading to irreversible airflow limitation.<sup>1</sup> Globally, COPD impacts around 4% of the general population, with a prevalence rising to approximately 10% among those aged 40 years and above.<sup>2</sup> The 2019 Global Burden of Disease study reports that COPD is the third most common cause of death globally among elderly individuals.<sup>3</sup> COPD presents a substantial health and economic burden both to individuals and society, driven by its high prevalence, rising incidence, and severe mortality rate, making it a major global public health challenge.

Inflammatory processes are fundamentally involved in the development and progression of COPD.<sup>4,5</sup> Inflammatory cells secrete mediators and proteolytic enzymes that contribute to the progressive destruction of airway and lung parenchymal structures, ultimately promoting airway remodeling and airflow obstruction.<sup>6,7</sup> Previous studies have shown that neutrophils, lymphocytes, and monocytes/macrophages constitute the main inflammatory cells contributing to the chronic inflammation of COPD.<sup>8</sup> Furthermore, the immune system is believed to serve as a critical driving mechanism in the disease's pathogenesis.<sup>9</sup> A substantial body of evidence suggests that individuals with COPD exhibit heightened immune cell infiltration in lung tissue, accompanied by an enhanced immune response.<sup>9,10</sup>

The C-reactive protein (CRP) is a widely recognized biomarker of inflammation, crucial for assessing infections and various inflammatory disorders.<sup>11</sup> Lymphocytes serve as pivotal elements in immune responses, and alterations in immune activation or suppression can result in changes in lymphocyte counts.<sup>12,13</sup> Recently, the C-reactive protein to lymphocytes ratio (CLR), as an emerging inflammatory indicator, can reflect the balance between systemic inflammatory and immune responses.<sup>14</sup> Various studies have shown that elevated CLR levels have been connected to poor outcomes across a spectrum of conditions, including SARS-CoV-2 pneumonia,<sup>14</sup> myocardial infarction,<sup>15</sup> periprosthetic joint infection,<sup>16</sup> and malignant diseases.<sup>17</sup> CLR has emerged as a promising tool for predicting both disease prognosis and diagnostic assessment.

Given the significant roles of inflammation and immune dysregulation in the development of COPD, CLR could be considered a possible indicator of COPD risk. However, the relationship between CLR and COPD has not been thoroughly explored to date. Therefore, the primary objective of our study was to examine the potential association between CLR and the risk of COPD in US adults through a cross-sectional design.

## Materials and Methods

### Study Population

The National Health and Nutrition Examination Survey (NHANES), conducted by the Centers for Disease Control and Prevention (CDC), is a nationally representative program designed to evaluate the health and nutritional status of the non-institutionalized US population. Utilizing a multistage, stratified probability sampling strategy, NHANES collects comprehensive data through standardized questionnaires, physical examinations, and laboratory analyses. This rich dataset encompasses a wide range of information, including demographic characteristics, chronic disease profiles, biomarkers, lifestyle behaviors, and environmental exposures. Data are released biennially to ensure both timeliness and national representativeness. All survey protocols were approved by the Research Ethics Review Board of the National Center for Health Statistics (NCHS), and informed consent was secured from all participants. Detailed information regarding survey methods and protocols is available on the official NCHS website.

In accordance with the Ethical Review Methods for Life Science and Medical Research Involving Human Beings, our study meets the exemption criteria outlined in Article 32 of the regulation: (1) utilizing publicly available data obtained through legal means, or data collected through observation without interfering with public behavior; and (2) employing anonymized information for research purposes. We made use of legally obtained public data and ensured that no public behavior was influenced or disrupted during the research process. Furthermore, all data analyzed were anonymized, ensuring compliance with ethical standards as stipulated by the regulation. The Medical Ethics Committee of Beijing Luhe Hospital affiliated with Capital Medical University has approved this study and waived informed consent (ethical number: 2025-LHKY-029-01).

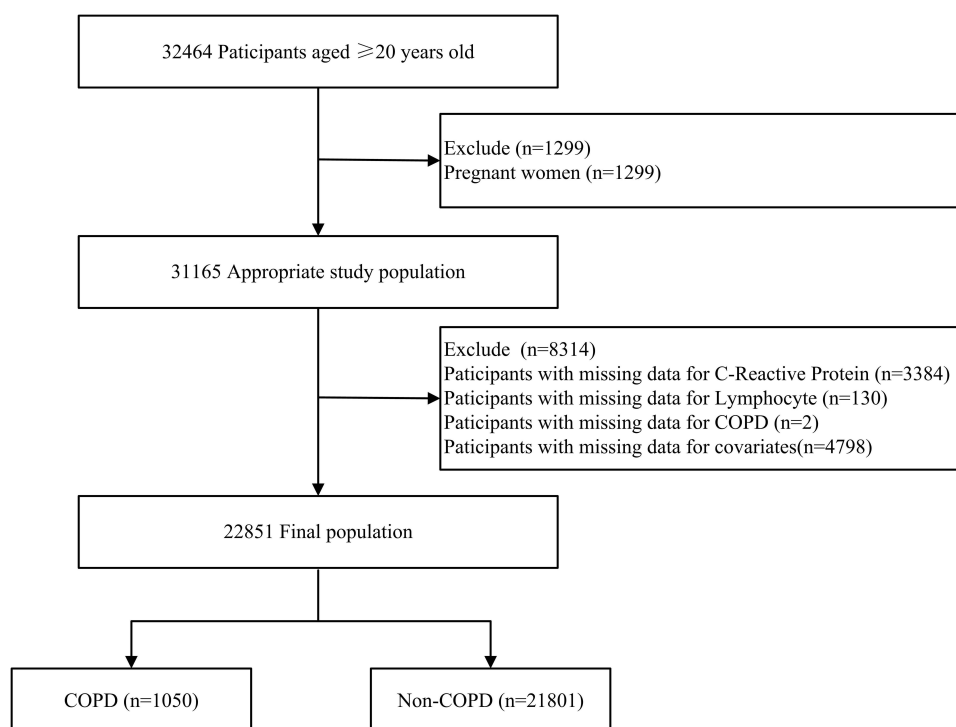
This research adopted a cross-sectional design, drawing on data from NHANES collected between 1999 and 2010. Only adult participants were included. Additionally, we excluded individuals who were pregnant ( $n=1299$ ), those missing relevant COPD survey data ( $n=2$ ), and participants with incomplete records for CRP ( $n=3384$ ), lymphocytes ( $n=130$ ), or covariates ( $n=4798$ ), including 572 for body mass index (BMI), 411 for marital status, 18 for smoking status, 33 for education level, 1899 for drinking status, 1855 for poverty income ratio (PIR), 9 for hypertension, and 1 for cardiovascular disease (CVD) (Figure 1).

### C-Reactive Protein to Lymphocyte Ratio

Whole blood samples from eligible participants were obtained at the NHANES Mobile Examination Center (MEC) and subsequently sent to a laboratory for further analysis. In this study, CLR was computed as the ratio of CRP (mg/L) to lymphocyte count (1000 cells/ $\mu$ L).<sup>18</sup> To ensure data reliability, NHANES enforced rigorous quality control measures throughout both the data collection and laboratory testing processes.

### COPD

COPD diagnosis was confirmed by meeting at least one of the following criteria:<sup>19</sup> (1) a post-bronchodilator FEV1/FVC ratio less than 0.70; (2) a physician or healthcare professional-confirmed diagnosis of emphysema; or (3) in individuals aged 40 years or above, who have a history of smoking, chronic bronchitis, and are undergoing treatment with inhaled corticosteroids, mast cell stabilizers, selective phosphodiesterase-4 inhibitors, or leukotriene modifiers.



**Figure 1** Flow chart of participants selection.

**Abbreviation:** COPD, Chronic obstructive pulmonary disease.

## Covariates

Data collection and documentation were performed by trained investigators. The study incorporated the following data categories: (1) demographics characteristics, including age (years), sex, race/ethnicity, educational level, marital status, drinking status, smoking status, the PIR, and BMI (kg/m<sup>2</sup>); (2) comorbid conditions, including CVD, hypertension, and diabetes; (3) laboratory parameters, such as the counts of segmented neutrophils (1000 cell/ $\mu$ L), eosinophils (1000 cells/ $\mu$ L), monocyte (1000cells/ $\mu$ L), basophils (1000cells/ $\mu$ L), platelet (1000 cells/ $\mu$ L), red blood cell (million cells/ $\mu$ L).

Sex was classified as either male or female. Race/ethnicity was divided into categories: non-Hispanic White, non-Hispanic Black, Mexican American, other Hispanic, or other races. Education levels were classified as above high school, high school or equivalent, and less than high school. Marital status was grouped into two categories: married/living with a partner or living alone. Drinking status was classified as current, former, or never. Smoking status was categorized as former smoker, current smoker, or never smoked. The PIR was divided into three distinct groups:  $\leq 1.30$ , 1.31–3.50, and  $> 3.50$ . The BMI was calculated using weight and height.

The diagnosis of CVD was confirmed through interviews utilizing a standardized questionnaire assessing medical conditions, which included the question:

Has a doctor or other health expert ever informed you that you have congestive heart failure/coronary heart disease/angina pectoris/myocardial Infarction/stroke?

A participant was considered to have CVD if they answered “yes” to any of the questions listed above.<sup>20</sup> Hypertension was identified if the average systolic blood pressure was  $\geq 140$  mmHg, the average diastolic blood pressure was  $\geq 90$  mmHg, there was a history of antihypertensive drugs use, or hypertension had been diagnosed previously.<sup>21</sup> Diabetes was diagnosed if any of the following criteria were met: fasting glucose  $\geq 7.0$  mmol/l, random blood glucose  $\geq 11.1$  mmol/l, two-hour oral glucose tolerance test blood glucose  $\geq 11.1$  mmol/l, hemoglobin A1c  $\geq 6.5\%$ , the use of insulin or diabetes medications, or a physician confirmed diagnosis of diabetes.<sup>22</sup>

## Statistical Analysis

By NHANES analysis guidelines, this study incorporated complex sampling designs and sampling weights, which included variables such as MEC exam weights for two years (WTMEC2YR) and four years (WTMEC4YR), along with the masked variance pseudo-cluster (SDMVPSU) and masked variance pseudo-stratum (SDMVSTRA).<sup>23</sup> For the 1999–2002 cycles, the weights were calculated as  $1/3 \times \text{WTMEC4YR}$ , while for the 2003–2010 cycles, they were adjusted to  $1/6 \times \text{WTMEC2YR}$ .

A number of demographic and laboratory factors were collected on the participants based on previous literature and clinical practice.<sup>15,24</sup> Given our large sample size, the proportion of missing values for covariates was less than 10%. Due to the relatively low percentage of missing data, we opted to exclude these missing values directly. Categorical variables for the COPD and without COPD groups were presented as survey-weighted percentages (%). Based on the distribution of continuous variables, they were summarized as either survey-weighted mean with standard deviation (SD) or median with interquartile range (IQR). The differences among groups were assessed by one-way ANOVA, the Kruskal–Wallis test, or chi-square tests.

Given the skewed distribution of CLR, the data were transformed using the natural logarithm (LN) prior to conducting statistical analysis. In the subsequent analyses exploring the associations with COPD, the CLR was treated as a continuous variable with 1-unit increment in ln-transformed data or categorized into tertiles. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariable logistic regression models. Five models were employed: Model 1 was unadjusted; Model 2 adjusted for age, sex, race/ethnicity, and NHANES cycle; Model 3 further adjusted for education level, marital status, drinking status, smoking status, PIR, and BMI, building on Model 2; Model 4 included all variables in Model 3 in addition to comorbidities, such as CVD, hypertension, and diabetes; Model 5 was fully adjusted.

To explore the dose-response relationship between ln-transformed CLR and COPD, we conducted a restricted cubic spline (RCS) analysis with 3 knots. Furthermore, the association was further evaluated using a two-piecewise logistic regression model, adjusting for all covariates in Model 5.

Additionally, we performed stratified analyses based on sex, age (20–60 years versus  $\geq 60$  years), BMI ( $< 25$  versus 25–30 or  $\geq 30$  kg/m<sup>2</sup>), smoking status (non-smokers versus smokers), CVD, hypertension, and diabetes to assess whether the relationship between ln-transformed CLR and COPD remains consistent across different subgroups. A sensitivity analysis was also performed following multiple imputations for missing data to enhance the reliability of the results.

Data analysis was performed using Free Statistics software version 2.0 and R 4.2.2 (<http://www.R-project.org>, The R Foundation). A P-value  $< 0.05$  (two-sided) was regarded as statistically significant in all analyses.

## Results

### Baseline Characteristics

A total of 22,851 individuals were successfully enrolled in this study between 1999 and 2010 (Figure 1). Table 1 summarizes the demographic and clinical characteristics of a sample that represents 163.18 million US adults, categorized according to whether or not they have COPD. 6.82 million individuals were identified with COPD. The mean age was 46.71 (16.57) years, and 50.54% were female. Notably, participants in the COPD group tended to be older, have higher income levels and educational attainment, be current smokers and drinkers, and have a higher prevalence of CVD, diabetes, and hypertension. Moreover, participants with COPD had a lower lymphocyte number and higher levels of C-reactive protein in comparison to those without COPD. (Table 1)

### Association Between CLR and COPD

Because CLR exhibited a skewed distribution, we applied a ln transformation to normalize its distribution. The association between ln-transformed CLR and COPD is shown in Table 2 across five models. In model 1, when ln-transformed CLR was considered as a continuous variable, it showed a significant positive association with the risk of COPD (OR, 1.29; 95% CI, 1.21–1.38;  $P < 0.001$ ). Besides, this relationship continued to be significant even after adjusting for different variables. In Model 5, the result showed that each 1-unit increase of ln-transformed CLR was linked to a 14% higher risk of COPD after adjusting for all covariates (OR, 1.14; 95% CI, 1.04–1.25;  $P = 0.005$ ).

**Table 1** Weighted Baseline Characteristics of Participants in the NHANES 1999–2010 Cycles

Patient Characteristic	Total	with COPD	without COPD	p-value
Weighted population, n (in millions)	163.18	6.82	156.36	
<b>Demographic information</b>				
Age, Mean (SD), years	46.71 (16.57)	59.53 (13.21)	46.15 (16.48)	<0.001
Sex, n (in millions), %				0.234
Male	80.71 (49.46)	3.51 (51.52)	77.19 (49.37)	
Female	82.47 (50.54)	3.30 (48.48)	79.16 (50.63)	
Race/ethnicity, n (in millions), %				<0.001
Non-Hispanic White	119.41 (73.18)	5.87 (86.06)	113.54 (72.62)	
Non-Hispanic Black	16.21 (9.94)	0.45 (6.69)	15.75 (10.08)	
Mexican American	12.09 (7.41)	0.07 (1.13)	12.02 (7.69)	
Other Hispanic	7.62 (4.67)	0.12 (1.82)	7.50 (4.80)	
Other	7.82 (4.79)	0.29 (4.29)	7.53 (4.82)	
Marital status, n (in millions), %				0.537
Married/Living with a partner	106.63 (65.35)	4.38 (64.30)	102.24 (65.39)	
Never married/Other	56.54 (34.65)	2.43 (35.70)	54.11 (34.61)	
Poverty income ratio, n (in millions), %				<0.001
≤1.3	32.30 (19.80)	1.78 (26.13)	30.52 (19.52)	
1.3–3.5	58.81 (36.04)	2.45 (36.00)	56.35 (36.04)	
>3.5	72.06 (44.16)	2.58 (37.88)	69.48 (44.44)	
Educational level, n (in millions), %				<0.001
Less than high school	30.12 (18.46)	1.88 (27.66)	28.24 (18.06)	
High school or equivalent	40.95 (25.10)	1.83 (26.89)	39.12 (25.02)	
Above high school	92.09 (56.44)	3.10 (45.45)	88.99 (56.92)	
Smoking status, n (in millions), %				<0.001
Never	83.39 (51.11)	1.11 (16.33)	82.28 (52.62)	
Former	41.21 (25.25)	3.22 (47.30)	37.98 (24.29)	
Current	38.57 (23.64)	2.48 (36.37)	36.09 (23.08)	
Drinking status, n (in millions), %				<0.001
Never	18.52 (11.35)	0.43 (6.44)	18.08 (11.56)	
Former	27.42 (16.81)	2.13 (31.32)	25.29 (16.18)	
Current	117.23 (71.84)	4.24 (62.24)	112.98 (72.26)	
Body mass index, Mean (SD), kg/m <sup>2</sup>	28.43 (6.51)	28.40 (6.72)	28.43 (6.50)	0.923
<b>Disease status</b>				
Cardiovascular disease, n (in millions), %	14.06 (8.62)	1.75 (25.76)	12.30 (7.87)	<0.001
Hypertension, n (in millions), %	59.10 (36.22)	3.87 (56.88)	55.22 (35.32)	<0.001
Diabetes, n (in millions), %	18.20 (11.15)	1.27 (18.65)	16.92 (10.83)	<0.001
<b>Biochemical indicators</b>				
Segmented neutrophils number, Mean (SD), 1000cells/μL	4.30(1.65)	4.67(1.83)	4.28(1.64)	<0.001
Eosinophils number, Median (IQR), 1000cells/μL	0.20 (0.10, 0.30)	0.20 (0.10, 0.30)	0.20 (0.10, 0.30)	<0.001
Lymphocyte number, Median (IQR), 1000cells/μL	2.00 (1.60, 2.50)	1.90 (1.50, 2.40)	2.00 (1.60, 2.50)	<0.001
Monocyte number, Median (IQR), 1000cells/μL	0.56(0.19)	0.56(0.21)	0.56(0.19)	0.002
Basophils number, Median (IQR), 1000cells/μL	0.00(0.00,0.10)	0.00(0.00,0.10)	0.00(0.00,0.10)	0.016
Red blood cell count, Mean (SD), million cells/μL	4.73(0.49)	4.68(0.49)	4.73(0.49)	0.007
Platelet count, Mean (SD), 1000cells/μL	265.49(67.82)	269.52(75.86)	265.32(67.44)	0.157
C-reactive protein, Median (IQR), mg/L	2.10(0.80,4.8)	2.80(1.2,6.7)	2.00(0.80,4.7)	<0.001

**Abbreviations:** NHANES, National Health and Nutrition Examination Survey; SD, standard deviation; IQR, interquartile range.

Moreover, when ln-transformed CLR was categorized into tertiles, the associations with COPD were consistent with the trends observed in the continuous analyses. Compared to individuals in tertile 1(T1), those in T3 exhibited a higher risk of COPD (OR, 1.33; 95% CI, 1.02–1.73;  $P=0.038$ ; Table 2, model 5). Furthermore, in all models, the risk of COPD progressively increased with each higher tertile of ln-transformed CLR (all  $P$  for trend  $<0.05$ ).

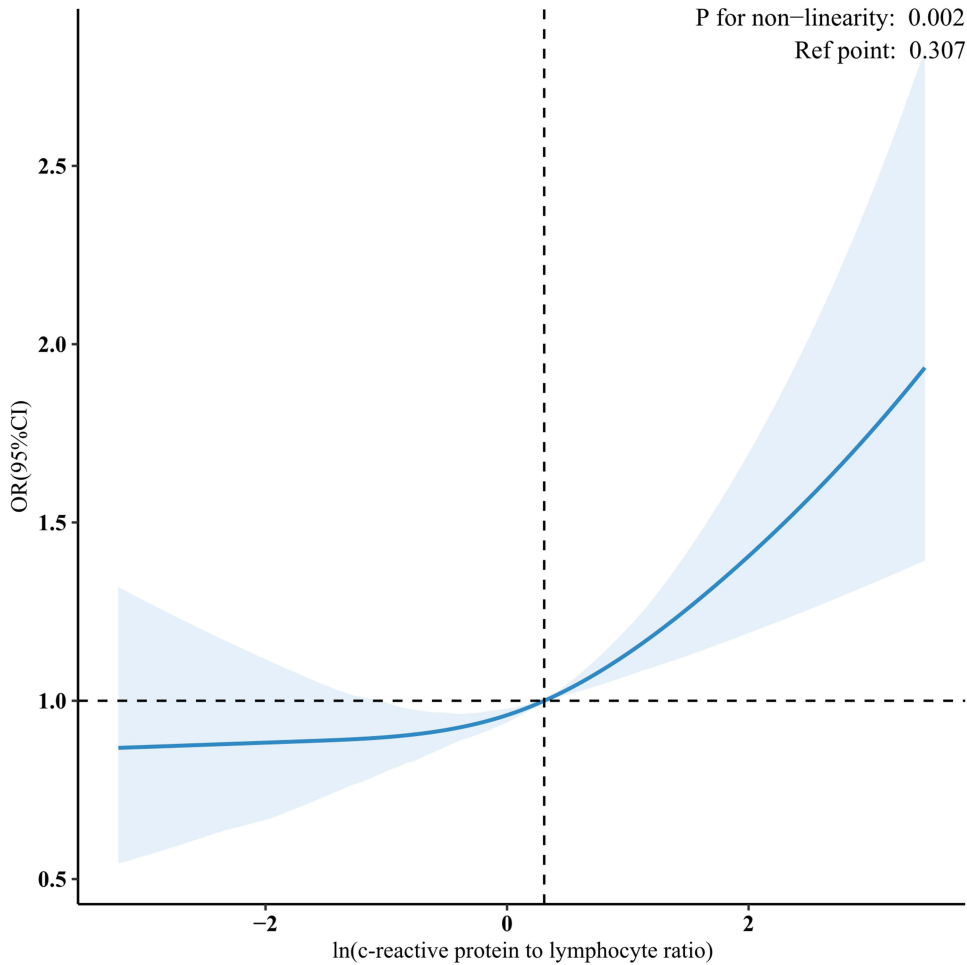
**Table 2** Association Between Ln Transformed C-Reactive Protein to Lymphocyte Ratio and Chronic Obstructive Pulmonary Disease

	Model 1		Model 2		Model 3		Model 4		Model 5	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
CLR ln transformed	1.29 (1.21–1.38)	<0.001	1.21 (1.12–1.32)	<0.001	1.18 (1.08–1.29)	<0.001	1.17 (1.07–1.28)	<0.001	1.14 (1.04–1.25)	0.005
CLR ln transformed, Tertiles										
T1	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
T2	1.38 (1.11–1.70)	0.003	1.14 (0.91–1.43)	0.254	1.07 (0.84–1.36)	0.569	1.06(0.84–1.35)	0.615	1.03 (0.81–1.30)	0.820
T3	1.94 (1.57–2.40)	<0.001	1.60 (1.26–2.04)	<0.001	1.44 (1.11–1.88)	0.007	1.42(1.09–1.85)	0.010	1.33 (1.02–1.73)	0.038
Trend test		<0.001		<0.001		0.006		0.008		0.032

**Notes:** Model 1 was crude model; Model 2 was adjusted for NHANES cycle, age, sex, race/ethnicity; Model 3 was adjusted for Model 2+ marital status, poverty income ratio, educational level, smoking status, drinking status, body mass index; Model 4 was adjusted for Model 3+ cardiovascular disease, hypertension, diabetes; Model 5 was adjusted for Model 4+segmented neutrophils number, platelet count, eosinophils number, monocyte number, basophils number, red blood cell count.

**Abbreviations:** CLR, C-reactive protein to lymphocyte ratio; OR, odds ratio; CI, confidence interval; Ref, reference; NHANES, National Health and Nutrition Examination Survey.

Accordingly, RCS demonstrated a nonlinear connection between ln-transformed CLR and COPD (P for non-linearity=0.002) (Figure 2). When ln-transformed CLR was  $\geq 0.307$ , the adjusted OR was 1.18 (95% CI, 1.01–1.38; P=0.030). No association was observed between ln-transformed CLR and COPD in individuals with ln-transformed CLR  $<0.307$  (P=0.700) (Table 3).



**Figure 2** Weighted restricted cubic spline curve describing the dose-response relationship between ln-transformed C-reactive protein to lymphocyte ratio and chronic obstructive pulmonary disease.

**Notes:** Adjusted for NHANES cycle, age, sex, race/ethnicity, educational level, marital status, drinking status, smoking status, poverty income ratio, body mass index, cardiovascular disease, hypertension, diabetes, segmented neutrophils number, platelet count, eosinophils number, monocyte number, basophils number, red blood cell count. Only 99% of the data is displayed.

**Abbreviations:** OR, odds ratio; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey.

**Table 3** Threshold Effect Analysis of the Relationship of Ln-Transformed C-Reactive Protein to Lymphocyte Ratio with Chronic Obstructive Pulmonary Disease

CLR In Transformed	Adjusted Model*	
	OR (95% CI)	p-value
<0.307	1.03 (0.87–1.23)	0.700
≥0.307	1.18 (1.01–1.38)	0.030

**Notes:** \*Weighted analysis, adjusted for NHANES cycle, age, sex, race/ethnicity, marital status, poverty income ratio, educational level, smoking status, drinking status, body mass index, cardiovascular disease, hypertension, diabetes, segmented neutrophils number, platelet count, eosinophils number, monocyte number, basophils number, red blood cell count. Only 99% of the data is displayed.

**Abbreviations:** CLR, C-reactive protein to lymphocyte ratio; OR, odds ratio; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey.

## Subgroup Analyses

To assess potential variations in the relationship between ln-transformed CLR and COPD, a stratified analysis was conducted across different subgroups. No significant interactions were observed in any subgroup (Figure 3).

## Sensitivity Analysis

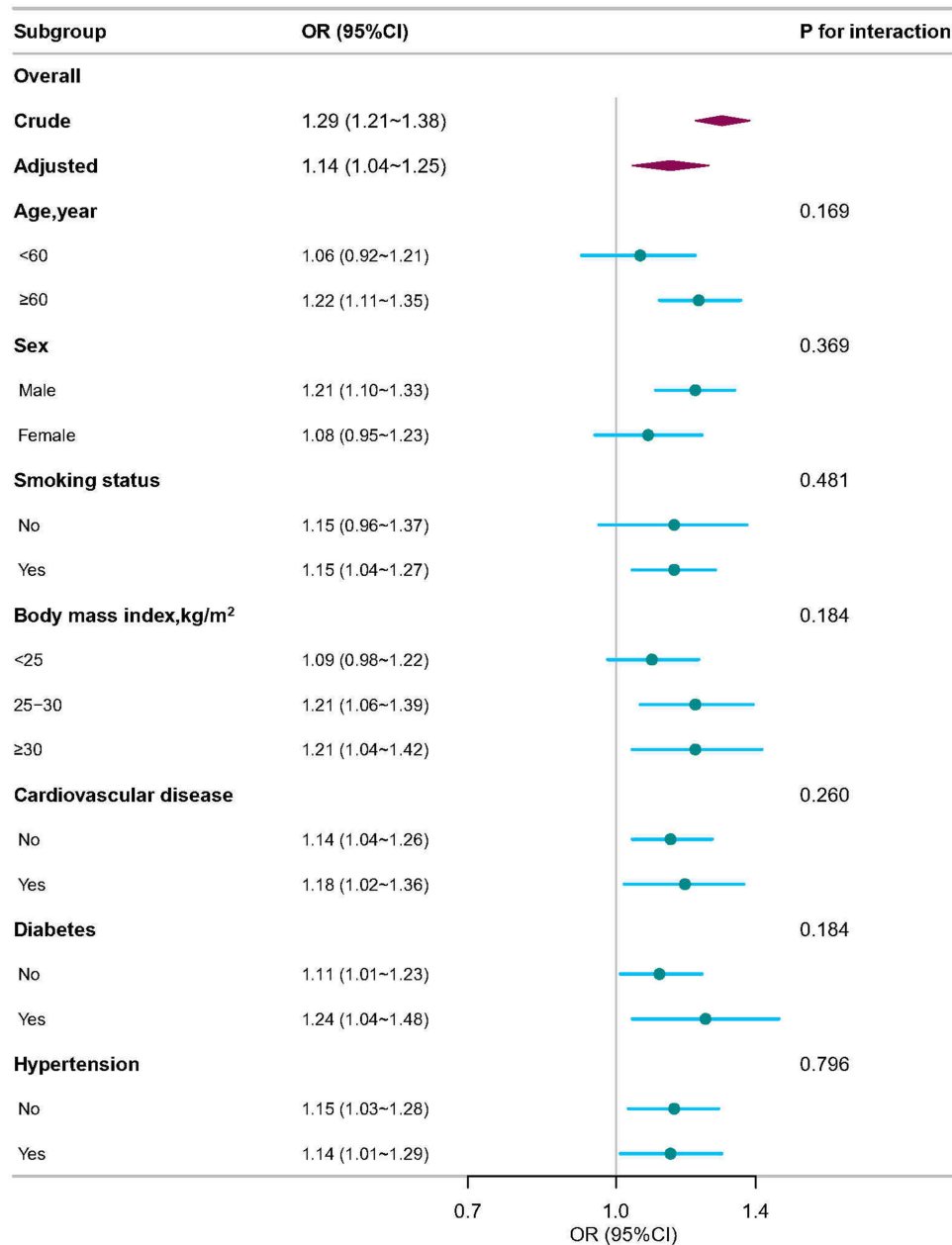
Multiple imputation was applied in the sensitivity analysis to handle missing data. Among the 27649 participants, 1211 (4.4%) were diagnosed with COPD. The association between ln-transformed CLR and COPD remained consistent. After controlling for the potential confounders, there was a 17% increase in COPD risk for each 1-unit increase in ln transformed CLR (95% CI, 1.10–1.23;  $P < 0.001$ ; Table 4). The adjusted OR for ln-transformed CLR and COPD in T3 was 1.43 when compared to individuals in T1 (95% CI, 1.20–1.72,  $P < 0.001$ ) (Table 4).

## Discussion

Based on a nationally representative population of US adults from NHANES, this study identified a positive association between CLR and COPD after controlling for multiple covariates. Sensitivity and subgroup analyses further validated the stability of these findings. Additionally, an inverse L-shaped relationship and threshold effect between CLR and the risk of COPD offered new insights into their complex interaction.

CRP is an acute-phase protein primarily synthesized by hepatocytes.<sup>11</sup> Recent studies have shown a significant link between higher CRP levels and decreased lung function, as well as an increased risk of COPD.<sup>25–27</sup> Lymphocytes are essential components of the immune system, activated in response to the entry of pathogens into the human body. A longitudinal cohort study showed that smokers with COPD had lower blood lymphocyte counts than those without COPD (1.8 vs 2.3 1000cells/ $\mu$ L;  $p < 0.001$ ) and that declining lymphocytes were associated with worse outcomes.<sup>28</sup> Another retrospective cohort study confirmed that lymphocyte levels dramatically decreased in patients with COPD compared to healthy volunteers.<sup>29</sup> Some biomarkers derived from peripheral blood lymphocyte count, including the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, have been reported as predictive factors for COPD progression and outcomes.<sup>1,30,31</sup> Considering these findings, the CLR, defined as the ratio of CRP to the lymphocyte count, may serve as a novel biomarker for the progression of COPD. The investigation revealed a notable association between elevated CLR levels and an increased risk of COPD. This link persisted even after accounting for various potential confounding factors. Additionally, we further analyzed the dose-response relationship between CLR and COPD risk and identified a threshold effect. The risk of COPD only begins to increase when CLR reaches a certain level.

CLR can effectively reflect the systemic inflammatory and immune status. This perspective may help elucidate the mechanisms of the relationship between CLR and the risk of COPD. Long-term chronic inflammation and oxidative stress can damage the structure and function of lung tissues.<sup>24</sup> CRP, a commonly used marker for systemic inflammation,



**Figure 3** Subgroup analyses for the association of ln-transformed C-reactive protein to lymphocyte ratio and chronic obstructive pulmonary disease. **Notes:** The subgroups were defined based on sex (male versus female), age (20–60 years versus ≥60 years), body mass index (<25 versus 25–30 or ≥30 kg/m<sup>2</sup>), smoking status (non-smokers versus smokers), cardiovascular disease (yes versus no), hypertension (yes versus no), and diabetes (yes versus no). “Crude” was unadjusted model. “Adjusted” was the full adjusted model. Except for the stratification component itself, each stratification factor was adjusted for all other variables (NHANES cycle, age, sex, race/ethnicity, educational level, marital status, drinking status, smoking status, poverty income ratio, body mass index, cardiovascular disease, hypertension, diabetes, segmented neutrophils number, platelet count, eosinophils number, monocyte number, basophils number, red blood cell count). **Abbreviations:** OR, odds ratio; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey.

may also be involved in regulating lung function.<sup>32</sup> Additionally, impaired immune function is a significant contributor to COPD development.<sup>33</sup> The number of peripheral blood lymphocytes can indicate the host’s cytotoxic immune response and overall health.<sup>17</sup> Lymphocytes produce cytotoxic perforins and granzyme B, which can induce cell death and apoptosis, key features of emphysema pathology.<sup>33</sup>

The strengths of our investigation include providing new evidence regarding the association between CLR and the risk of COPD. The study population was thoroughly defined and relatively homogeneous, derived from a large, nationally representative sample of US adults. This method enabled effective adjustment for confounders and minimized their influence on the results. Due to their affordability and ubiquity, routine blood tests can be conducted in virtually

**Table 4** Association Between Ln Transformed CLR and Chronic Obstructive Pulmonary Disease After Multiple Imputations of Missing Data Among Participants in the NHANES 1999–2010 Cycles

	Unweighted Participants		Crude Model		Adjusted Model	
	Total	Event (%)	OR (95% CI)	p-value	OR (95% CI)	p-value
CLR ln transformed	27649	1211(4.4)	1.31 (1.26–1.37)	<0.001	1.17 (1.10–1.23)	<0.001
CLR ln transformed, Tertiles						
T1	9213	275(3.0)	1 (Ref)		1 (Ref)	
T2	9210	382(4.1)	1.41 (1.20–1.65)	<0.001	1.12 (0.93–1.34)	0.225
T3	9226	554(6.0)	2.08 (1.79–2.41)	<0.001	1.43 (1.20–1.72)	<0.001
Trend test				<0.001		<0.001

**Notes:** Crude model: unadjusted. Adjusted model: adjusted for NHANES cycle, age, sex, race/ethnicity, marital status, poverty income ratio, educational level, smoking status, drinking status, body mass index, cardiovascular disease, hypertension, diabetes, segmented neutrophils number, platelet count, eosinophils number, monocyte number, basophils number, red blood cell count.

**Abbreviations:** CLR, C-reactive protein to lymphocyte ratio; OR, odds ratio; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey.

every healthcare environment. The detection of biomarkers could enhance early, tailored interventions, improve the allocation of available medical resources, and ultimately lower disease prevalence. Our findings could assist healthcare providers in formulating monitoring and treatment strategies for patients.

However, there are several limitations that should be considered. Firstly, the retrospective design restricts the capacity to completely control for confounding bias and determine causal relationships. Secondly, considering the characteristics of the NHANES database, we relied on criteria like self-reported data to indicate COPD diagnosis, which may be susceptible to reporting bias. Thirdly, levels of CRP and lymphocytes may be affected by various factors, including immune status and recent acute infections, which were not fully controlled for in this study. Moreover, Additionally, despite the application of regression models, subgroup analyses, and sensitivity analyses, unmeasured or unrecognized confounding factors cannot be ruled out. Longitudinal studies in the future are crucial for establishing causality and investigating the mechanisms that underlie the connection between CLR and COPD.

## Conclusions

Our research identified a strong link between CLR levels and the risk of COPD, with higher CLR levels correlating with an increased risk of the disease. These results indicated that CLR may be a useful biomarker for evaluating COPD risk.

## Abbreviations

COPD, Chronic obstructive pulmonary disease; CLR, C-reactive protein to lymphocyte ratio; OR, odds ratio; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; NCHS, the National Center for Health Statistics; CRP, C-reactive protein; MEC, the Mobile Examination Center; BMI, body mass index; PIR, poverty income ratio; CVD, cardiovascular disease; SD, standard deviation; IQR, interquartile range; SDMVSTRA, masked variance pseudo-stratum; SDMVPSU, masked variance pseudo-cluster; WTMEC2YR, full sample 2-year MEC exam weight; WTMEC4YR, full sample 4-year MEC exam weight.

## Data Sharing Statement

The datasets used and analyzed in the present study are accessible through the NHANES repository at <https://wwwn.cdc.gov/nchs/nhanes/default.aspx>.

## Ethics Approval and Informed Consent

The NHANES protocol received approval from the NCHS Research Ethics Review Board. Informed consent was obtained from all participants before their inclusion in the study. In addition, the Medical Ethics Committee of Beijing Luhe Hospital affiliated with Capital Medical University has approved this study and waived informed consent. The ethical number was 2025-LHKY-029-01.

## 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

There is no funding to report.

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Paliogiannis P, Fois AG, Sotgia S, et al. Neutrophil to lymphocyte ratio and clinical outcomes in COPD: recent evidence and future perspectives. *Eur Respir Rev*. 2018;27(147):170113. doi:10.1183/16000617.0113-2017
2. Murgia N, Gambelunghe A. Occupational COPD—The most under-recognized occupational lung disease? *Respirol Carlton Vic*. 2022;27(6):399. doi:10.1111/resp.14272
3. Collaborators G 2019 D and I. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet Lond Engl*. 2020;396(10258):1204. doi:10.1016/S0140-6736(20)30925-9
4. Benjamin JT, Plosa EJ, Sucre JM, et al. Neutrophilic inflammation during lung development disrupts elastin assembly and predisposes adult mice to COPD. *J Clin Invest*. 2021;131(1):e139481,139481. doi:10.1172/JCI139481
5. Barnes PJ. Cellular and molecular mechanisms of asthma and COPD. *Clin Sci Lond Engl* 1979. 2017;131(13):1541–1558. doi:10.1042/CS20160487
6. Hirota N, Martin JG. Mechanisms of airway remodeling. *Chest*. 2013;144(3):1026–1032. doi:10.1378/chest.12-3073
7. Richmond BW, Du RH, Han W, et al. Bacterial-derived neutrophilic inflammation drives lung remodeling in a mouse model of chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol*. 2018;58(6):736–744. doi:10.1165/rcmb.2017-0329OC
8. Wang Y, Xu J, Meng Y, Adcock IM, Yao X. Role of inflammatory cells in airway remodeling in COPD. *Int J Chron Obstruct Pulmon Dis*. 2018;13:3341–3348. doi:10.2147/COPD.S176122
9. Cao Z, Wu T, Fang Y, et al. Dissecting causal relationships between immune cells, plasma metabolites, and COPD: a mediating Mendelian randomization study. *Front Immunol*. 2024;15:1406234. doi:10.3389/fimmu.2024.1406234
10. Villaseñor-Altamirano AB, Jain D, Jeong Y, et al. Activation of CD8+ T cells in chronic obstructive pulmonary disease lung. *Am J Respir Crit Care Med*. 2023;208(11):1177–1195. doi:10.1164/rccm.202305-0924OC
11. Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. *Front Immunol*. 2018;9:754. doi:10.3389/fimmu.2018.00754
12. Cui Z, Wang L, Li H, Feng M. Study on immune status alterations in patients with sepsis. *Int Immunopharmacol*. 2023;118:110048. doi:10.1016/j.intimp.2023.110048
13. Caramori G, Casolari P, Barczyk A, Durham AL, Di Stefano A, Adcock I. COPD immunopathology. *Semin Immunopathol*. 2016;38(4):497–515. doi:10.1007/s00281-016-0561-5
14. Cillóniz C, Torres A, Garcia-Vidal C, et al. The value of C-reactive protein-to-lymphocyte ratio in predicting the severity of SARS-CoV-2 pneumonia. *Arch Bronconeumol*. 2021;57:79–82. doi:10.1016/j.arbres.2020.07.038
15. He L, Xie H, Du Y, Xie X, Zhang Y. The relationship between C-reactive protein to lymphocyte ratio and the prevalence of myocardial infarction in US adults: a cross-sectional study. *Heliyon*. 2023;9(7):e17776. doi:10.1016/j.heliyon.2023.e17776
16. Shi W, Jiang Y, Tian H, et al. C-reactive protein-to-albumin ratio (CAR) and C-reactive protein-to-lymphocyte ratio (CLR) are valuable inflammatory biomarker combination for the accurate prediction of periprosthetic joint infection. *Infect Drug Resist*. 2023;16:477–486. doi:10.2147/IDR.S398958
17. Fan Z, Luo G, Gong Y, et al. Prognostic value of the C-reactive protein/lymphocyte ratio in pancreatic cancer. *Ann Surg Oncol*. 2020;27(10):4017–4025. doi:10.1245/s10434-020-08301-3
18. Huang CY, Wu SC, Yen YH, Yang JCS, Hsu SY, Hsieh CH. Assessing the predictive utility of the C-reactive protein-to-lymphocyte ratio for mortality in isolated traumatic brain injury: a single-center retrospective analysis. *Diagnostics*. 2024;14(18):2065. doi:10.3390/diagnostics14182065
19. Tian TL, Zhi TY, Xie ML, Jiang YL, Qu XK. Dietary inflammatory index and all-cause mortality in adults with COPD: a prospective cohort study from the NHANES 1999–2018. *Front Nutr*. 2024;11:1421450. doi:10.3389/fnut.2024.1421450
20. Zhang Q, Xiao S, Jiao X, Shen Y. The triglyceride-glucose index is a predictor for cardiovascular and all-cause mortality in CVD patients with diabetes or pre-diabetes: evidence from NHANES 2001–2018. *Cardiovasc Diabetol*. 2023;22(1):279. doi:10.1186/s12933-023-02030-z
21. Wu D, Qu C, Huang P, et al. Water intake and handgrip strength in US adults: a cross-sectional study based on NHANES 2011–2014 data. *Nutrients*. 2023;15(20):4477. doi:10.3390/nu15204477
22. Liu H, Wang D, Wu F, Dong Z, Yu S. Association between inflammatory potential of diet and self-reported severe headache or migraine: a cross-sectional study of the national health and nutrition examination survey. *Nutr Burbank Los Angel Cty Calif*. 2023;113:112098. doi:10.1016/j.nut.2023.112098

23. Johnson CL, Paulose-Ram R, Ogden CL, et al. National health and nutrition examination survey: analytic guidelines, 1999-2010. *Vital Health Stat* 2. **2013**;(161):1–24.
24. Cai C, Zeng W, Wang H, Ren S. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR) as biomarkers in diagnosis evaluation of acute exacerbation of chronic obstructive pulmonary disease: a retrospective, observational study. *Int J Chron Obstruct Pulmon Dis*. **2024**;19:933–943. doi:10.2147/COPD.S452444
25. Hancox RJ, Poulton R, Greene JM, et al. Systemic inflammation and lung function in young adults. *Thorax*. **2007**;62(12):1064. doi:10.1136/thx.2006.076877
26. Olafsdóttir IS, Gíslason T, Thjódleifsson B, et al. Gender differences in the association between C-reactive protein, lung function impairment, and COPD. *Int J Chron Obstruct Pulmon Dis*. **2007**;2(4):635–642.
27. Bolton CE, Schumacher W, Cockcroft JR, et al. The CRP genotype, serum levels and lung function in men: the Caerphilly prospective study. *Clin Sci Lond Engl* 1979. **2011**;120(8):347–355. doi:10.1042/CS20100504
28. Semenzato U, Biondini D, Bazzan E, et al. Low-blood lymphocyte number and lymphocyte decline as key factors in COPD outcomes: a longitudinal cohort study. *Respir Int Rev Thorac Dis*. **2021**;100(7):618–630. doi:10.1159/000515180
29. Liao QQ, Mo YJ, Zhu KW, et al. Platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and eosinophil-to-lymphocyte ratio (ELR) as biomarkers in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). *Int J Chron Obstruct Pulmon Dis*. **2024**;19:501–518. doi:10.2147/COPD.S447519
30. Zinellu A, Zinellu E, Mangoni AA, et al. Clinical significance of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in acute exacerbations of COPD: present and future. *Eur Respir Rev Off J Eur Respir Soc*. **2022**;31(166):220095. doi:10.1183/16000617.0095-2022
31. Paliogiannis P, Fois AG, Sotgia S, et al. The neutrophil-to-lymphocyte ratio as a marker of chronic obstructive pulmonary disease and its exacerbations: a systematic review and meta-analysis. *Eur J Clin Invest*. **2018**;48(8):e12984. doi:10.1111/eci.12984
32. Agassandian M, Shurin GV, Ma Y, Shurin MR. C-reactive protein and lung diseases. *Int J Biochem Cell Biol*. **2014**;53:77–88. doi:10.1016/j.biocel.2014.05.016
33. Nurwidya F, Damayanti T, Yunus F. The role of innate and adaptive immune cells in the immunopathogenesis of chronic obstructive pulmonary disease. *Tuberc Respir Dis*. **2016**;79(1):5–13. doi:10.4046/trd.2016.79.1.5

## International Journal of Chronic Obstructive Pulmonary Disease

### Publish your work in this journal

The International Journal of COPD is an international, peer-reviewed journal of therapeutics and pharmacology focusing on concise rapid reporting of clinical studies and reviews in COPD. Special focus is given to the pathophysiological processes underlying the disease, intervention programs, patient focused education, and self management protocols. This journal is indexed on PubMed Central, MedLine and CAS. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-chronic-obstructive-pulmonary-disease-journal>

**Dovepress**  
Taylor & Francis Group