

The Relationship of Lymphocyte to High-Density Lipoprotein Ratio with Pulmonary Function in COPD

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Purpose: This study aimed to explore the relation between lymphocyte to high-density lipoprotein ratio (LHR) and pulmonary function of chronic obstructive pulmonary disease (COPD) patients compared with neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR).

Patients and Methods: In total, 154 participants (n = 77 with COPD and n = 77 without COPD) were recruited. LHR, NLR, PLR, lung function and other data were collected and compared. Pearson's correlation test and the receiver operating characteristics curves were used to compare the utility of LHR, NLR and PLR. Besides, univariate and multivariate logistic regression analyses were conducted.

Results: COPD patients with poorer lung function had a lower LHR level ($P < 0.001$). In low LHR group, more patients underwent greater airflow limitation than the other group ($P = 0.006$). LHR positively correlated with forced expiratory volume in 1 second in percent of the predicted value ($FEV_1\%$) ($r = 0.333$, $P = 0.003$). At a cut-off value of 2.08, the sensitivity and specificity of LHR in predicting $FEV_1\% < 50$ were 93.2% and 55.6%, respectively, with an AUC of 0.770 ($P = 0.001$) better than NLR and PLR. Based on logistic regression analyses, it was proved that LHR was associated with decreased risk of $FEV_1 < 50\%$ predicted in COPD patients (odds ratio = 0.198, 95% CI: 0.048–0.811, $P = 0.024$).

Conclusion: In contrast with NLR and PLR, LHR has higher accuracy for predicting pulmonary function in COPD; lower LHR level is independently associated with poorer pulmonary function.

Keywords: COPD, pulmonary function, lymphocytes, high-density lipoprotein

Introduction

Chronic obstructive pulmonary disease (COPD), a common chronic airway inflammatory disease characterized by persistent respiratory symptoms and airflow limitation, causes heavy social and economic burden owing to its high prevalence and relevant disability rate and mortality.^{1,2} Chronic inflammation predominantly affects the lung parenchyma and peripheral airways and results in largely irreversible and progressive airflow limitation in COPD.³ Inflammation is a complex set of interactions including neutrophils and lymphocytes. Acanfora⁴ observed a negative correlation between relative lymphocyte counts and mortality in elderly patients with severe COPD. It was reported that the neutrophil-lymphocyte ratio (NLR) was a favorable marker of systemic inflammation, acute exacerbation of COPD and mortality.^{5,6} Moreover, the platelet-lymphocyte ratio (PLR) may be a valuable

index of ongoing inflammation and the disease severity of COPD.⁷ Nevertheless, Günay⁸ found no significant differences of NLR among I to IV groups divided according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) and no studies reported the relationship of PLR and GOLD, which imply that a more credible biomarker of pulmonary function needs to be put forward. In addition, serum high-density lipoprotein (HDL) level might associate with COPD. A previous study showed that COPD individuals had a lower level of HDL than healthy controls.⁹ However, Park¹⁰ showed HDL-C levels were elevated in cohort with COPD compared to a reference population without COPD, but it was demonstrated that as the setting of emphysema being established, HDL might have dysfunctional properties and lose protective effect.¹¹ Furthermore, lymphocyte to HDL ratio (LHR), representing both the lymphocyte counts and serum HDL levels, was advocated as a new indicator of inflammation and metabolic syndrome (MetS).¹² However, none of the studies has investigated the potential value of LHR to serve as a biomarker of COPD, despite the fact that COPD is a chronic inflammatory disease.

Therefore, the aim of this cross-sectional study is to explore the relation between the LHR and the pulmonary function of COPD patients and compare the indicative role of LHR on COPD patients' pulmonary function with NLR and PLR.

Patients and Methods

Study Population

Between February 2018 and February 2019, we performed a cross-sectional research on COPD patients. One hundred and thirty-four subjects diagnosed with COPD were enrolled from the respiratory ward of the Third Affiliated Hospital of Wenzhou Medical University, 23 of them with missing data (9 subjects without LHR and 14 subjects without FEV₁%), and 3 of them with outliers were excluded. The inclusion criteria and exclusion criteria of patients were as follows: Inclusion criteria: 1) age more than 40 years; 2) diagnosis of COPD with GOLD ≥ 2 ¹³ as defined in the GOLD guidelines¹ with symptoms of dyspnea, chronic cough, sputum production or wheezing;¹⁴ Exclusion criteria:¹² 1) malignant tumor (n = 3); 2) hepatic insufficiency (n = 1) and renal insufficiency (n = 4); 3) heart diseases (n = 13); 4) autoimmune diseases (n = 2); 5) other lung diseases (n = 8); 31 subjects meeting the exclusion criteria were excluded. Finally, a total of 77 patients

were selected. All subjects with COPD were stratified into severity grades of airflow limitation based on FEV₁ as percent of predicted with cut-offs according to GOLD grades 1–4.^{4,13,15} And 77 age- and sex- matched healthy controls were included as control group who met the same inclusion and exclusion criteria as the COPD patients, except for the diagnosis of COPD.

The study was approved by the Ethics Committee of the Third Affiliated Hospital of Wenzhou Medical University and the registration number of Ethics Committee was YJ20170015. The study was conducted in accordance with the Declaration of Helsinki. All subjects signed a written informed consent form.

Data Collection

Data on age, gender, body mass index (BMI), smoking status and duration of disease were collected by questionnaires. Blood samples were collected to analyze blood routine parameters, blood biochemistry and arterial blood gas. Computable parameters such as LHR, NLR, PLR of COPD patients and healthy controls were calculated. Forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), FEV₁/FVC, FEV₁ in percent of the predicted value (FEV₁%) of COPD patients were recorded as significant indicators of the severity of pulmonary function. What is more, we also collected scales of COPD patients, including St. George's Respiratory Questionnaire (SGRQ)¹⁶ and BODE (BMI, airway obstruction, dyspnoea, severe exacerbations) index (BODE stages 1, 2, 3 and 4 were defined by BODE 0–2, 3–4, 5–6, and 7–10 points, respectively).¹⁷

Diagnostic Criteria of COPD

Patients with COPD were categorized in severity grades 1–4 using spirometry (GOLD 1: FEV₁ $\geq$ 80% predicted; GOLD 2: 50% $\leq$ FEV₁ < 80% predicted; GOLD 3: 30% $\leq$ FEV₁ < 50% predicted; GOLD 4: FEV₁ < 30% predicted).¹⁴

Statistical Analysis

All statistical analysis was performed using SPSS 25.0 (IBM Analytics). Continuous variables of normal distribution were presented as mean $\pm$ standard deviation. The independent sample *t*-test and the Mann–Whitney *U*-test were used to compare the differences of clinical characteristics between COPD patients and healthy controls, low LHR group and high LHR group. The data of patients stratified on the basis of FEV₁% were compared through

one-way analysis of variance (ANOVA) with Bonferroni as post hoc test or Welch's test. Additionally, categorical variables were expressed as counts and percentages, and intergroup comparisons were analyzed through Chi-squared (χ^2) test or Fisher's exact test. Relationships between LHR/NLR/PLR and FEV₁% were evaluated by Pearson's correlation test, while relationship between LHR and BODE index was evaluated by Spearman correlation test. In order to estimate the value of the novel indicator LHR for predicting pulmonary function compared with NLR and PLR, the receiver operating characteristics (ROC) curves were plotted. Propensity score matching (PS matching) (1:1 matching, caliper 0.1) was used to select healthy controls and adjust for imbalance of age, gender and smoking status in COPD patients. We used univariate logistic regression analysis to identify the variables associated with poor pulmonary function. Furthermore, multivariate logistic regression analysis was used to explain the contribution of the LHR in pulmonary function, controlling for confounders with $P < 0.1$ in univariate logistic regression. To make OR estimates more reasonable, LHR was standardized by z-score in logistic regression analyses. Two-sided P values < 0.05 were considered significant in the other analyses.

Results

Baseline Characteristics of the Study Subjects

As shown in [Table S1](#), among the 154 research candidates, 77 were diagnosed as COPD while 77 were age- and sex-matched healthy controls. Our results manifested that, compared with healthy controls, COPD patients had a higher level of neutrophils ($P < 0.001$), NLR ($P < 0.001$), PLR ($P < 0.001$) and a lower level of lymphocytes ($P < 0.001$), HDL ($P < 0.001$). Moreover, we also found that a novel marker LHR was statistically lower in COPD than healthy controls ($P = 0.018$).

To gain a deeper understanding of the relationships between the three indicators above-mentioned and COPD severity of airflow limitation, we categorized 77 patients into three groups according to FEV₁% (T1, FEV₁% ≥ 50 , $n = 18$; T2, $30 \leq \text{FEV}_1\% < 50$, $n = 35$; T3, FEV₁% < 30 , $n = 24$). As shown in [Table 1](#), the differences were insignificant among these three groups in terms of gender, smoking status, white blood cells, neutrophils, platelets, triglycerides, total cholesterol (TC), low-density lipoprotein (LDL), NLR and PLR. However, age, BMI, lymphocytes, especially the LHR descended gradually from T1 to T3 group as FEV₁% decreased ($P = 0.003$, $P = 0.001$, $P = 0.009$, $P < 0.001$,

Table 1 Baseline Characteristics of COPD Patients According to FEV₁%

Clinical Characteristics	FEV ₁ % ≥ 50 (n = 18)	$30 \leq \text{FEV}_1\% < 50$ (n = 35)	FEV ₁ % < 30 (n = 24)	P value
Age (years)	73.39 $\pm$ 10.47	72.34 $\pm$ 7.26	66.54 $\pm$ 6.01	0.003
Male sex, n (%)	13 (72.2)	27 (77.1)	23 (95.8)	0.073
Smoking status				0.285
Never-smoker, n (%)	4 (22.2)	11 (31.4)	2 (8.3)	
Former smoker, n (%)	10 (55.6)	17 (48.6)	16 (66.7)	
Current smoker, n (%)	4 (22.2)	7 (20.0)	6 (25.0)	
BMI (kg/m ²)	23.19 $\pm$ 3.32	21.25 $\pm$ 3.53	19.09 $\pm$ 3.02	0.001
WBC ($\times 10^9$ /L)	7.23 $\pm$ 2.22	6.84 $\pm$ 2.86	7.22 $\pm$ 2.72	0.824
Lymphocytes ($\times 10^9$ /L)	1.93 $\pm$ 0.64	1.46 $\pm$ 0.57	1.43 $\pm$ 0.46	0.009
Neutrophils ($\times 10^9$ /L)	4.56 $\pm$ 1.89	4.73 $\pm$ 2.76	4.99 $\pm$ 2.38	0.849
Platelets ($\times 10^9$ /L)	258.28 $\pm$ 86.87	222.60 $\pm$ 65.49	214.33 $\pm$ 62.10	0.113
Triglycerides (mmol/L)	1.36 $\pm$ 0.79	1.02 $\pm$ 0.43	0.90 $\pm$ 0.36	0.078
TC (mmol/L)	4.32 $\pm$ 0.89	4.29 $\pm$ 0.89	4.33 $\pm$ 0.77	0.981
HDL (mmol/L)	1.01 $\pm$ 0.28	1.09 $\pm$ 0.24	1.22 $\pm$ 0.24	0.028
LDL (mmol/L)	2.63 $\pm$ 0.72	2.63 $\pm$ 0.79	2.63 $\pm$ 0.68	1.000
NLR	2.55 $\pm$ 1.22	4.20 $\pm$ 4.22	4.01 $\pm$ 2.61	0.204
PLR	144.06 $\pm$ 56.60	179.95 $\pm$ 93.77	170.22 $\pm$ 99.57	0.380
LHR	1.98 $\pm$ 0.65	1.40 $\pm$ 0.58	1.25 $\pm$ 0.52	< 0.001

Notes: Data are presented as mean $\pm$ SD unless indicated otherwise.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁%, forced expiratory volume in 1 second in percent of the predicted value; BMI, body mass index; WBC, white blood cells; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LHR, lymphocyte to HDL ratio; SD, standard deviation.

respectively). On the contrary, the HDL level was ascending ($P = 0.028$).

In order to further explore the clinical values of LHR, subjects with COPD were divided into two groups according to the LHR median. In comparison to high LHR group ($LHR \geq 1.42$, $n = 38$), low LHR group ($LHR < 1.42$, $n = 39$) had statistically lower FEV₁, FVC, FEV₁%, platelets, triglycerides and pH levels. Conversely, incidences of higher SGRQ scores ($SGRQ \geq 25$), severer air flow limitation and advanced BODE stage and partial pressure of carbon dioxide in arterial blood (PaCO₂) in low LHR group were observably increased. No other significant differences were found in the rest of the studied parameters. Complete data are described in Table 2.

Comparisons of the LHR, NLR and PLR in COPD

Among COPD patients, we discovered patients with FEV₁% ≥ 50 had a significantly higher level of LHR than patients with $30 \leq FEV_1\% < 50$ ($P = 0.002$) or FEV₁% < 30 ($P < 0.001$). However, there were no differences of NLR nor PLR among each category of pulmonary function (Figure 1A).

Pearson's correlation test illustrated that LHR was positively related to FEV₁% ($r = 0.333$, $P = 0.003$) while NLR and PLR were not (Figure 1B). Afterwards, the ROC curve analysis was performed to evaluate the utility of LHR, NLR and PLR for predicting poor pulmonary function (FEV₁% < 50). The analysis showed that the area under the curve (AUC) values of NLR and PLR were 0.617 (95% CI: 0.478–0.756, $P = 0.137$) and 0.575 (95% CI: 0.425–0.725, $P = 0.339$). In contrast, at a cut-off value of 2.08, the sensitivity and specificity of the LHR in predicting poor pulmonary function were 93.2% and 55.6%, respectively, with an AUC of 0.770 (95% CI: 0.643–0.898, $P = 0.001$) (Figure 1C). It suggested that when it came to the severity of airway obstruction in COPD, LHR was positively associated with pulmonary function and had a higher predictive value compared with NLR and PLR.

Declined LHR Level is Related to Poor Pulmonary Function

Corresponding to above-mentioned analyses, participants with low LHR level had statistically lower FEV₁ ($P = 0.030$), FVC ($P = 0.039$) and notably lower FEV₁% ($P = 0.018$) (Figure 2A). In low LHR group, 87.2% suffered from poor pulmonary function (FEV₁% < 50) while the

Table 2 Baseline Characteristics of COPD Patients According to LHR Median

Clinical Characteristics	LHR < 1.42 (n = 39)	LHR $\geq$ 1.42 (n = 38)	P value
Age (years)	70.10 $\pm$ 7.18	71.47 $\pm$ 9.19	0.467
Male sex, n (%)	34 (87.2)	29 (76.3)	0.217
Smoking status			0.733
Never-smoker, n (%)	6 (15.4)	12 (31.6)	
Former smoker, n (%)	28 (71.8)	15 (39.5)	
Current smoker, n (%)	5 (12.8)	11 (28.9)	
BMI (kg/m ²)	20.47 $\pm$ 3.64	21.60 $\pm$ 3.55	0.175
Duration of disease $\geq$ 5 years, n (%)	23 (59.0)	21 (55.3)	0.742
FEV ₁ (L)	0.82 $\pm$ 0.32	1.02 $\pm$ 0.45	0.030
FVC (L)	1.63 $\pm$ 0.46	1.91 $\pm$ 0.71	0.039
FEV ₁ %	34.58 $\pm$ 14.21	42.22 $\pm$ 13.44	0.018
FEV ₁ /FVC	49.63 $\pm$ 9.23	52.62 $\pm$ 8.18	0.137
SGRQ $\geq$ 25, n (%)	32 (82.1)	23 (60.5)	0.037
Degree of air flow limitation			0.006
FEV ₁ % $\geq$ 50, n (%)	5 (12.8)	13 (34.2)	
30 $\leq$ FEV ₁ % $<$ 50, n (%)	17 (43.6)	18 (47.4)	
FEV ₁ % $<$ 30, n (%)	17 (43.6)	7 (18.4)	
BODE stages			0.042
BODE 1, n (%)	8 (20.5)	13 (34.2)	
BODE 2, n (%)	13 (33.3)	17 (44.7)	
BODE 3, n (%)	12 (30.8)	4 (10.5)	
BODE 4, n (%)	6 (15.4)	4 (10.5)	
WBC ($\times 10^9/L$)	6.94 $\pm$ 2.97	7.16 $\pm$ 2.32	0.717
Neutrophils ($\times 10^9/L$)	5.10 $\pm$ 2.81	4.44 $\pm$ 1.98	0.237
RBC ($\times 10^{12}/L$)	4.33 $\pm$ 0.42	4.24 $\pm$ 0.54	0.377
Hemoglobin (g/L)	130.65 $\pm$ 11.96	129.86 $\pm$ 17.02	0.815
Platelet ($\times 10^9/L$)	209.79 $\pm$ 58.93	247.42 $\pm$ 78.09	0.020
Albumin (g/L)	36.17 $\pm$ 2.87	36.61 $\pm$ 3.32	0.534
Creatinine (μ mol/L)	66.43 $\pm$ 11.66	69.18 $\pm$ 13.31	0.338
Triglycerides (mmol/L)	0.85 $\pm$ 0.33	1.28 $\pm$ 0.62	< 0.001
TC (mmol/L)	4.40 $\pm$ 0.78	4.22 $\pm$ 0.90	0.334
LDL (mmol/L)	2.66 $\pm$ 0.74	2.60 $\pm$ 0.73	0.730
pH value	7.40 $\pm$ 0.03	7.41 $\pm$ 0.02	0.024
PaO ₂ (mmHg)	71.52 $\pm$ 14.78	74.78 $\pm$ 13.97	0.324
PaCO ₂ (mmHg)	47.00 $\pm$ 8.62	42.96 $\pm$ 5.47	0.017
SpO ₂	93.06 $\pm$ 4.05	94.34 $\pm$ 2.76	0.110

Notes: Data are presented as mean $\pm$ SD unless indicated otherwise.

Abbreviations: COPD, chronic obstructive pulmonary disease; LHR, lymphocyte to high-density lipoprotein ratio; BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV₁%, FEV₁ in percent of the predicted value; SGRQ, St. George's Respiratory Questionnaire; BODE, BMI, airway obstruction, dyspnoea, severe exacerbations; WBC, white blood cells; RBC, red blood cells; TC, total cholesterol; LDL, low-density lipoprotein; PaO₂, partial pressure of oxygen in arterial blood; PaCO₂, partial pressure of carbon dioxide in arterial blood; SpO₂, oxygen saturation; SD, standard deviation.

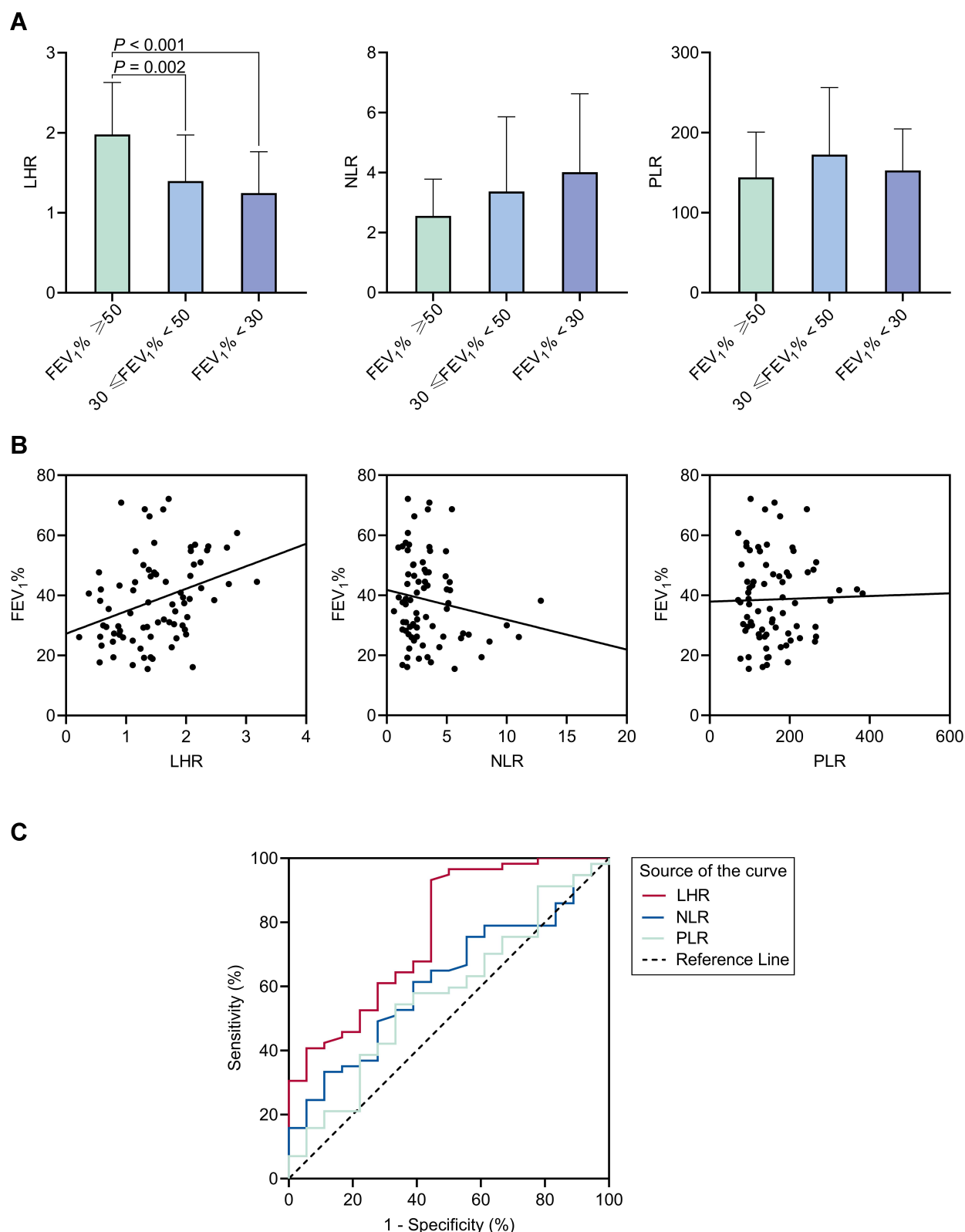


Figure 1 Comparisons of LHR, NLR and PLR in COPD patients. **(A)** LHR, NLR and PLR levels of COPD patients according to FEV₁%. **(B)** Correlations of the LHR, NLR and PLR with FEV₁%. LHR, $r = 0.333$, $P = 0.003$; NLR, $r = -0.161$, $P = 0.169$; and PLR, $r = 0.022$, $P = 0.849$. **(C)** ROC curves of the LHR, NLR and PLR for FEV₁% < 50 of COPD patients. The area under ROC curve (AUC) of LHR: 0.770, 95% CI: 0.643–0.898, $P = 0.001$; AUC of NLR: 0.617, 95% CI: 0.478–0.756, $P = 0.137$; and AUC of PLR: 0.575, 95% CI: 0.425–0.725, $P = 0.339$.

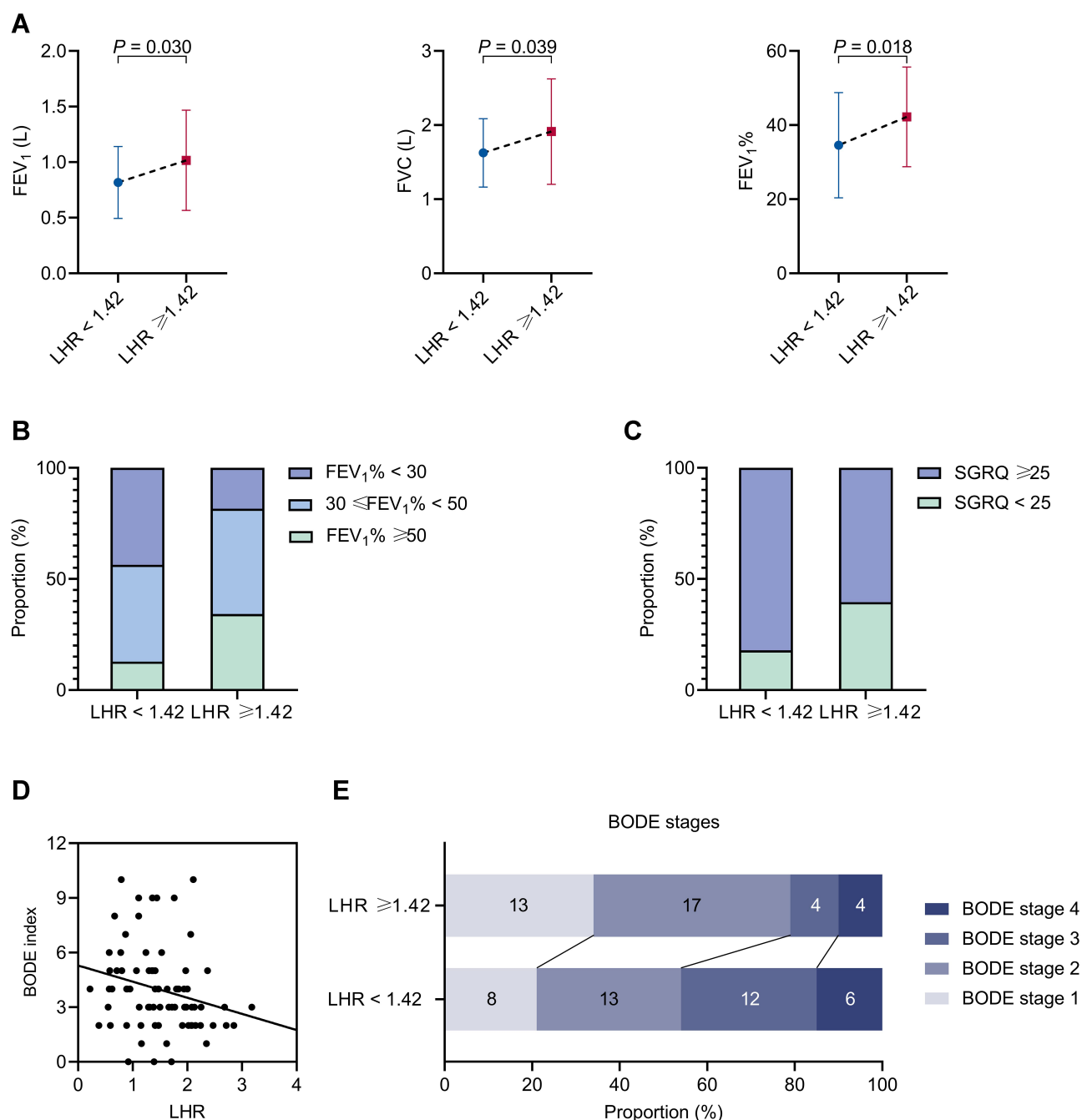


Figure 2 Comparisons of the condition of COPD patients according to the LHR median. **(A)** The FEV₁, FVC and FEV₁% level of COPD patients according to LHR. **(B)** The air flow limitation degree of COPD patients according to LHR. **(C)** The proportion of COPD patients with high SGRQ scores according to LHR. **(D)** Correlations of the BODE index with LHR, $\rho = -0.312, P = 0.006$. **(E)** The BODE stages of COPD patients according to LHR.

proportion fell to 65.8% in high LHR group ($P = 0.006$, Figure 2B). Besides, low LHR group comprised larger proportion of patients with $\text{SGRQ} \geq 25$ in contrast with high LHR group ($P = 0.037$, Figure 2C). Declined LHR level was also linked with advanced BODE index ($\rho = -0.312, P = 0.006$, Figure 2D; $P = 0.042$, Figure 2E). These results implied that reduced LHR levels were

related to disease severity and unfavorable outcomes of COPD.

Further, 33 subjects were selected after PS matching from low LHR group and high LHR group, respectively, to offset the impact of age, sex and smoking status in COPD patients when assessing the influence of LHR on parameters of pulmonary function. It demonstrated a higher

level of FEV₁, FVC, FEV₁% and FEV₁/FVC ($P = 0.003$, $P = 0.009$, $P = 0.005$, $P = 0.021$, respectively) in high LHR group of COPD patients (Table S2).

For the sake of determining the independent factors of pulmonary function, variables were subjected to univariate logistic regression analyses. Consequently, BMI ($P = 0.006$), FEV₁/FVC ($P < 0.001$), PaCO₂ ($P = 0.002$), standardized LHR ($P = 0.001$) were observed to have significant correlations with FEV₁% < 50 (Table 3). To control other potential confounding variables, multivariate logistic regression analyses were performed. In Model 1, nothing was adjusted (odds ratio [OR] = 0.296, 95% CI: 0.145–0.603, $P = 0.001$). After adjusted for age, gender, smoking status, and duration of disease in Model 2, the linkage between standardized LHR and FEV₁% < 50 remained significant (odds ratio [OR] = 0.191, 95% CI: 0.071–0.519, $P = 0.001$). On the basis of Model 2, we also made adjustments for BMI, FEV₁/FVC, creatinine and PaCO₂ in Model 3, and found that one unit increase in standardized LHR would reduce the risk of poor pulmonary function (FEV₁% < 50) by 80.2% (odds ratio [OR] = 0.198, 95% CI: 0.048–0.811, $P = 0.024$). We substantially concluded that LHR is an independent marker of poor pulmonary function and increased LHR is associated with a reduced risk for COPD (Table 4).

Discussion

Our data indicated that lung function deteriorated with reduced LHR generated by low lymphocyte counts and high serum HDL level. It implied the potential correlation between lymphocyte counts or serum HDL level and lung function in COPD patients.

In the present study, lymphocyte counts were higher in COPD patients with FEV₁% greater than 50 comparing with the others. Previous studies regarding lymphocytes and COPD are consistent with our findings. Autophagy has a fundamental role in the degradative pathway of lymphocytes, which plays critical roles in the development and pathogenesis of COPD inflammation.^{18,19} Lower lymphocyte counts were reported in patients with acute exacerbation of COPD than in the stable patients or the healthy controls.²⁰ Acanfora⁴ identified that low relative lymphocyte counts were related to higher mortality in elderly severe COPD patients. Aging and COPD are associated with psychological stress, which leads to a significant increase in systemic cortisol production. Increased cortisol levels secreted by elderly COPD patients can give rise to gradual decrease in relative lymphocyte count.⁴ Furthermore, low lymphocyte counts

Table 3 Univariate Logistic Regression Analyses of Factors for FEV₁% < 50

Variables	OR	95% CI	P value
Gender, female	0.468	0.134–1.637	0.235
Age (years)			
<60	1.000		
60–69	0.333	0.034–3.261	0.345
70–79	0.406	0.044–3.758	0.427
≥80	0.375	0.032–4.369	0.434
Smoking status			
Never-smoker	1.000		
Former smoker	1.015	0.270–3.821	0.982
Current smoker	1.000	0.205–4.879	1.000
BMI	0.795	0.676–0.936	0.006
Duration of disease ≥ 5 years	1.238	0.421–3.639	0.698
FEV ₁ /FVC	0.842	0.771–0.920	< 0.001
WBC	0.967	0.796–1.175	0.736
Neutrophils	1.050	0.835–1.320	0.676
RBC	0.689	0.228–2.081	0.509
Hemoglobin	0.998	0.962–1.035	0.906
Platelets	0.994	0.986–1.002	0.138
Albumin	0.937	0.788–1.114	0.463
Creatinine	0.963	0.923–1.004	0.076
Triglycerides	0.405	0.127–1.298	0.128
TC	0.988	0.526–1.857	0.971
LDL	0.992	0.480–2.051	0.983
pH value	< 0.001	< 0.001–143.197	0.137
PaO ₂	0.987	0.953–1.023	0.468
PaCO ₂	1.303	1.104–1.538	0.002
SpO ₂	0.904	0.756–1.080	0.266
NLR	1.355	0.947–1.938	0.097
PLR	1.005	0.996–1.014	0.279
LHR (standardized)	0.296	0.145–0.603	0.001

Abbreviations: FEV₁%, forced expiratory volume in 1 second in percent of the predicted value; BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; WBC, white blood cells; RBC, red blood cells; TC, total cholesterol; LDL, low-density lipoprotein; PaO₂, partial pressure of oxygen in arterial blood; PaCO₂, partial pressure of carbon dioxide in arterial blood; SpO₂, oxygen saturation; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LHR, lymphocyte to high-density lipoprotein ratio.

might be put down to the impaired immunity. Since lymphocytes are crucial components of immune system, lymphopenia possesses a higher risk of respiratory tract infections, which are the most common causes of COPD exacerbations.¹ Besides, malnutrition could also be responsible. Low lymphocyte counts qualify as a factor associated with nutritional risk²¹ whilst COPD severity is positively correlated with malnutrition.²² A vicious circle produced by neurohumoral activation and the immune

Table 4 Adjusted Odds Ratio (95% CI) of Standardized LHR for FEV₁% < 50

	OR	95% CI	P value
Model 1	0.296	0.145–0.603	0.001
Model 2	0.191	0.071–0.519	0.001
Model 3	0.198	0.048–0.811	0.024

Notes: Model 1 is univariate analysis. Model 2 is adjusted by age; gender; smoking status; and duration of disease. Model 3 is adjusted by age; gender; smoking status; duration of disease; BMI; FEV₁/FVC; creatinine; and PaCO₂.

Abbreviations: LHR, lymphocyte to high-density lipoprotein ratio; FEV₁%, forced expiratory volume in 1 second in percent of the predicted value; BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PaCO₂, partial pressure of carbon dioxide in arterial blood.

system demodulation increasing the secretion of cortisol may be to blame,⁴ as outlined in Figure 3.

There are contradictory results about HDL and COPD. Kaisar²³ revealed that lower serum HDL level exacerbated the lung function in COPD patients, whereas elevated levels of HDL-C were found in cohort with COPD compared to a reference population without COPD.¹⁰ Moreover, Reed²⁴ stated that advanced COPD was associated with increased serum HDL level. Similarly, the inverse correlation between

HDL levels and pulmonary function has been reported recently.²⁵ In our research, serum HDL levels were also elevated in patients with FEV₁% less than 30. This change might be partially attributable to the oral steroid use, which was an independent predictor of increased HDL-C in multivariate modeling.²⁴ As shown in Figure 3, the underlying mechanism of HDL attenuating lung function in COPD patients involves the dual anti-inflammatory and pro-inflammatory nature of HDL,²⁶ COPD states associated with a chronic acute-phase response may trigger HDL to be dysfunctional and pro-inflammatory, thus further deteriorating disease status. Moreover, apolipoprotein M (apoM), as variation of a component of HDL, is elevated gradually with the COPD severity.²⁷ ApoM and HDL are implicated in COPD pathogenesis, especially emphysema, via effecting ceramide, sphingosine-1-phosphate cellular levels and α_1 -antitrypsin.²⁸

Consequently, we speculated that LHR, incorporating lymphocyte counts and serum HDL levels, was a feasible novel marker of the COPD airflow limitation severity. In the current study, LHR levels were related positively to FEV₁% and could estimate lower FEV₁% with a fair

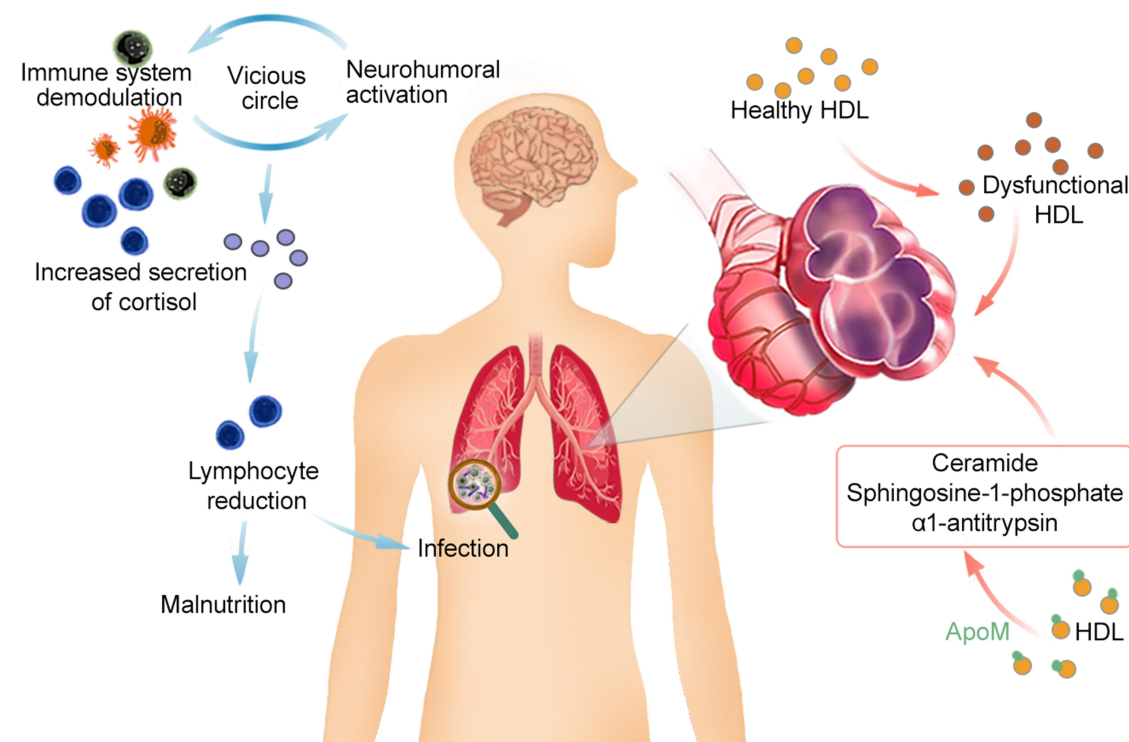


Figure 3 Role of the lymphocytes and HDL in COPD. A vicious circle produced by neurohumoral activation and immune system demodulation increases the secretion of cortisol, which causes the lymphocyte reduction. Lymphopenia possesses a higher risk of respiratory tract infections and malnutrition. As for HDL, COPD states trigger HDL to be dysfunctional and pro-inflammatory. And apolipoprotein M (apoM), as variations of a component of HDL, is implicated in COPD pathogenesis with HDL, especially emphysema, via effecting ceramide, sphingosine-1-phosphate cellular levels and α_1 -antitrypsin. Lymphocyte reduction and HDL conspire to deteriorate COPD status.

accuracy. Nevertheless, we found it insignificant when it came to NLR and PLR. Parallel results were observed in several researches. Günay⁸ stated that NLR was significantly different between controls and COPD patients, but not between patients with stable and exacerbated COPD. Lee²⁹ found no significant correlation of NLR with FEV₁.

Furthermore, our data suggested that the LHR was associated with other outcome indicators of COPD. Among these COPD participants in our study, patients with elevated LHR levels showed lower BODE index and SGRQ scores, which represent the severity of COPD and health-related quality of life in COPD, respectively.^{30–32} The predictive role of LHR against lower FEV₁% was substantiated via logistic regression analysis subsequently. Interestingly, some researchers have reported that current smokers had decreased HDL, which imply smoking status may play a potential role in the result of higher FEV₁ in the LHR > 1.42 group in our study in conjunction with “healthy smoker” phenomenon.^{33–36} In our study, to weaken the influence of smoking status in COPD patients, we selected smoking-matched patients, and among them higher levels of lung function indexes were still found in high LHR group.

However, there are several limitations in our study. First, this preliminary study is a single-center cross-sectional survey limited on retrospective cohort. Second, the sample size is relatively small. Third, our work lacks exploring the cellular and molecular mechanisms of the impact of LHR on COPD. Prospective cohort studies with more participants recruited from multiple centers are needed to clarify this issue. And further researches need to be carried out to elucidate the role of LHR in COPD progression.

In conclusion, as a novel and promising marker, LHR can be calculated from the parameters of blood routine fast and conveniently. Lower levels of LHR were independently associated with poorer pulmonary function. It has predictive value for severer airway obstruction in COPD better than NLR and PLR. Our preliminary study could provide reference for clinicians to judge rapidly the pulmonary function of COPD patients. More attention should be attached to the LHR in clinical work.

Abbreviations

COPD, chronic obstructive pulmonary disease; LHR, lymphocyte to high-density lipoprotein ratio; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio;

FEV₁%, forced expiratory volume in 1 second in percent of the predicted value; FEV₁, forced expiratory volume in 1 second; BODE, body mass index, airway obstruction, dyspnoea, severe exacerbations; SGRQ, St. George’s Respiratory Questionnaire; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; MetS, metabolic syndrome; BMI, body mass index; FVC, forced vital capacity; ROC, receiver operating characteristics; PaCO₂, partial pressure of carbon dioxide in arterial blood; AUC, the area under the curve; PaO₂, partial pressure of oxygen in arterial blood; SpO₂, oxygen saturation; PS matching, propensity score matching; apoM, apolipoprotein M.

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Author Contributions

Yiben Huang: Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Writing – original draft, Writing – review and editing. Bingqian Jiang: Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review and editing. Xiaqi Miao: Data curation, Investigation, Writing – original draft, Writing – review and editing. Jiedong Ma, Jianing Wang, Keke Ding, Xianjing Chen, Qiaoming Hu, Fangyi Fu, Tian Zeng, Jingyu Hu, Binbin Hu: Data curation, Investigation, Writing – review and editing. Dehao Yang, Xiaodiao Zhang: Conceptualization, Data curation, Investigation, Supervision, Writing – review and editing. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest.

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