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ORIGINAL RESEARCH

Association Between Neutrophil to Lymphocyte Ratio/Serum Albumin Ratio and Chronic Obstructive Pulmonary Disease: Results from NHANES 1999-2018

Congfeng Li[1], Ting Ao[2], Yingxiu Huang[2], Lin Ding[1], Peng Zhen[2], Ming Hu[2], Jinxiang Wang[1]

[1]Department of Pulmonary and Critical Care Medicine, Beijing Luhe Hospital, Capital Medical University, Beijing, People's Republic of China; [2]Department of Infectious Disease, Beijing Luhe Hospital, Capital Medical University, Beijing, People's Republic of China

Correspondence: Jinxiang Wang, Department of Pulmonary and Critical Care Medicine, Beijing Luhe Hospital, Capital Medical University, No. 82, Xinhua South Road, Tongzhou District, Beijing, 101100, People's Republic of China, Tel +86 13911469017, Email wangjx0090@sina.com

Background: The neutrophil-to-lymphocyte ratio (NLR) and serum albumin (ALB) are associated with the development and progression of chronic obstructive pulmonary disease (COPD). However, the relationship between NLR/ALB and COPD remains to be fully elucidated.

Objective: The primary objective of this study was to investigate the potential correlation between NLR/ALB and COPD, with the aim of identifying a potential biomarker that could serve as a rapid assessment for COPD.

Methods: We performed a retrospective analysis involving 39,055 participants extracted from the National Health and Nutrition Examination Survey (NHANES) dataset, which covered the period from 1999 to 2018. We utilized weighted multivariable logistic regression models to evaluate the association between NLR/ALB and COPD. Additionally, a restricted cubic spline (RCS) model was applied to investigate the potential non-linear relationship between NLR/ALB and the risk of COPD.

Results: Weighted multivariate logistic regression revealed a significant link between ln-transformed NLR/ALB and heightened COPD risk [odds ratio (OR): 1.35, 95% confidence interval (CI): 1.17–1.55; P<0.001)]. When ln-transformed NLR/ALB was converted into categorial variables (quartiles, Q), compared to the first quartile (Q1) of ln-transformed NLR/ALB, COPD risk for the greatest Q4 group was significantly higher. Meanwhile, a nonlinear association between ln-transformed NLR/ALB was observed. Subgroup and sensitivity analyses further validated the robustness and consistency of these findings.

Conclusion: Elevated NLR/ALB is associated with an increased risk of COPD, showing nonlinear patterns and threshold effects. NLR/ALB may serve as a potential biomarker for the occurrence of COPD.

Keywords: neutrophil to lymphocyte ratio/serum albumin ratio, chronic obstructive pulmonary disease, inflammation, national health and nutrition examination survey

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a prevalent chronic respiratory disorder characterized by progressive pulmonary tissue damage and irreversible airflow limitation, representing a critical public health burden with high health care costs due to frequent hospitalizations, loss of productivity, and disability.[1,2] Approximately 4% of the global population was affected by COPD, and this proportion can exceed 10% among individuals aged 40 years and above.[3,4] Per the 2019 Global Burden of Disease Study, COPD ranks as the third most common cause of mortality in the elderly population worldwide, exerting a significant impact on health and economic resources for both individuals and the broader society.[5] Given its rising prevalence and substantial morbidity burden, COPD prevention and management strategies require urgent optimization to mitigate its growing socioeconomic impact.

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COPD is a complex pathophysiological disorder characterized by systemic inflammation, which drives the destruction of airway and lung parenchyma, ultimately leading to airflow limitation. Inflammatory cells, including neutrophils and lymphocytes, play a pivotal role in the inflammatory cascade of COPD.[6] The Neutrophil to Lymphocyte Ratio (NLR), a crucial marker of inflammatory status, has been significantly correlated with poor prognosis of stable COPD, exacerbations, lung function decline, hospitalization risk, and mortality in COPD.[7,8] Albumin (ALB), a clinical biomarker of malnutrition, is also linked to adverse outcomes in patients with chronic respiratory diseases.[9,10] NLR/ALB, as an emerging marker for immune and nutritional status assessment, was initially described by Zhao et al to mitigate the potential bias associated with the nutritional and immune profiles of cancer patients.[11] A previous study based on the Medical information Mart for intensive care IV (MIMIC-IV) database indicated that an elevated NLR/ALB ratio correlates with increased all-cause mortality among COPD patients.[12] However, the relationship between NLR/ALB and COPD risk is not well established. Considering the inflammation's critical role in COPD, further research is needed to clarify this association between NLR/ALB and the risk of COPD among adults in the United States through a cross-section design.

Materials and Methods

Data Source and Study Population

The National Health and Nutrition Examination Survey (NHANES) dataset, administered by the Centers for Disease Control and Prevention (CDC), evaluates the nutritional and health status of both children and adults across the United States, including those not residing in institutions, through a nationally representative program. NHANES utilizes a multistage, stratified probability sampling design to gather extensive data via physical examinations, standardized surveys, and lab tests. This comprehensive database includes a broad spectrum of information such as chronic disease prevalence, demographic features, lifestyle habits, environmental influences and laboratory tests performed at mobile examination centers. Biennial data releases ensure timeliness and maintain national representativeness. The data are publicly available and can be accessed through the NHANES website (https://www.cdc.gov/nchs/nhanes/). The study protocols were approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board, and written informed consent was obtained from all participants. For detailed information on protocols and survey methods, please visit the website at https://www.cdc.gov/.

This study complies with the Ethical Review Methods for Life Science and Medical Research Involving Human Beings, satisfying the exemption under Article 32 based on the following criteria: (1) the exclusive use of publicly accessible, legally obtained data from NHANES, which inherently involves no interference or disruption to public behavior as it constitutes secondary analysis of pre-existing, de-identified datasets; (2) the analysis of strictly anonymized (de-identified) information, as all NHANES public-use data undergo rigorous de-identification procedures prior to release. The Medical Ethics Committee of Beijing Luhe Hospital, Capital Medical University (Ethical Approval No. 2025-LHKY-029-01) reviewed and approved this protocol and granted a waiver of informed consent.

This study, which is cross-sectional in nature, utilized data encompassing the period from January 1999 to December 2018, extracted exclusively from adult participants within the NHANES dataset. During the 1998–2018 cycles, a total of 101,316 participants were initially included in the study. Exclusions were made for individuals under 20 years old (n=46,235). We methodically excluded participants based on specific criteria: pregnancy (N=1547), incomplete data regarding segmented neutrophil count (N=5233), lymphocyte count (N=0), albumin levels (N=828), absence of pertinent COPD survey data (N=3), and other relevant covariates (N=8415), including 12 for hypertension, 4 for cardiovascular disease(CVD), 819 for body mass index(BMI), 3540 for drinking status, 30 for smoking status, 38 for education level, 3535 for poverty income ratio(PIR), 341 for marital status, 71 for Alanine Aminotransferase (ALT), 15 for Aspartate Aminotransferase (AST), 10 for total bilirubin, as shown in Figure 1.

Measurements of NLR/ALB

At the NHANES Mobile Examination Center (MEC), blood samples were gathered from eligible participants and then forwarded to a lab for comprehensive analysis. The NLR/ALB ratio was calculated by dividing the neutrophil count by

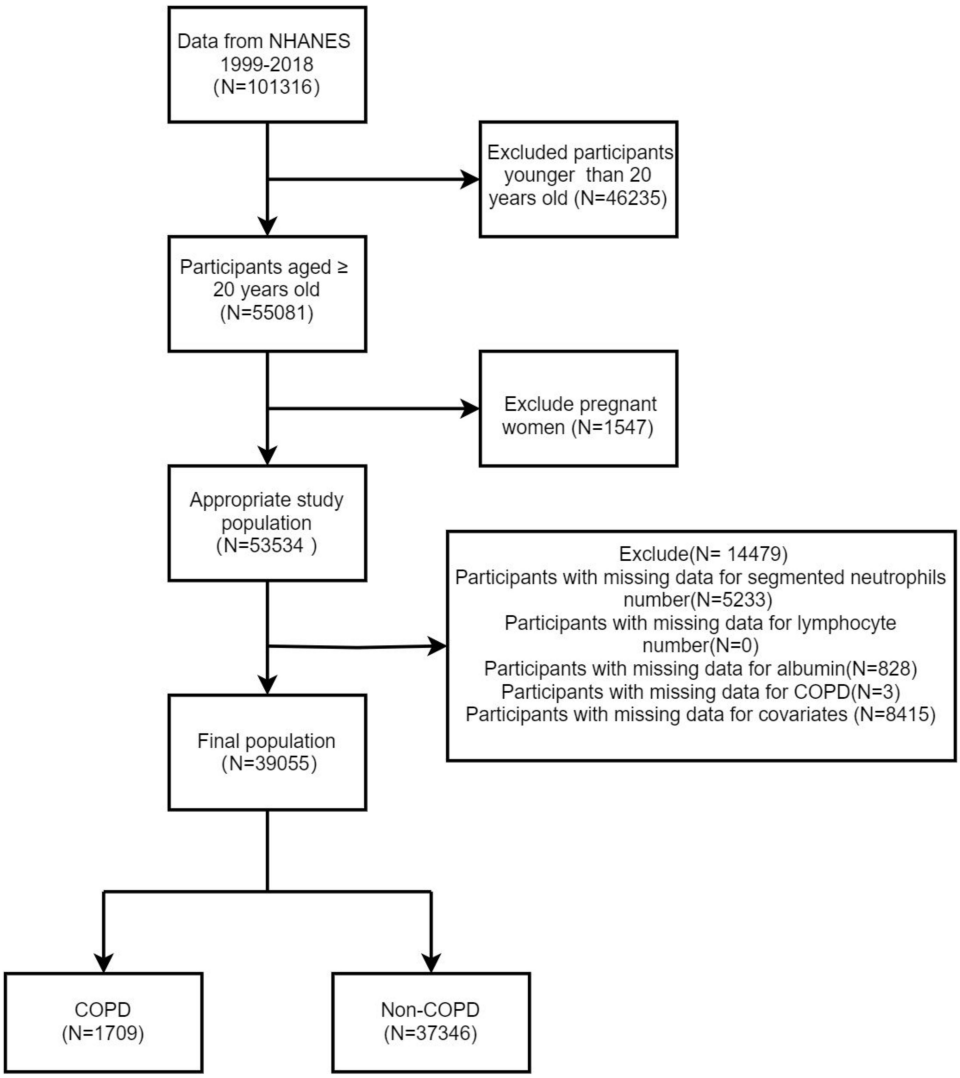

Figure 1 Flowchart of participants selection.
Abbreviations: NHANES, National Health and Nutrition Examination Survey; COPD, chronic obstructive lung disease.

the lymphocyte count—measured in thousands of cells per microliter—and subsequently by the albumin level, measured in grams per liter.[12] NLR itself was calculated simply as the neutrophil count divided by the lymphocyte count (1000cells/μL). To guarantee the reliability of the data, NHANES data collection and laboratory analyses followed federally mandated quality control protocols with documented compliance metrics.

Diagnostic Criteria of COPD

The diagnostic criteria for COPD include meeting at least one of the following conditions: (1) a post-bronchodilator ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) less than 0.70; (2) a physician-confirmed diagnosis of emphysema or confirmation by another healthcare professional; (3) Participants aged ≥40 years with chronic bronchitis and a history of smoking, currently receiving treatment with inhaled corticosteroids, leukotriene modifiers, mast cell stabilizers, or selective PDE-4 inhibitors.[13]

Covariates

Trained investigators collected and documented all data. This study collected data across the following categories: (1) demographic data included sex (female, male), age (years), race/ethnicity (Mexican American, non-Hispanic black, non-

Hispanic white, other Hispanic, others), educational level (above high school, high school or equivalent, less than high school), marital status (living with a partner, never married /married /other), smoking status (never, former, current), drinking status (never, former, current), BMI (kg/m^2), and PIR (1.3, 1.31–3.5, 3.5); (2) comorbidities, such as diabetes, hypertension and CVD; (3) lab tests, including white blood cell count (1000cells/μL), segmented neutrophils count (1000cells/μL), lymphocyte number (1000cells/μL), monocyte count (1000cells/μL), eosinophils count (1000cells/μL), basophils (1000cells/μL), red blood cell (million cells/μL), platelet count (1000cells/μL), ALT (U/L), AST (U/L), total bilirubin (μmol/L) and serum albumin (g/L).

The diagnosis of diabetes was established based on meeting any of the subsequent criteria: random blood glucose levels of 11.1 mmol/L or higher, fasting glucose levels exceeding 7.0 mmol/L, a two-hour post-load plasma glucose concentration exceeding 11.1 mmol/L, glycated hemoglobin (HbA1c) levels above 6.5%, administration of insulin or diabetic medications, or a medical diagnosis of diabetes.[14] Hypertension was diagnosed if there was a systolic blood pressure (SBP)≥140 mmHg, a diastolic blood pressure (DBP)≥90 mmHg, a history of taking medications for high blood pressure, or a prior medical identification of hypertension.[15] The identification of CVD was determined through interviews utilizing a standardized questionnaire that assessed various medical conditions, including inquiries about: Has a doctor or other health expert ever informed you that you have congestive heart failure /coronary heart disease /angina pectoris/myocardial Infarction/stroke? If participants responded "yes" to any of the mentioned questions above, they were considered to have CVD.[16]

Statistical Analysis

In accordance with the analytical guidelines provided by NHANES, this study applied sampling weights and adjusted for complex sampling designs. These included the two-year Mobile Examination Center (MEC) examination weights (WTMEC2YR) and the four-year weights (WTMEC4YR), as well as the masked variance pseudo-stratum (SDMVSTRA) and masked variance pseudo-cluster (SDMVPSU) to address the multistage probability sampling design of the survey.[17] For the survey cycles from 1999 to 2002, the sampling weights were calculated as one-third of the four-year weights (1/3xWTMEC4YR). For the cycles between 2003 and 2018, the weights were adjusted to one-sixth of the two-year weights (1/6xWTMEC2YR).

Drawing from prior literature and clinical experience, we collected a range of demographic and laboratory data from the participants.[18,19] Data for incomplete segmented neutrophils count, lymphocyte number and albumin were excluded. Meanwhile, given the large sample size and low missing data rate (<15%), we excluded cases with missing covariates directly. For continuous variables, we presented the survey-weighted means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on the variable's distribution. Continuous variables were summarized as either survey-weighted mean with standard deviation (SD) or median with interquartile range (IQR), based on their distribution. Categorical variables were expressed as survey-weighted percentages (%) for both the COPD and non-COPD groups. Group differences were assessed using chi-square test, Kruskal–Wallis test, or one-way ANOVA as appropriate.

A natural logarithm (LN) transformation was applied to address the skewness in the NLR/ALB distribution before proceeding with the statistical analysis. When examining the associations with COPD, the NLR/ALB ratio was either categorized into quartiles (Q) or treated as a continuous variable with 1-unit increments of its ln-transformed values. Weighted multivariable logistic regression models were employed to calculate odds ratios (ORs) along with their corresponding 95% confidence intervals (CIs). To adjust for potential confounding factors, four different models were applied: Model 1 was crude model; Model 2 was adjusted for NHANES cycle, sex, age, race/ethnicity, PIR, educational level, marital status, smoking status, drinking status, BMI; Model 3 incorporated adjustments for all variables included in Model 2, in addition to diabetes, hypertension, and cardiovascular disease; Model 4 extended the adjustments to include white blood cell count, monocyte count, basophil count, eosinophil count, platelet count and red blood cell count, Alanine Aminotransferase, Aspartate Aminotransferase and total bilirubin.

To investigate the association between the ln-transformed NLR/ALB and COPD in terms of dose-response, we utilized a restricted cubic spline (RCS) analysis using three knots. Moreover, we conducted a two-piece logistic regression analysis, taking into account all covariates from Model 4, to further assess the association between ln-transformed NLR/ALB and COPD.

We conducted a subgroup analysis based on sex, age (<60 or ≥60 years), BMI (<25, 25–30, or >30 kg/m^2), smoking status (never, former, current), the presence of hypertension, diabetes, and CVD to determine if the association between ln-transformed NLR/ALB and COPD remained consistent across these various subgroups. Additionally, to enhance the reliability of our findings, we conducted multiple imputations for missing data and subsequently performed a sensitivity analysis.

Data analysis was conducted using R (version 4.2.3) (http://www.R-project.org, The R Foundation) and Free Statistics software (version 2.1). All P values were two-tailed, and statistical significance was defined as a P-value less than 0.05.

Results

Demographic and Clinical Characteristics of the Study

This study successfully recruited a total of 39,055 participants from January 1999- December 2018. Of these participants, 1709 were identified diagnosed with COPD, while 37,346 were classified as non-COPD (as depicted in Figure 1 and Table 1S). Table 1 presents the weighted basic characteristics of a sample representing 171.13 million US adults, stratified by the presence or absence of COPD. The weighted analysis revealed that approximately 6.97 million adults were identified with COPD, compared to 164.16 million without the condition. The average age was 47.27 (16.74) years, with 49.4% being male. Notably, individuals in the COPD group were typically older, had lower income, were more likely past drinkers and smokers, and exhibited a greater incidence of diabetes, hypertension and CVD. Additionally, when compared to individuals without COPD, participants with COPD exhibited higher counts of white blood cells, segmented neutrophils, monocytes, and basophils.

Relationship Between NLR/ALB and COPD

Given the skewed distribution of NLR/ALB, we normalized its distribution by applying a ln-transformation. Table 2 presents the relationship of the ln-transformed NLR/ALB with COPD across four models. Model 1 (unadjusted) revealed that ln-transformed NLR/ALB was positively linked to COPD risk (OR 2.23, 95% CI 1.96–2.52, P < 0.001) when treated as a continuous variable. The statistical significance of this association was maintained following adjustment for multiple

Table 1 Weighted Baseline Characteristics of Participants in the NHANES 1999–2018 Cycles

Patient Characteristic	Total	Without COPD	With COPD	*p*-value
Weighted population, n (in millions)	171.13	164.16	6.97	
Demographic information				
Age, Mean (SD), years	47.27 (16.74)	46.71 (16.65)	60.53 (12.80)	<0.001
Sex, n (in millions), %				
Male	84.61 (49.4)	81.07 (49.4)	35.43 (50.8)	0.436
Female	86.52 (50.6)	83.08 (50.6)	34.31 (49.2)	
Race (%)				
Non-Hispanic White	121.16 (70.8)	115.32 (70.2)	5.84 (83.8)	<0.001
Non-Hispanic Black	17.13 (10.0)	16.69 (10.2)	4.42 (6.3)	
Mexican American	13.23 (7.7)	13.13 (8.0)	0.10 (1.4)	
Other Hispanic	8.85 (5.2)	8.70 (5.3)	0.15 (2.2)	
Others	10.76 (6.3)	10.32 (6.3)	0.44 (6.3)	
Marry (%)				
Married/Living with a partner	110.19 (64.4)	105.78 (64.4)	44.03 (63.1)	0.393
Never married/Other	60.94 (35.6)	58.37 (35.6)	2.57 (36.9)	

(*Continued*)

Table 1 (Continued).

Patient Characteristic	Total	Without COPD	With COPD	*p*-value
PIR (%)				
≤1.3	35.24 (20.6)	33.34 (20.3)	1.90 (27.3)	<0.001
13–3.5	61.35 (35.8)	58.74 (35.8)	2.61 (37.4)	
>3.5	74.54 (43.6)	72.08 (43.9)	2.46 (35.3)	
Education (%)				
Less than high school	27.39 (16.0)	25.70 (15.7)	1.69 (24.2)	<0.001
High school or equivalent	41.19 (24.1)	39.36 (24.0)	1.83 (26.3)	
Above high school	102.55 (59.9)	99.10 (60.4)	3.45 (49.5)	
Smoke (%)				
Never	91.05 (53.2)	89.91 (54.8)	1.14 (16.4)	<0.001
Former	43.35 (25.3)	40.05 (24.4)	3.31 (47.4)	
Current	36.73 (21.5)	34.20 (20.8)	2.53 (36.2)	
Drink (%)				
Never	18.36 (10.7)	17.94 (10.9)	0.42 (6.0)	<0.001
Former	27.27 (15.9)	25.17 (15.3)	2.10 (30.1)	
Current	125.50 (73.3)	121.04 (73.7)	4.46 (63.9)	
Body Mass Index, Mean (SD), $kg.m^2$	28.82 (6.73)	28.80 (6.70)	29.28 (7.38)	0.079
Disease status				
Cardiovascular disease, n (in millions), %	14.95 (8.7)	12.97 (7.9)	1.98 (28.4)	<0.001
Hypertension, n (in millions), %	64.06 (37.4)	59.93 (36.5)	4.13 (59.3)	<0.001
Diabetes, n (in millions), %	22.03 (12.9)	20.39 (12.4)	1.63 (23.4)	<0.001
Biochemical indicators				
White blood cell count, Median (IQR), 1000 cells/μL	6.90 (5.70, 8.40)	6.90 (5.70, 8.40)	7.40 (6.10, 8.90)	<0.001
Lymphocyte number, Median (IQR), 1000 cells/μL	2.00 (1.60, 2.50)	2.00 (1.60, 2.50)	2.00 (1.50, 2.50)	0.001
Monocyte number, Median (IQR), 1000cells/μL	0.50 (0.40, 0.70)	0.50 (0.40, 0.70)	0.60 (0.50, 0.70)	<0.001
Segmented neutrophils number, Median (IQR), 1000cells/μL	4.00 (3.20, 5.10)	4.00 (3.10, 5.10)	4.50 (3.50, 5.60)	<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
Basophils number, Median (IQR), 1000cells/μL	0.00 (0.00, 0.10)	0.00 (0.00, 0.10)	0.10 (0.00, 0.10)	<0.001
Red blood cell count, Mean (SD), million cells/μL	4.72 (0.48)	4.72 (0.48)	4.65 (0.50)	0.001
Platelet count, Mean (SD), 1000cells/μL	253.72 (65.80)	253.58 (65.50)	257.20 (72.39)	0.097
Alanine Aminotransferase, Median (IQR), U/L	21.00 (16.00, 29.00)	21.00 (16.00, 29.00)	20.00 (16.00, 27.00)	0.07
Aspartate Aminotransferase, Median (IQR), U/L	23.00 (19.00, 27.00)	23.00 (19.00, 27.00)	23.00 (20.00, 27.00)	0.054
Total bilirubin, Median (IQR), μmol/L	10.26 (8.55, 13.68)	10.26 (8.55, 13.68)	10.26 (8.55, 13.68)	0.156
Albumin, Mean (SD), g/L	42.86 (3.31)	42.91 (3.30)	41.79 (3.37)	<0.001
NLR/ALB, Median (IQR)	0.05 (0.04, 0.06)	0.05 (0.03, 0.06)	0.05 (0.04, 0.08)	<0.001
NLR/ALB ln transformed, Mean (SD)	−3.07 (0.45)	−2.91 (0.45)	−2.91 (0.52)	<0.001

Abbreviations: NHANES, National Health and Nutrition Examination Survey; SD, standard deviation; IQR, interquartile range; PIR, Poverty income ratio; NLR/ALB, neutrophil-lymphocyte ratio/albumin ratio.

confounding factors. In the fully adjusted Model 4, each 1-unit increase in ln-transformed NLR/ALB was associated with a 35% higher risk of COPD (OR, 1.35; 95% CI: 1.17–1.55; P < 0.001). Moreover, categorical analysis using ln-transformed NLR/ALB quartiles demonstrated COPD risk associations that were concordant with the continuous variable findings. Participants in the highest quartile (Q4) had a 25% greater COPD risk compared to those in Q1 (adjusted OR 1.25, 95% CI 1.02–1.54; P=0.035; see Model 4 in Table 2). Furthermore, across all models, the risk of COPD escalated

Table 2 Association Between Ln Transformed NLR/ALB and Chronic Obstructive Pulmonary Disease

	Model 1		Model 2		Model 3		Model 4	
	OR (95CI)	***p*-value**	**OR (95CI)**	***p*-value**	**OR (95CI)**	***p*-value**	**OR (95CI)**	***p*-value**
NLR/ALB ln transformed	2.23(1.96–2.52)	<0.001	1.35(1.19–1.53)		1.31(1.16–1.49)	<0.001	1.35(1.17–1.55)	<0.001
NLR/ALB ln transformed, Quartiles								
Q1	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q2	1.12(0.9–1.41)	0.308	0.98(0.77–1.25)	0.894	0.99(0.78–1.26)	0.944	0.98(0.78–1.25)	0.889
Q3	1.32(1.07–1.64)	0.011	0.99(0.78–1.25)	0.921	0.99(0.78–1.26)	0.931	0.98(0.77–1.24)	0.868
Q4	2.23(1.87–2.72)	<0.001	1.26(1.03–1.55)	0.028	1.24(1.01–1.52)	0.041	1.25(1.02–1.54)	0.035
Trend test		<0.001		0.008		0.012		0.016

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

Abbreviations: NLR/ALB, Neutrophil to Lymphocyte Ratio/Serum Albumin ratio; OR, odds ratio; CI, confidence interval; Ref, reference; NHANES, National Health and Nutrition Examination Survey; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase.

with each ascending quartile of ln-transformed NLR/ALB (all P for trend < 0.05). Accordingly, nonlinear modeling using RCS showed a significant curvilinear association between ln-transformed NLR/ALB and COPD (P-nonlinear <0.001) (Figure 2). A significant threshold effect was observed at ln-transformed NLR/ALB = −2.93, with adjusted OR = 2.20 (95% CI 1.65–2.92, P<0.01) above this value but no association below it (P=0.81) (Table 3).

Subgroup Analyses

To investigate the potential interaction effects, we analyzed the ln-transformed NLR/ALB-COPD association across clinically relevant subgroups. Significant interactions were identified in the CVD subgroup (see detailed in Figure 3).

Sensitivity Analysis

In the sensitivity analysis of our study, multiple imputation was employed to address missing data. Of the 47470 participants, 2003 (4.2%) were identified as having COPD. We observed a consistent, statistically significant relationship between ln-transformed NLR/ALB and COPD risk across all analytical models. Following adjustment for potential confounding variables, we observed a 29% elevation in COPD risk per 1-unit increase in ln-transformed NLR/ALB (OR 1.29, 95% CI 1.14–1.42, P<0.001; Table 2S). Compared to Q1, Q4 participants showed a 25% higher COPD risk (adjusted OR 1.25, 95% CI 1.03–1.51, P=0.016) (Table 2S).

Discussion

Drawing upon the nationally representative NHANES database of US adults population, our research revealed a significant positive correlation between NLR/ALB and the risk of COPD after adjusting for a range of potential confounding factors. Additionally, subgroup and sensitivity analyses and further validation procedures were employed to confirm the robustness of these findings. Notably, the study also uncovered a non-linear association and threshold effect between NLR/ALB and COPD risk, providing novel insights into the intricate interplay between these variables. Nevertheless, the robustness of this finding necessitates additional validation.

COPD is a complex respiratory syndrome involving progressive airflow limitation that is not fully reversible, accompanied by chronic inflammation of the airways and lung parenchyma. NLR, as a biomarker of systemic inflammation and immune activation, has been widely used to assess the inflammatory status and predict the prognosis of patients with COPD.[20,21] Studies have demonstrated that NLR is significantly linked to the degree of inflammation, mortality and disease severity in patients with COPD[22] and other inflammatory diseases and malignancies.[23] Additionally, NLR has also been found to be associated with comorbidities in COPD, such as obstructive sleep apnea (OSA) and asthma.[24,25] ALB, as a key indicator of nutritional status and inflammation regulation, holds dual significance in patients with COPD. Low levels of albumin not only reflect malnutrition but are also associated with systemic

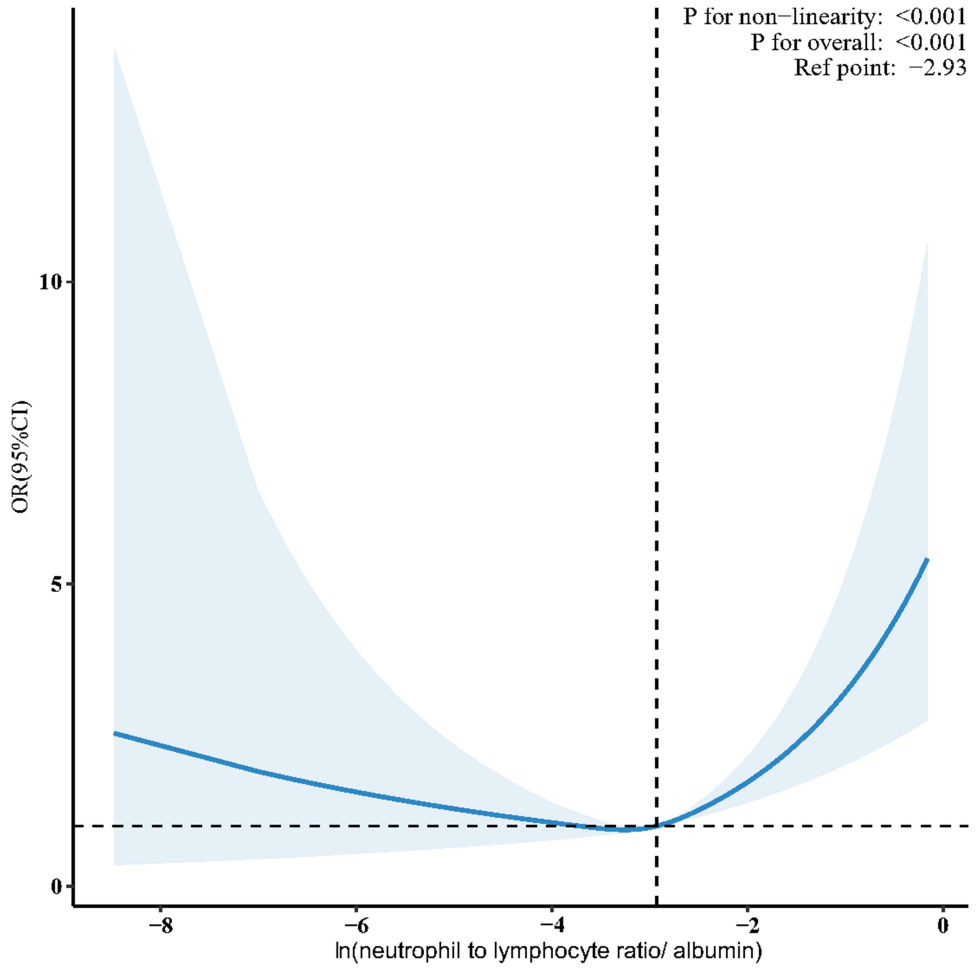

Figure 2 Weighted restricted cubic spline curve describing the dose-response relationship between ln-transformed NLR/ALB and chronic.
Notes: Adjusted for NHANES cycle, age, sex, race/ethnicity, marital status, poverty income ratio, educational level, smoking status, drinking status, body mass index, cardiovascular disease, hypertension, diabetes, white blood cell, platelet count, eosinophils number, monocyte number, basophils number, red blood cell count, ALT, AST, total bilirubin.
Abbreviations: NHANES, National Health and Nutrition Examination Survey; NLR/ALB, neutrophil-lymphocyte ratio/albumin ratio; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase.

inflammation and oxidative stress, independently predicting mortality risk in COPD patients as well as the prognosis of critically ill patients.[9,26] Studies have shown that decreased albumin levels are significantly correlated with reduced muscle mass, decline in lung function, and increased risk of acute exacerbations in COPD patients.[9,27,28] Although NLR and ALB have been extensively studied individually, research exploring their combined effects remains relatively limited. Studies have demonstrated that high levels of NLR/ALB are associated with poor prognosis in both esophageal squamous cell carcinoma and gastric cancer patients.[11,29] Moreover, similar findings have been reported in retrospective studies, where individuals with esophageal squamous cell carcinoma (ESCC) and elevated NLR/pre-Alb experienced poorer overall survival outcomes relative to those with lower ratios.[30] Previous research has examined the correlation between NLR/ALB and COPD prognosis. For instance, Liu et al focused on the predictive value of NLR/ALB for all-cause mortality in critically ill COPD patients, using data from the MIMIC database, which includes ICU patients. Their study demonstrated that NLR/ALB significantly predicts mortality in this subgroup.[12] In contrast, our study investigates the correlation between NLR/ALB and the presence of COPD in a broader patient population, using data from the NHANES database, which is nationally representative. Our findings reveal a significant correlation between NLR/ALB and COPD occurrence, offering new insights and complementing Liu et al's work. This research provides valuable references for future studies and clinical practice.

Table 3 Threshold Effect Analysis of the Relationship of Ln Transformed NLR/ALB with Chronic Obstructive Pulmonary Disease

NLR/ALB ln Transformed	Adjusted Model[#]	
	OR 95% CI	*p*-value
<-2.93	0.96(0.72–1.30)	0.81
≥-2.93	2.20(1.65–2.92)	<0.01

Notes: [#]Weighted analysis: NHANES cycle, age, sex, race/ethnicity, marital status, poverty income ratio, educational level, smoking status, drinking status, body mass index, cardiovascular disease, hypertension, diabetes, white blood cell, platelet count, eosinophils number, monocyte number, basophils number, red blood cell count, ALT, AST, total bilirubin. Only 99% of the data is displayed.

Abbreviations: NLR/ALB, Neutrophil to Lymphocyte Ratio/Serum Albumin ratio; OR, odds ratio; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase.

Aligning with the evidence that excessive inflammatory responses and immune dysfunction are critical in the development and progression of COPD, our study identified elevated neutrophil levels in patients with COPD. Studies reveal that 70% of COPD patients have heightened inflammatory markers, driven significantly by neutrophils in the lung's innate immune response. These neutrophils are associated with diminished lung function and alveolar destruction, and they can induce inflammatory lung injury in both neonates and adults.[31–34] In COPD, chronic inflammation results in the accumulation of neutrophils and lymphocytes, which release inflammatory mediators that cause irreversible tissue damage and a decline in lung function.[35] Elevated neutrophil counts are correlated with disease severity, whereas lymphopenia, which serves as a stress marker, is linked to poor outcomes and compromised immune defense.[36–39] The potential mechanism may involve increased neutrophils driving systemic and respiratory chronic inflammation, whereas decreased lymphocytes result in weakened immune defense and reduced disease resistance.[20] NLR/ALB, reflecting the balance between neutrophils and lymphocytes, may indicate the degree of systemic inflammation and immune compromise. Elevated NLR suggests heightened neutrophil-driven inflammation, while low ALB levels may signal malnutrition and further impaired immune function. Together, these factors exacerbate the inflammatory cascade, contributing to COPD pathogenesis. Thus, the NLR/ALB ratio could serve as a biomarker reflecting the complex interplay of inflammation and immune dysfunction in COPD. The specific mechanisms require further investigation in the future. Meanwhile, in the subgroup analysis, we found interaction in the CVD subgroup, the underlying mechanisms may require further investigation.

Our analysis identified a nonlinear association between the ln-transformed NLR/ALB, revealing a critical threshold effect indicative of disrupted immune-homeostatic balance. Mechanistically, this inflection point demarcates a pathophysiological transition wherein systemic inflammation overrides endogenous protective mechanisms. The underlying derangement involves two synergistic pathways: (1) NLR elevation, driven by neutrophilic hyperactivation (direct tissue injury via proteases/ROS) and lymphopenia (impaired immunoregulation), can lead to a decline in lung function through several mechanisms: excessive activation of NE causing collagen degradation, sustained activation of NF-κB driving chronic inflammation, and enhancement of mucus secretion and airway remodeling.[40,41] and (2) Hypoalbuminemia, which is associated with higher inflammatory responses and attenuates antioxidant, anti-inflammatory, and endothelial-stabilizing capacities.[42,43] Beyond the threshold, these perturbations initiate a feedforward cycle—exacerbating oxidative stress, unchecked protease activity, and compromised tissue repair—culminating in accelerated lung injury. The identification of this inflection point may provide a clinically actionable threshold for predicting accelerated pulmonary deterioration in COPD, where systemic inflammation-immune dysregulation overwhelms pulmonary compensatory capacity.

Our study offers several notable strengths. First, our study provides new insights into the relationship between NLR/ALB and COPD risk by integrating both inflammatory and nutritional factors, offering a more comprehensive and

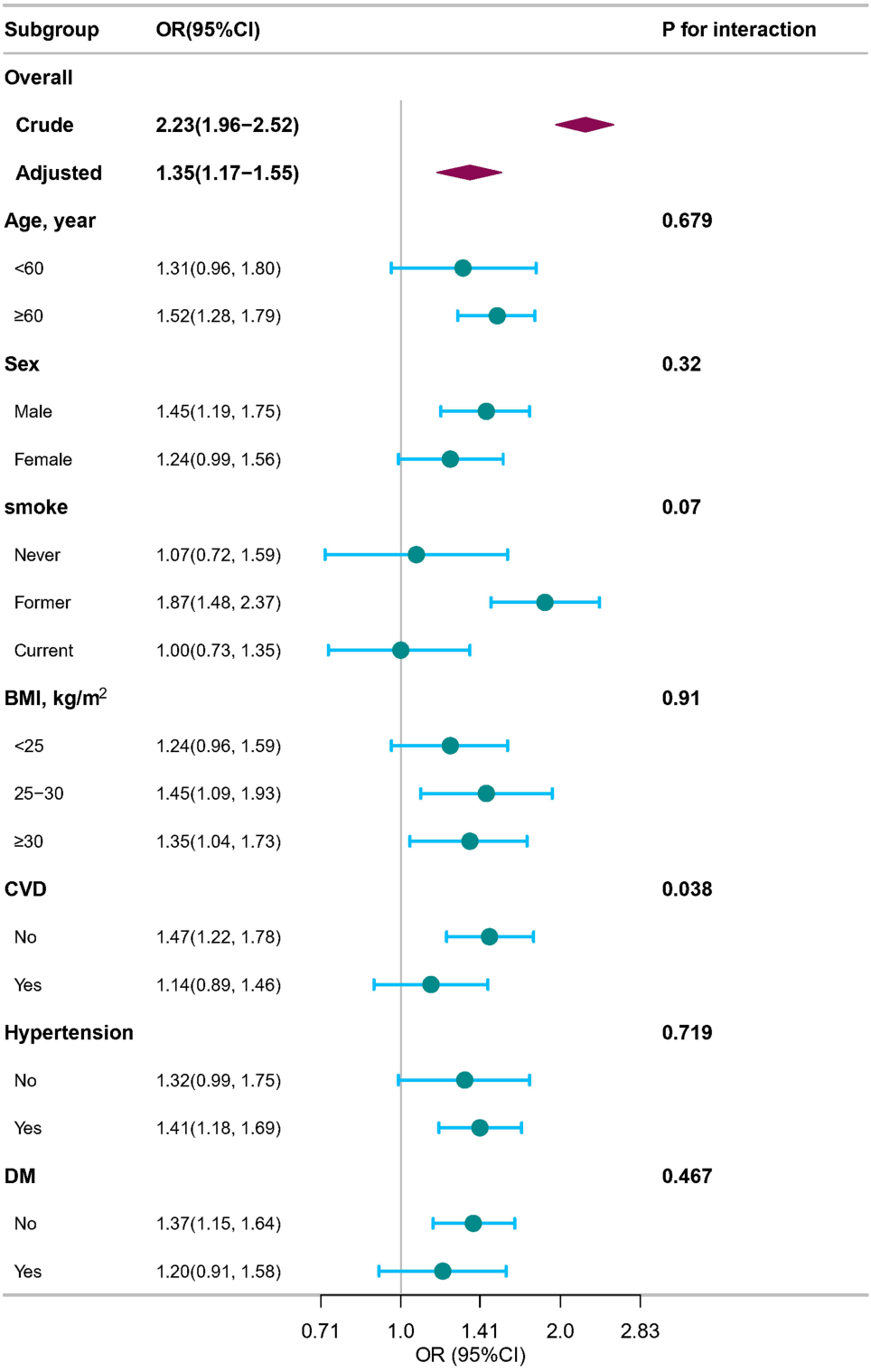

Figure 3 Subgroup analyses for the association of ln-transformed NLR/ALB and chronic obstructive pulmonary disease.
Notes: Adjusted for NHANES cycle, age, sex, race/ethnicity, marital status, poverty income ratio, educational level, smoking status, drinking status, body mass index, cardiovascular disease, hypertension, diabetes, white blood cell, platelet count, eosinophils number, monocyte number, basophils number, red blood cell count, ALT, AST, total bilirubin.
Abbreviations: NHANES, National Health and Nutrition Examination Survey; NLR/ALB, neutrophil-lymphocyte ratio/albumin ratio; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase.

holistic view of the disease pathophysiology and potentially reflecting the overall health status of patients more accurately. Second, our study leveraged a substantial and nationally representative cohort of American adults, meticulously selected to ensure homogeneity. This approach facilitated a robust control for potential confounders, thereby bolstering the reliability of our results. Third, NLR/ALB serves as an accessible and economical marker, easily obtained from routine blood tests across a wide range of healthcare environments. Its ease of access and low cost make it a practical tool for widespread application. Furthermore, the identification of these biomarkers can lead to timely and tailored interventions, enhance the allocation of medical resources, and may contribute to a decrease in the overall incidence of the disease. Finally, our findings could assist healthcare providers in devising more efficient surveillance and therapeutic approaches for COPD patients.

Nonetheless, several limitations of our study warrant consideration. First, the levels of NLR and albumin, measured at a single time point in this study, can be influenced by various factors such as a patient's immune status and nutritional status, as well as being affected by recent acute infections. These potential influences were not fully accounted for in our analysis. Second, given the nature of the NHANES database, cross-sectional studies can only show associations and cannot establish causality, our identification of COPD diagnoses was based on a comprehensive set of criteria that included survey questionnaires, spirometry tests, and confirmation by healthcare professionals, along with consideration of patients within a certain age group based on their symptoms and treatment history. However, this method might have limitations, such as potential reporting bias from subjective assessments and survey responses, and insufficient sensitivity for detecting early-stage disease. These limitations could impact the accuracy and consistency of case identification, thus affecting the reliability of our findings. Third, despite our comprehensive methodological approach, which included the use of regression analysis, subgroup and sensitivity analyses to mitigate potential biases, we recognize that the potential for unmeasured or unrecognized confounding factors persists. Such factors might still influence our results and interpretations, thus necessitating a cautious interpretation of our findings. Fourth, a limitation of our study is the lack of analysis regarding racial or ethnic differences in the association between NLR/ALB and COPD. Given the significant health disparities in COPD prevalence and outcomes, this may limit our ability to fully understand the impact of these factors on different populations. Future prospective research is necessary to confirm the causal relationship and to investigate the mechanisms by which NLR/ALB is associated with COPD.

To address these limitations and further support the implications of our research for future exploration, we suggest the following potential avenues for future studies: First, longitudinal studies that measure NLR and ALB levels at multiple time points could provide a more dynamic understanding of their relationship with COPD progression. This approach would help account for temporal variations and better capture the influence of acute infections and other transient factors. Second, validation studies using independent cohorts with detailed clinical data, including early-stage COPD cases, could enhance the accuracy and generalizability of our findings. Third, prospective studies with stringent diagnostic criteria and minimized reporting bias could establish more reliable causal relationships. Lastly, mechanistic studies exploring the underlying pathways linking NLR/ALB to COPD could elucidate the specific biological mechanisms and identify potential therapeutic targets.

Conclusions

Our study demonstrated a robust association between elevated NLR/ALB levels and an increased risk of COPD, suggesting that NLR/ALB may serve as a potential biomarker for assessing the likelihood of developing this condition. This finding highlights the potential for early detection and intervention in COPD management. Elevated NLR/ALB levels may reflect underlying systemic inflammation and immune dysfunction, which are key drivers in the pathogenesis of COPD. Identifying individuals with elevated NLR/ALB could enable targeted interventions to reduce inflammation and improve immune function, potentially slowing disease progression. Future longitudinal studies are needed to further explore whether there is a causal relationship between NLR/ALB and COPD risk.

Abbreviations

COPD, Chronic obstructive pulmonary disease; NLR, neutrophil to lymphocyte ratio; NLR/ALB, neutrophil to lymphocyte ratio/serum albumin; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; CI, confidence

interval; Q, quartile; ALB, albumin; CDC, Centers for Disease Control and Prevention; NCHS, the National Center for Health Statistics; MEC, the Mobile Examination Center; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; PIR, poverty income ratio; BMI, body mass index; CVD, cardiovascular disease; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; WTMEC2YR, full sample 2-year MEC exam weight; WTMEC4YR, full sample 4-year MEC exam weight; SDMVPSU, masked variance pseudo-cluster; SDMVSTRA, masked variance pseudo stratum; SDMVSTRA, masked variance pseudo-stratum; SD, standard deviation; IQR, inter-quartile range; RCS, restricted cubic spline.

Data Sharing Statement

The datasets utilized and examined in this study can be accessed via the NHANES database, available at https://www.cdc.gov/nchs/nhanes/default.aspx.

Ethics Approval and Informed Consent

The study protocol of NHANES was sanctioned by the NCHS Research Ethics Review Board. Consent was provided by all participants prior to their participation in the research. Furthermore, this study was endorsed by the Medical Ethics Committee at Beijing Luhe Hospital, Capital Medical University, and informed consent was exempted. The ethical approval number is 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.

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Disclosure

All authors declare no conflicts of interest in this work.

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