Am J Transl Res 2025;17(12):9341-9352
www.ajtr.org /ISSN:1943-8141/AJTR0166554

Original Article

Difference in the ratio of low-density lipoprotein to lymphocytes between acute exacerbation of and stable phase of chronic obstructive pulmonary disease patients

Xinle Shu[1], Ying Zhang[1], Yuan Yang[2]

[1]Department of Geriatrics, Hanzhong Central Hospital, No. 22, Kangfu Road, Beiguan Subdistrict, Hantai District, Hanzhong 723000, Shaanxi, China; [2]Department of Respiratory and Critical Care Medicine, Hanzhong Central Hospital, No. 22, Kangfu Road, Beiguan Subdistrict, Hantai District, Hanzhong 723000, Shaanxi, China

Received June 3, 2025; Accepted November 23, 2025; Epub December 15, 2025; Published December 30, 2025

Abstract: Objective: To examine difference in the low-density lipoprotein cholesterol/lymphocyte (LDL-C/LYM) ratio between the acute exacerbation and stable phases of chronic obstructive pulmonary disease (COPD) and assess its diagnostic and prognostic value. Methods: A total of 196 hospitalized COPD patients were retrospectively analyzed, including 96 in the acute exacerbation phase and 100 in the stable phase. Demographics, inflammatory markers [C-reactive protein (CRP), interleukin-6 (IL-6), white blood cell count (WBC), monocyte percentage (MO%)], pulmonary function indices [percentage of predicted forced expiratory volume in one second (FEV_1% pred), FEV_1/forced vital capacity (FVC), peak expiratory flow (PEF)], and LDL-C/LYM ratios were collected. Intergroup comparisons, correlation analyses, and receiver operating characteristic (ROC) curve analysis were performed. Results: LDL-C/LYM ratio was significantly higher during acute exacerbation ($P < 0.001$), positively correlated with CRP, IL-6, WBC, and MO% ($r = 0.404$-0.606), and negatively with FEV_1% pred, FEV_1/FVC, and PEF ($r = -0.310$ to -0.402) (all $P < 0.001$). No significant correlation between LDL-C/LYM ratio and pulmonary function indices were found in the stable group. ROC analysis showed that the LDL-C/LYM ratio had the highest diagnostic accuracy for acute exacerbation [area under the curve (AUC) = 0.828], outperforming other markers, and it correlated positively with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging ($r = 0.419$, $P < 0.001$). Conclusion: The LDL-C/LYM ratio is elevated during COPD exacerbations and reflects inflammation and lung function decline, serving as a simple biomarker for diagnosis and prognosis.

Keywords: Chronic obstructive pulmonary disease, acute exacerbation, stable phase, low-density lipoprotein cholesterol/lymphocyte ratio

Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic inflammatory respiratory disease characterized by persistent airflow obstruction. As a pressing global public health challenge, it imposes immense socioeconomic and healthcare burdens, mainly attributed to its high morbidity and mortality [1]. The World Health Organization has ranked COPD among the leading causes of global deaths and disabilities, and its prevalence and mortality have continued to rise over recent decades. For instance, 2019 statistics indicated that approximately 212.3 million COPD cases were recorded worldwide, with the disease being responsible for around 3.3 million deaths that year [2]. This upward trend, potentially linked to aging populations and environmental factors, places substantial economic pressure on societies and families [3].

COPD progression is characterized by alternating acute exacerbations and stable phases [4]. Acute exacerbations represent critical episodes during which patients experience worsening dyspnea, increased coughing, enhanced sputum production, and changes in sputum appearance within a short timeframe [5]. Frequent acute exacerbations in COPD patients are asso-

https://doi.org/10.62347/QISZ2275

ciated with accelerated decline in pulmonary function, diminished patient quality of life, and an increased likelihood of hospital admission and mortality [6, 7]. Although symptoms are milder during stable phases, patients still exhibit progressive loss of pulmonary function, which continually impairs daily activities and occupational capacity [8].

In recent years, there has been growing research interest in identifying reliable biomarkers to effectively assess COPD severity, progression, and clinical outcomes. Among these potential biomarkers, the low-density lipoprotein cholesterol/lymphocyte (LDL-C/LYM) ratio has emerged as a novel indicator for evaluating inflammatory status. Notably, low-density lipoprotein cholesterol (LDL-C) is involved not only in lipid metabolism but also in the regulation of inflammatory responses; in contrast, lymphocytes serve a pivotal function in immune defense and inflammatory modulation [9, 10]. Given that inflammation serves as a core driver of COPD pathogenesis and exacerbation, the LDL-C/LYM ratio may offer valuable insights into patients' inflammatory and immune status, thereby supporting clinical assessment [11, 12]. However, studies specifically focusing on LDL-C/LYM ratio differences between the acute exacerbation and stable phases of COPD remain relatively limited.

The current study seeks to evaluate the potential clinical utility of the LDL-C/LYM ratio in the management of COPD. To accomplish this objective, it compares the ratio levels between COPD patients in acute exacerbation and stable phases. Ultimately, this study intends to offer novel insights and evidence to facilitate the refinement of COPD diagnostic and therapeutic approaches.

Materials and methods

Research subjects

This retrospective study recruited 196 patients diagnosed with COPD who were hospitalized at Hanzhong Central Hospital between October 2021 and April 2023. The study design was examined and authorized by the Medical Ethics Committee of Hanzhong Central Hospital (approval number: HZC-24665). The calculation of sample size was conducted via G*Power 3.1 software. Preliminary data showed that the mean LDL-C/LYM ratio was 3.2 ± 0.8 during the acute exacerbation phase and 1.9 ± 0.6 in the stable phase. Based on these data, a minimum sample size of 86 patients per group was calculated. This sample size was determined to guarantee 90% statistical power, with a set significance level of $\alpha = 0.05$ and an effect size of 0.5. Following the screening of participants based on pre-established inclusion and exclusion criteria, a total of 196 qualified patients were ultimately included for subsequent data analysis.

Inclusion criteria: (1) confirmation of COPD diagnosis in line with the guidelines issued by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [13, 14], which required verification via a post-bronchodilator ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) < 0.7; (2) age of 18 years or older; (3) completion and availability of comprehensive clinical documentation, including laboratory test results and pulmonary function measurement data, corresponding to either the acute exacerbation phase or stable phase of COPD.

Exclusion criteria: (1) severe comorbid conditions such as malignancy, congestive heart failure, or hepatic/renal failure; (2) human immunodeficiency virus infection or current use of immunosuppressive therapy; (3) recent history (within three months) of acute cardiovascular or cerebrovascular events, or significant infections.

Patients enrolled in the study were categorized into an acute exacerbation group (n = 96) and a stable phase (n = 100) according to their clinical condition at the time of hospital admission.

The acute exacerbation group consisted of COPD patients with an acute deterioration in respiratory symptoms. Specifically, patients presented with at least two of the symptoms including heightened dyspnea, increased sputum production, or purulent sputum. Additionally, these symptom exacerbations required escalated therapeutic interventions (e.g., administration of antibiotics or systemic corticosteroids) or hospital admission. Before enrollment, other potential causes of respiratory symptom worsening, such as pneumonia or heart failure, were ruled out through comprehensive clinical evaluations, imaging examinations, and laboratory tests.

The stable phase group included COPD patients whose clinical symptoms had been stable for a minimum of three months. Key criteria for inclusion were no history of acute exacerbations during this period, and no use of systemic glucocorticoids or antibiotics in the month prior to study enrollment [15].

Data collection

Data regarding the demographic features and clinical particulars of all enrolled patients were retrieved from the electronic medical record system of Hanzhong Central Hospital. The collected variables included basic information such as age, gender, smoking status, and smoking pack-year history; disease-related history including the number of previous COPD acute exacerbations, comorbidities (cardiovascular disease and diabetes mellitus), and duration of COPD; clinical management and staging indicators like utilization of long-term oxygen therapy, GOLD stage (based on post-bronchodilator pulmonary function), and body mass index (BMI); as well as symptom and nutritional assessment parameters including COPD Assessment Test (CAT) score and serum albumin concentration.

The CAT is a well-validated questionnaire consisting of 8 items, specifically developed to assess the severity of symptoms unique to COPD. Its total score spans from 0 to 40, where higher scores correspond to more intense symptoms that exert a greater impact on patients' daily activities. The severity of COPD was categorized following the GOLD 2021 guidelines, which take the percentage of predicted forced expiratory volume in 1 second (FEV_1% predicted) post-bronchodilator administration as the core basis: GOLD 1 (mild, FEV_1% predicted ≥ 80%), GOLD 2 (moderate, FEV_1% predicted 50-79%), GOLD 3 (severe, FEV_1% predicted 30-49%), and GOLD 4 (very severe, FEV_1% predicted < 30%).

Venous blood specimens were collected from all participating patients in a fasting state (≥ 8 hours) on the morning subsequent to hospital admission. The computation of the LDL-C/LYM ratio and the detection of inflammatory indicators were two primary dimensions for laboratory tests. For the computation of the LDL-C/LYM ratio, LDL-C was measured using an automated biochemical analyzer and determined LYM through a complete blood count assay. Thereafter, the ratio was derived based on the formula "LDL-C/LYM = LDL-C concentration ÷ Lymphocyte count". For the detection of inflammatory indicators, C-reactive protein (CRP) was measured via the immunoturbidimetry technique (Roche Diagnostics), interleukin-6 (IL-6) was quantified by a sandwich ELISA (R&D Systems), and white blood cell count (WBC) and monocyte percentage (MO%) were analyzed via an automated hematology analyzer (Roche Cobas 8000, which can calculate MO% as the percentage of monocytes in total WBCs).

Pulmonary function tests were performed at different time points for patients to ensure data reflected the actual disease phase. For the stable phase group, tests were conducted after patients' conditions stabilized (usually 3-5 days after admission, when symptoms such as cough and dyspnea were controlled); for the acute exacerbation group, tests were completed before discharge, i.e., after acute symptoms were alleviated and lung function returned to a relatively stable state (confirmed by clinicians). All pulmonary function tests were performed using a MasterScreen PFT spirometer (Jaeger, Germany), in compliance with the standards established by the American Thoracic Society and European Respiratory Society.

Statistical methods

Statistical analyses for this study were conducted using SPSS 26.0 and GraphPad Prism 9.0 software. Continuous variables exhibiting a normal distribution were reported as mean ± standard deviation, with intergroup comparisons performed via the independent samples t-test. Data with non-normal distribution are expressed as median (M) and quartiles (P25, P75), and comparisons were performed using the Mann-Whitney U test. Categorical variables were presented as frequencies (percentages), and group disparities were evaluated using the chi-square test. Pearson's correlation analysis was employed to explore linear associations between the LDL-C/LYM ratio and both inflammatory markers (CRP, IL-6, WBC, MO%) and pulmonary function parameters (FEV_1% pred, FEV_1/FVC, PEF). Receiver operating characteristic (ROC) curve analysis was utilized to assess the diagnostic utility of the LDL-C/LYM ratio in identifying acute exacerbations and predicting one-year mortality, with the area under the curve

Table 1. Comparison of general information

	Acute Exacerbation Phase (n = 96)	Stable Phase (n = 100)	$t/\chi^2/Z$	P
Age (years)	72.38 ± 9.29	68.42 ± 11.03	2.713	0.007
Male	62 (64.58)	73 (73.00)	1.619	0.203
Smokers	33 (34.38)	41 (41.00)	0.915	0.339
Previous Acute Exacerbation	65 (67.71)	43 (43.00)	12.087	< 0.001
Comorbid Cardiovascular Disease	37 (38.54)	56 (56.00)	5.987	0.014
Comorbid Diabetes	13 (13.54)	21 (21.00)	1.900	0.168
Long-Term Oxygen Therapy Use	10 (10.42)	7 (7.00)	0.722	0.396
GOLD Classification (3-4)	39 (40.63)	22 (22.00)	7.926	0.005
BMI (kg/m^2)	22.59 ± 4.04	23.29 ± 3.79	-1.252	0.212
Disease Course (years)	5.0 (0.11, 10.0)	3.0 (2.0, 8.5)	0.501	0.616
CAT Score	17.40 ± 5.27	16.23 ± 4.41	1.688	0.093
Serum Albumin (g/L)	36.78 ± 4.24	39.37 ± 4.37	-4.209	< 0.001

GOLD, Global Initiative for Chronic Obstructive Lung Disease; BMI, Body Mass Index; CAT, Chronic Obstructive Pulmonary Disease Assessment Test.

(AUC) quantifying its discriminative capacity. The optimal threshold for the LDL-C/LYM ratio was identified by maximizing Youden's index (sensitivity + specificity - 1), which balances sensitivity and specificity. For survival analyses, patients were stratified into high and low LDL-C/LYM groups based on the optimal cutoff derived from ROC analysis. A two-tailed *P*-value < 0.05 was deemed statistically significant across all analyses.

Results

Comparison of general information

No significant intergroup differences were observed in sex distribution, smoking history, diabetes comorbidity, long-term oxygen therapy use, BMI, disease duration, and CAT scores (all P > 0.05). However, several variables differed significantly between groups. Patients in the acute exacerbation phase were older (72.38 ± 9.29 vs. 68.42 ± 11.03 years, t = 2.713, P = 0.007), had a higher prevalence of previous acute exacerbations (67.71% vs. 43.00%, χ^2 = 12.087, P < 0.001), more frequent cardiovascular disease comorbidity (38.54% vs. 56.00%, χ^2 = 5.987, P = 0.014), and a higher proportion of GOLD stage 3-4 cases (40.63% vs. 22.00%, χ^2 = 7.926, P = 0.005). Additionally, serum albumin levels were significantly lower in the acute exacerbation phase group (36.78 ± 4.24 vs. 39.37 ± 4.37 g/L, t = -4.209, P < 0.001). See **Table 1**.

Comparison of LDL-C/LYM ratio, pulmonary function, and inflammatory indicators

The LDL-C/LYM ratio was markedly elevated in the exacerbation group compared to the stable group (P < 0.001). Concurrently, all pulmonary function parameters (FEV_1% predicted, FEV_1/FVC ratio, and PEF) demonstrated significant reduction during exacerbation (all P < 0.05). Inflammatory markers including CRP, IL-6, WBC count, and MO% were substantially higher in the acute exacerbation phase (all P < 0.05). See **Figure 1**.

Correlation between LDL-C/LYM ratio and inflammatory indicators

Pearson correlation analysis was used to examine the relationships between the LDL-C/LYM ratio and inflammatory markers. In COPD patients in the acute exacerbation phase, the LDL-C/LYM ratio exhibited strong positive correlations with four inflammatory indicators: CRP (r = 0.404, P < 0.001), IL-6 (r = 0.538, P < 0.001), WBC (r = 0.606, P < 0.001), and MO% (r = 0.551, P < 0.001). By comparison, the correlation profile of the stable phase group differed notably. The LDL-C/LYM ratio showed only a weak positive correlation with three inflammatory markers: IL-6 (r = 0.287, P = 0.004), WBC (r = 0.262, P = 0.009), and MO% (r = 0.329, P = 0.001). No statistically significant correlation was observed between CRP and the LDL-C/LYM ratio (r = 0.162, P = 0.108). See **Figure 2**.

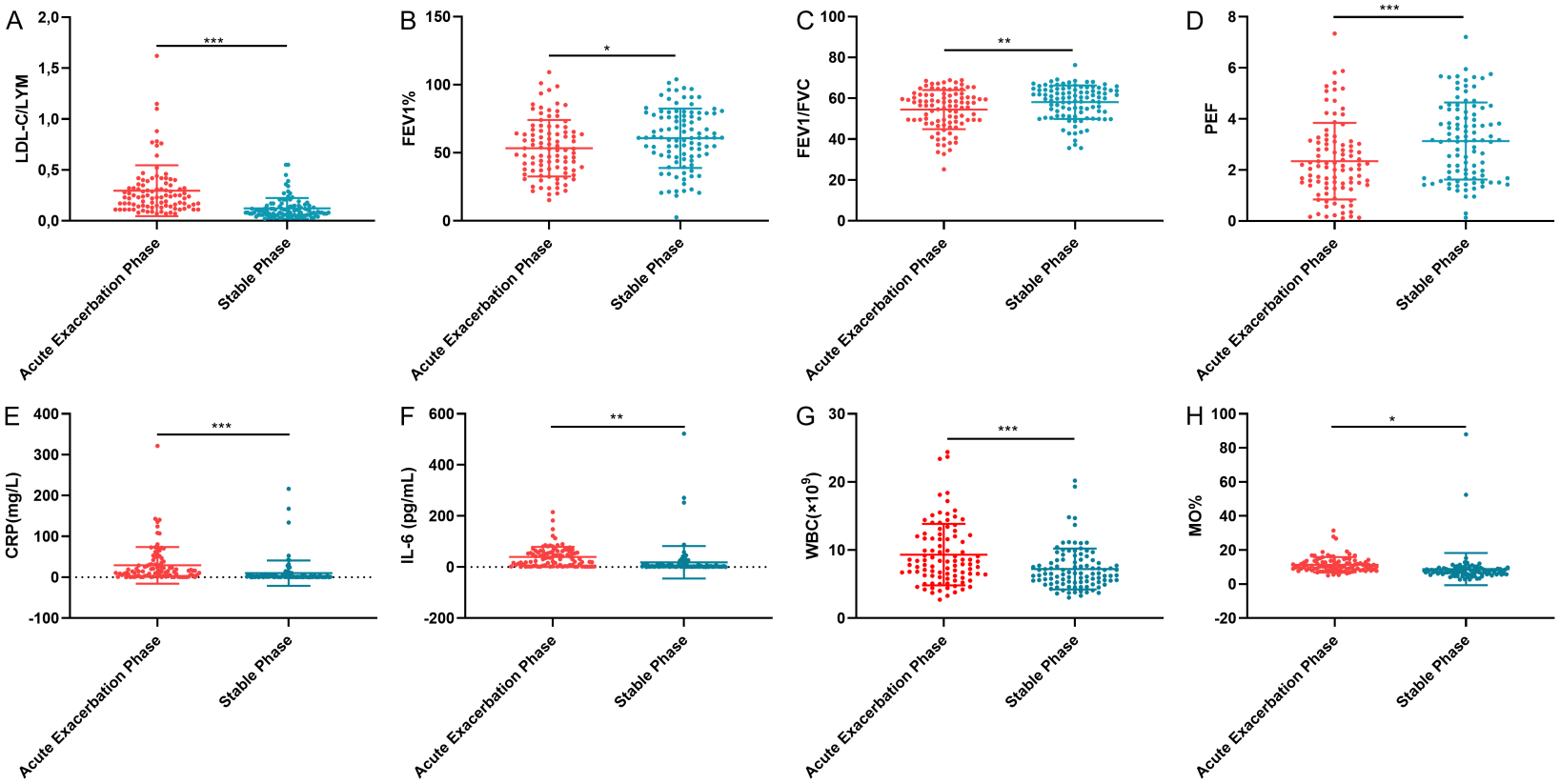

Figure 1. Comparison of LDL-C/LYM ratio, pulmonary function, and inflammatory indicators between the two groups of patients. Low-Density Lipoprotein Cholesterol/Lymphocyte (LDL-C/LYM); Forced Expiratory Volume in 1 Second Percentage (FEV_1%); Forced Expiratory Volume in 1 Second/Forced Vital Capacity (FEV_1/FVC); Peak Expiratory Flow (PEF); C-Reactive Protein (CRP); Interleukin-6 (IL-6); White Blood Cell (WBC); Monocyte Percentage (MO%); **P < 0.05, **P < 0.01, ***P < 0.001.

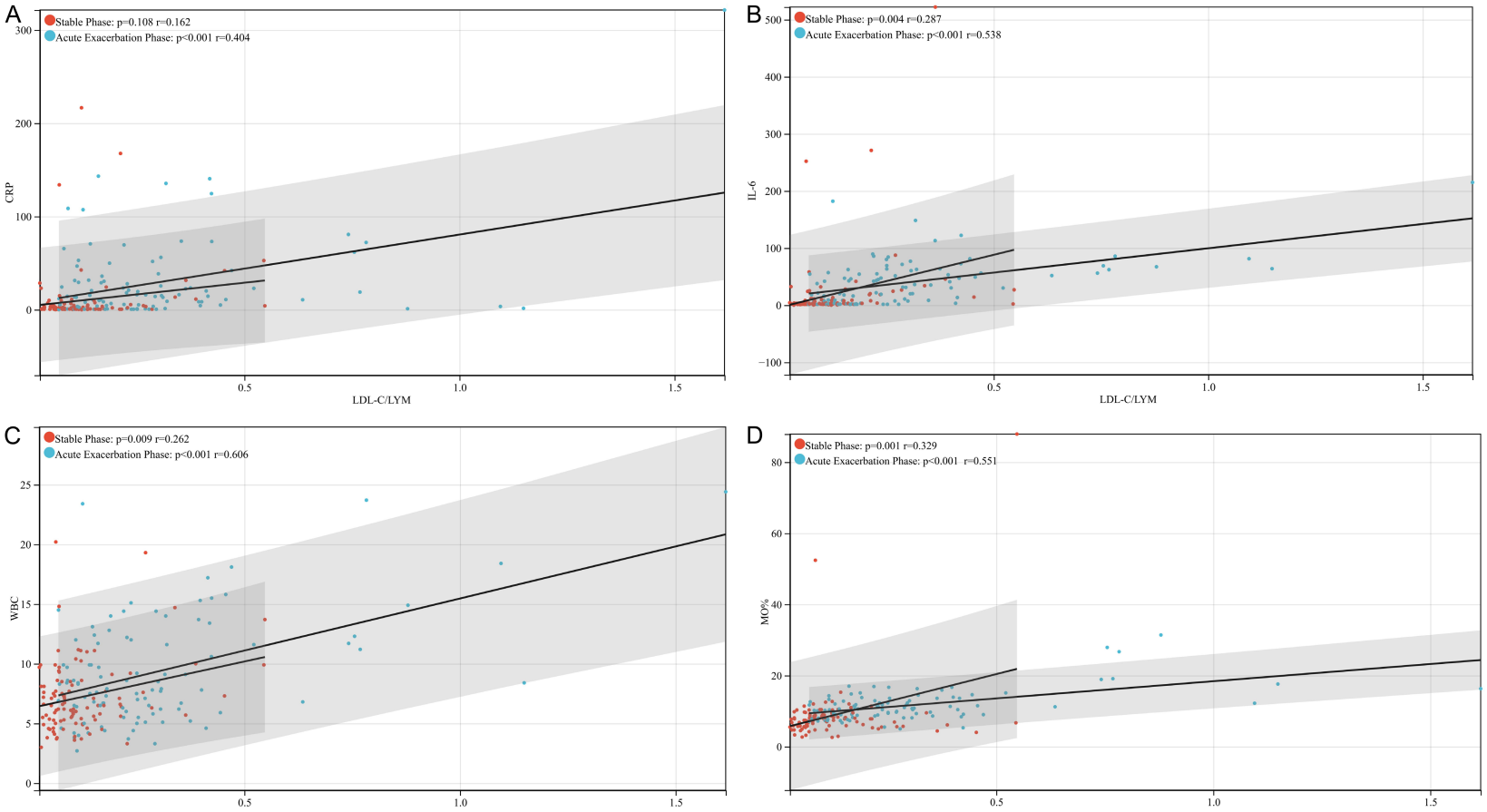

Figure 2. Correlation between LDL-C/LYM ratio and inflammatory indicators. A. Correlation between Low-Density Lipoprotein Cholesterol/Lymphocyte (LDL-C/LYM) ratio and C-Reactive Protein (CRP); B. Correlation between LDL-C/LYM ratio and Interleukin-6 (IL-6); C. Correlation between LDL-C/LYM ratio and White Blood Cell (WBC); D. Correlation between LDL-C/LYM ratio and Monocyte Percentage (MO%).

Correlation between LDL-C/LYM ratio and pulmonary function

Pearson correlation analysis was conducted to explore the associations between the LDL-C/LYM ratio and pulmonary function indices in COPD patients. In the acute exacerbation phase, the LDL-C/LYM ratio showed significant negative correlations with three core pulmonary function parameters: FEV_1% predicted ($r = -0.402$, $P < 0.001$), FEV_1/FVC ($r = -0.394$, $P < 0.001$), and PEF ($r = -0.310$, $P < 0.001$). In contrast, the correlation pattern between the LDL-C/LYM ratio and these pulmonary function indicators changed markedly in the stable phase. No statistically significant correlations were observed between the LDL-C/LYM ratio and FEV_1% predicted ($P = 0.679$), FEV_1/FVC ($P = 0.351$), or PEF ($P = 0.158$) in stable-phase patients. See **Figure 3**.

Diagnostic value of LDL-C/LYM ratio and inflammatory indicators for COPD acute exacerbation

ROC curve was performed to evaluate the ability of the LDL-C/LYM ratio and inflammatory markers to distinguish COPD acute exacerbation from stable phases. All indicators showed significant diagnostic value, with varying performance. The LDL-C/LYM ratio had the strongest discriminatory ability (AUC = 0.828, 95% CI: 0.772-0.885), achieving 70.00% sensitivity and 80.21% specificity at the optimal cutoff of 0.13. Among inflammatory markers, MO% ranked second (AUC = 0.784, 95% CI: 0.721-0.848), followed by CRP (AUC = 0.755, 95% CI: 0.685-0.825) and IL-6 (AUC = 0.766, 95% CI: 0.698-0.836). The AUC of WBC is relatively low, at only 0.649 (95% CI: 0.572-0.726). See **Figure 4**.

Association between LDL-C/LYM ratio and GOLD classification in patients with acute exacerbation

Figure 5 shows that in patients with acute exacerbation of COPD, the LDL-C/LYM ratio is significantly positively correlated with the GOLD stage (correlation coefficient $r = 0.419$, $P < 0.001$).

Discussion

Acute exacerbations are critical events in COPD clinical management. Timely detection of these exacerbations and accurate prognostic assessment are essential for improving patients' clinical outcomes [16]. Notably, this study is the first to investigate changes in the LDL-C/LYM ratio and its clinical value across COPD's acute exacerbation and stable phases. It not only highlights the potential of this novel biomarker for dynamic disease monitoring but also offers new insights into the inflammatory mechanisms underlying COPD progression.

Our findings suggest that the LDL-C/LYM ratio was significantly higher in COPD patients during the acute exacerbation phase compared to the stable phase. This ratio displayed strong positive correlations with inflammatory markers, specifically CRP, IL-6, WBC, and MO%. Meanwhile, it showed significant negative correlations with pulmonary function parameters, including percentage of predicted FEV_1%, ratio of FEV_1/FVC, and PEF.

Furthermore, the LDL-C/LYM ratio performed better than traditional inflammatory indicators in identifying COPD acute exacerbations, and it also achieved higher accuracy in predicting one-year mortality among patients with acute exacerbations. These results confirm that the LDL-C/LYM ratio can serve as a comprehensive and clinically valuable biomarker, which is applicable for assessing disease severity and predicting prognosis in patients with COPD.

It is worth noting that in a large-scale cohort study, Goto and colleagues [17] found that the incidence of cardiovascular events was significantly higher at 30 days and one year after COPD acute exacerbations, with incidence rate ratios of 1.34 and 1.20, respectively. This observation implies that the metabolic-immune dysregulation, a key feature of COPD acute exacerbations, might accelerate the progression of atherosclerosis by amplifying pro-inflammatory signaling pathways. This finding further highlights the clinical significance of the LDL-C/LYM ratio. Given that the ratio integrates metabolic (LDL-C) and immune (lymphocyte count) indicators, it may serve as a potential link between COPD acute exacerbations, inflammatory responses, and cardiovascular comorbidities.

The increase in the LDL-C/LYM ratio detected in patients with acute exacerbation of COPD may be linked to the co-occurring dysregulation of lipid metabolism and impairment of immune

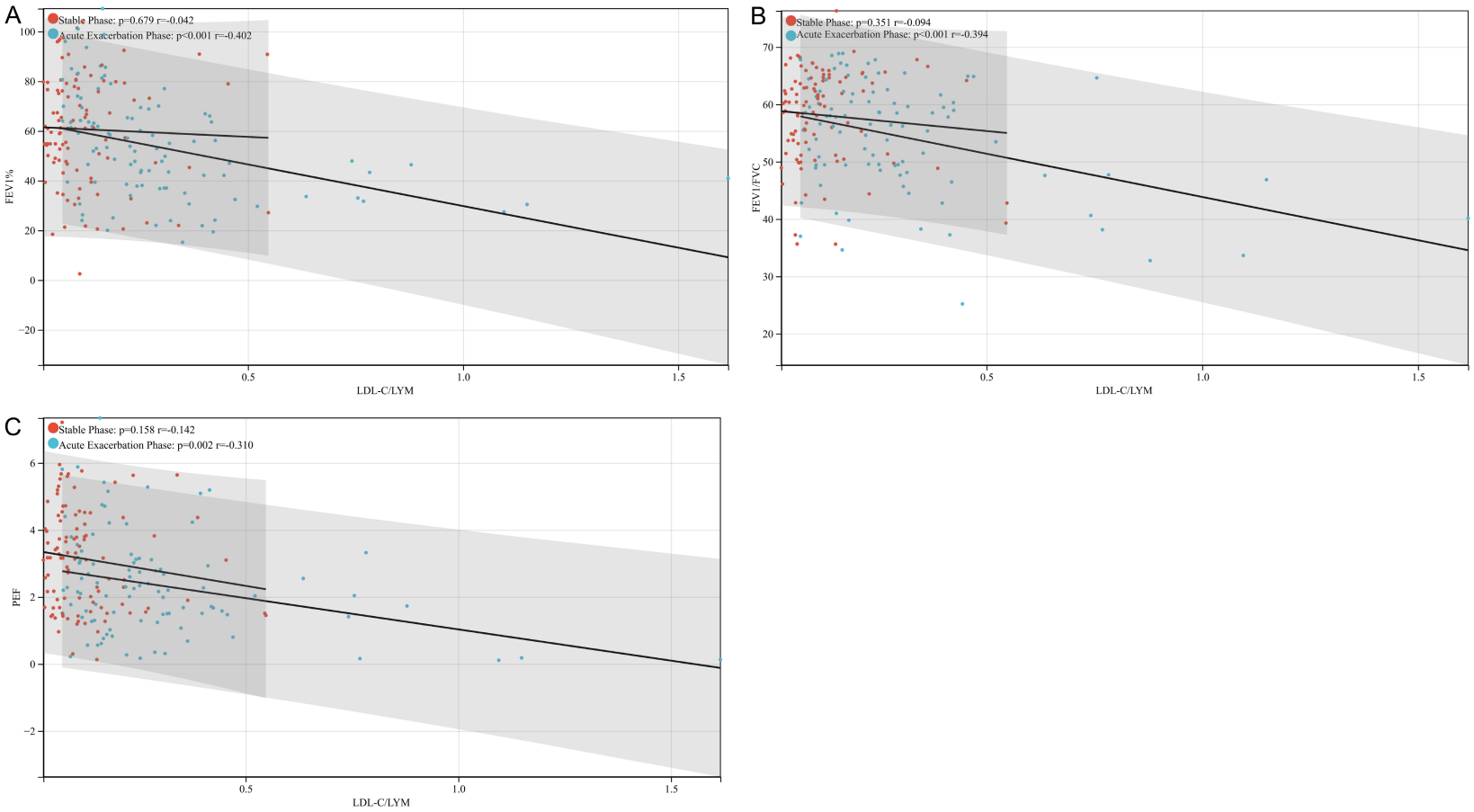

Figure 3. Correlation between LDL-C/LYM ratio and pulmonary function. A. Correlation between Low-Density Lipoprotein Cholesterol/Lymphocyte (LDL-C/LYM) ratio and predicted FEV_1%; B. Correlation between LDL-C/LYM ratio and Forced Expiratory Volume in 1 Second/Forced Vital Capacity (FEV_1/FVC); C. Correlation between LDL-C/LYM ratio and Peak Expiratory Flow (PEF).

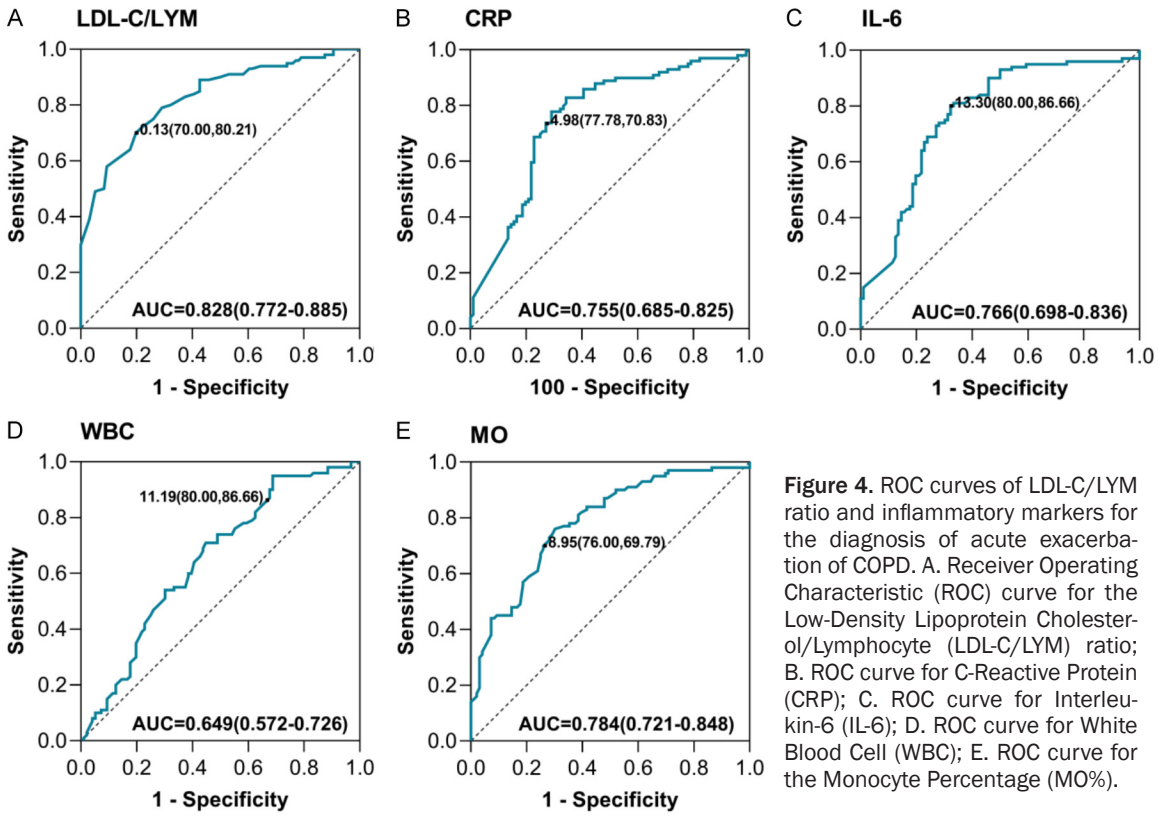

Figure 4. ROC curves of LDL-C/LYM ratio and inflammatory markers for the diagnosis of acute exacerbation of COPD. A. Receiver Operating Characteristic (ROC) curve for the Low-Density Lipoprotein Cholesterol/Lymphocyte (LDL-C/LYM) ratio; B. ROC curve for C-Reactive Protein (CRP); C. ROC curve for Interleukin-6 (IL-6); D. ROC curve for White Blood Cell (WBC); E. ROC curve for the Monocyte Percentage (MO%).

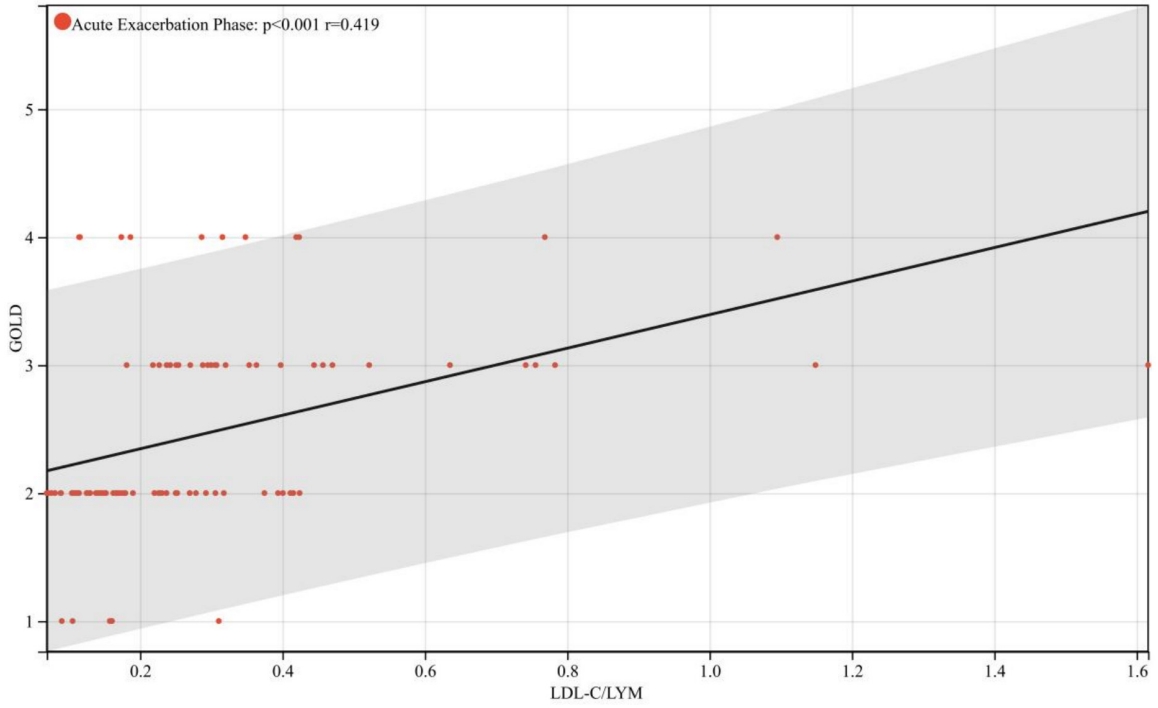

Figure 5. The correlation between the LDL-C/LYM ratio and the global initiative for GOLD staging. LDL-C/LYM: Low-Density Lipoprotein Cholesterol/Lymphocyte; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

function [18]. In the context of acute inflammatory states, activation of the stress response through the hypothalamic-pituitary-adrenal axis stimulates lipolysis, a process that increas-

es the release of free fatty acids and, in turn, causes a subsequent rise in LDL-C levels [19]. At the same time, ox-LDL is capable of activating the NF-κB signaling pathway in endothelial cells. This activation leads to increased secretion of pro-inflammatory cytokines, including IL-6, which further boosts the activation of leukocytes. Such a cascade of events forms a self-perpetuating cycle involving inflammatory responses and metabolic disorders [20].

In terms of pulmonary function prediction, Jang et al. [21] confirmed that $FEV_1/FVC < 0.5$ is an independent predictor of AECOPD (aOR = 5.16). However, it depends on a standardized pulmonary function tester, which limits the promotion in primary healthcare. This study found that LDL-C/LYM ratio was significantly negatively correlated with FEV_1/FVC, and it can be calculated only through routine blood tests. This is consistent with the conclusion proposed by Huang et al. [22], who pointed out that the LDL-C/LYM ratio can be used as a marker of the severity of COPD. This convenience makes it an effective supplement to FEV_1/FVC, especially in resource limited areas. In the acute exacerbation state of COPD, a large number of inflammatory cells, such as neutrophils and macrophages, are recruited to the lungs [23]. These cells will produce a large amount of reactive oxygen species (ROS) during the process of phagocytosing pathogens and participating in the inflammatory response, leading to oxidative stress. At the same time, as mentioned above, LDL-C in the acute exacerbation phase may be oxidized, and oxidized LDL-C can further promote the release of ROS by activating immune cells [24]. Excessive oxidative stress can act on the elastic fibers in the alveolar wall. It can cause the degradation of elastic fibers by activating matrix metalloproteinases (MMPs) [25]. MMPs can specifically degrade extracellular matrix components such as elastic fibers, and the imbalance between the synthesis and degradation of elastic fibers ultimately leads to the progression of emphysema and the decline of pulmonary function, which may explain the negative correlation between LDL-C/LYM and pulmonary function.

It is worth noting that no significant correlation was observed the LDL-C/LYM ratio and IL-6 or TNF-α in the stable phase, suggesting that dynamic changes of this ratio are more specific to acute inflammatory responses. This finding aligns with the disease heterogeneity of COPD: the acute exacerbation phase is mainly characterized by while the stable phase is more inclined to chronic low-grade inflammation with immune senescence. The strong correlation between the LDL-C/LYM ratio and the systemic inflammatory network indicates that this ratio may indirectly reflect the over activation of the Th1/Th17 pathway-mediated immune responses [26]. As key pro-inflammatory factors, IL-6 and WBC contribute to airway remodeling by stimulating the secretion of MMPs [27]. The negative correlation between LDL-C/LYM ratio and pulmonary function suggests that an elevated ratio reflects intensified oxidative stress, which can degrade elastic fibers in the alveolar wall and accelerate emphysema progression [28].

Compared with traditional inflammatory markers, the LDL-C/LYM ratio offers the advantage of integrating both metabolic and immunological information. This study demonstrates that the LDL-C/LYM ratio has a higher AUC than both MO% and CRP, and the specificity at its optimal cut-off value is superior, which may help reduce clinical misdiagnosis. Furthermore, in terms of prognosis prediction, patients with elevated LDL-C/LYM levels showed a significantly increased one-year mortality rate, indicating that this ratio can be used for risk stratification and to guide intensive treatment strategies.

In patients with COPD in the acute exacerbation phase, the LDL-C/LYM ratio was significantly positively correlated with the GOLD classification. This indicates that as the GOLD grade increases and the disease severity progresses, the LDL-C/LYM ratio also shows an upward trend. Although GOLD staging is primarily based on $FEV_1\%$, our study confirms a negative correlation between LDL-C/LYM ratio and $FEV_1\%$. This is not completely contradictory, because GOLD staging is a comprehensive evaluation of the disease, as it incorporates not only $FEV_1\%$ but also factors such as the frequency of acute exacerbations and the patient's clinical symptoms. In the acute exacerbation phase, as the condition deteriorates, changes in pulmonary function, systemic inflammatory responses and metabolic disorders appears. LDL-C/LYM can reflect the overall inflammatory and metabolic status, so it shows a positive correlation with the overall GOLD grade, while the negative correlation with $FEV_1\%$ may be due to the fact that the increase in LDL-C/LYM is

accompanied by more severe systemic inflammation, which in turn has a greater negative impact on pulmonary function, resulting in a decrease in FEV_1%.

The lack of significant correlation between LDL-C/LYM and IL-6/WBC in the stable phase may have several reasons. First, the sample size of this study may not be large enough. A relatively small sample size may reduce the statistical power, making it difficult to detect weak correlations that might exist. Second, in the stable phase of COPD, the level of systemic inflammation is generally lower compared to the acute exacerbation phase. IL-6 and WBC, as key pro-inflammatory cytokines, may be present at concentrations below the threshold that can establish a detectable correlation with LDL-C/LYM ratio. Third, the immune response pattern in the stable phase may differ. During stability, the immune system tends to be in a state of chronic low-grade inflammation with immune senescence, where the regulatory mechanisms of inflammatory cytokines may be distinct from those in acute exacerbation [29]. This could lead to a dissociation between the metabolic-immune index (LDL-C/LYM) and specific cytokines like IL-6 and WBC. Future studies with larger sample sizes focusing on the stable phase are needed to verify these hypotheses. Additionally, exploring the dynamic changes of LDL-C/LYM and cytokines during the transition from stable phase to acute exacerbation could provide more insights into their relationship. It should be noted that there may be potential bias in the timing of pulmonary function testing. The acute exacerbation group underwent pulmonary function tests before discharge (after clinical improvement), while the stable phase group was tested after stabilization during hospitalization. This difference in testing timing might lead to inconsistent disease states between the two groups, which could potentially affect the comparability of the results. However, considering that the pulmonary function of patients in the stable phase also has certain fluctuations, and the test for the acute exacerbation group was also carried out when the patient's condition had relatively improved to a certain extent, it can still reflect the overall pulmonary function status of patients in different phases. Future research can consider standardizing the timing of pulmonary function testing, such as conducting all tests at a fixed time point after the patient's condition stabilizes to reduce this potential bias.

In conclusion, the LDL-C/LYM ratio is significantly increased in the acute exacerbation phase of COPD and is closely related to the severity of inflammation and impairment of pulmonary function. Its excellent diagnostic and prognostic prediction efficacy provides a new tool for the precise management of COPD.

Disclosure of conflict of interest

None.

Address correspondence to: Yuan Yang, Department of Respiratory and Critical Care Medicine, Hanzhong Central Hospital, No. 22, Kangfu Road, Beiguan Subdistrict, Hantai District, Hanzhong 723000, Shaanxi, China. E-mail: 13219777839@163.com

References

[1] Guo P, Li R, Piao TH, Wang CL, Wu XL and Cai HY. Pathological mechanism and targeted drugs of COPD. Int J Chron Obstruct Pulmon Dis 2022; 17: 1565-1575.

[2] Safiri S, Carson-Chahhoud K, Noori M, Nejadghaderi SA, Sullman MJM, Ahmadian Heris J, Ansarin K, Mansournia MA, Collins GS, Kolahi AA and Kaufman JS. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019. BMJ 2022; 378: e069679.

[3] Fabbri LM, Celli BR, Agusti A, Criner GJ, Dransfield MT, Divo M, Krishnan JK, Lahousse L, Montes de Oca M, Salvi SS, Stolz D, Vanfleteren LEGW and Vogelmeier CF. COPD and multimorbidity: recognising and addressing a syndemic occurrence. Lancet Respir Med 2023; 11: 1020-1034.

[4] Ruan H, Zhang H, Wang J, Zhao H, Han W and Li J. Readmission rate for acute exacerbation of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respir Med 2023; 206: 107090.

[5] Qian Y, Cai C, Sun M, Lv D and Zhao Y. Analyses of factors associated with acute exacerbations of chronic obstructive pulmonary disease: a review. Int J Chron Obstruct Pulmon Dis 2023; 18: 2707-2723.

[6] Zinellu A, Zinellu E, Mangoni AA, Pau MC, Carru C, Pirina P and Fois AG. Clinical significance of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in acute exacerbations of COPD: present and future. Eur Respir Rev 2022; 31: 220095.

[7] Troosters T, Janssens W, Demeyer H and Rabinovich RA. Pulmonary rehabilitation and physi-

cal interventions. Eur Respir Rev 2023; 32: 220222.
[8] Kim SH, Hong CH, Shin MJ, Kim KU, Park TS, Park JY and Shin YB. Prevalence and clinical characteristics of Sarcopenia in older adult patients with stable chronic obstructive pulmonary disease: a cross-sectional and follow-up study. BMC Pulm Med 2024; 24: 219.
[9] Tasdighi E, Adhikari R, Almaadawy O, Leucker TM and Blaha MJ. LP(a): structure, genetics, associated cardiovascular risk, and emerging therapeutics. Annu Rev Pharmacol Toxicol 2024; 64: 135-157.
[10] Xu Y, Zhang L, Chen Z, Sun X, Zhao M, Wu Q and Hao J. The diagnostic value of systemic immune-inflammatory index (SII) and lymphocyte-albumin-neutrophil ratio (LANR) in chronic obstructive pulmonary disease with lung cancer. J Inflamm Res 2024; 17: 5555-5565.
[11] Dong K, Zheng Y, Wang Y and Guo Q. Predictive role of neutrophil percentage-to-albumin ratio, neutrophil-to-lymphocyte ratio, and systemic immune-inflammation index for mortality in patients with MASLD. Sci Rep 2024; 14: 30403.
[12] Calvier L, Herz J and Hansmann G. Interplay of low-density lipoprotein receptors, LRPs, and lipoproteins in pulmonary hypertension. JACC Basic Transl Sci 2022; 7: 164-180.
[13] Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, Frith P, Halpin DM, López Varela MV, Nishimura M, Roche N, Rodríguez-Roisin R, Sin DD, Singh D, Stockley R, Vestbo J, Wedzicha JA and Agustí A. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. Arch Bronconeumol 2017; 53: 128-149.
[14] Boesing M, Ottensarendt N, Luthi-Corridori G and Leuppi JD. The management of acute exacerbations in COPD: a retrospective observational study and clinical audit. J Clin Med 2023; 13: 19.
[15] Miravitlles M, Calle M, Molina J, Almagro P, Gomez JT, Trigueros JA, Cosio BG, Casanova C, Lopez-Campos JL, Riesco JA, Simonet P, Rigau D, Soriano JB, Ancochea J and Soler-Cataluña JJ. Spanish COPD guidelines (GesEPOC) 2021: updated pharmacological treatment of stable COPD. Arch Bronconeumol 2022; 58: 69-81.
[16] Hess DR. Respiratory care management of COPD exacerbations. Respir Care 2023; 68: 821-837.
[17] Goto T, Shimada YJ, Faridi MK, Camargo CA Jr and Hasegawa K. Incidence of acute cardiovascular event after acute exacerbation of COPD. J Gen Intern Med 2018; 33: 1461-1468.
[18] Kotlyarov S and Kotlyarova A. Molecular mechanisms of lipid metabolism disorders in infectious exacerbations of chronic obstructive pulmonary disease. Int J Mol Sci 2021; 22: 7634.
[19] Schobitz B, Reul JM and Holsboer F. The role of the hypothalamic-pituitary-adrenocortical system during inflammatory conditions. Crit Rev Neurobiol 1994; 8: 263-291.
[20] Prasad K and Mishra M. Mechanism of hypercholesterolemia-induced atherosclerosis. Rev Cardiovasc Med 2022; 23: 212.
[21] Jang JG, Kim Y, Shin SH, Min KH, Jung KS, Kim YI, Park S, Na JO, Lee H and Yoo KH. The role of FEV(1)/FVC in the prediction of acute exacerbation of COPD. Respir Med 2024; 234: 107780.
[22] Huang Y, Jiang B, Miao X, Ma J, Wang J, Ding K, Chen X, Hu Q, Fu F, Zeng T, Hu J, Hu B, Yang D and Zhang X. The relationship of lymphocyte to high-density lipoprotein ratio with pulmonary function in COPD. Int J Chron Obstruct Pulmon Dis 2020; 15: 3159-3169.
[23] Barnes PJ. Inflammatory endotypes in COPD. Allergy 2019; 74: 1249-1256.
[24] Shen Y, Yang T, Guo S, Li X, Chen L, Wang T and Wen F. Increased serum ox-LDL levels correlated with lung function, inflammation, and oxidative stress in COPD. Mediators Inflamm 2013; 2013: 972347.
[25] Dimic-Janjic S, Hoda MA, Milenkovic B, Kotur-Stevuljevic J, Stjepanovic M, Gompelmann D, Jankovic J, Miljkovic M, Milin-Lazovic J, Djurdjevic N, Maric D, Milivojevic I and Popevic S. The usefulness of MMP-9, TIMP-1 and MMP-9/TIMP-1 ratio for diagnosis and assessment of COPD severity. Eur J Med Res 2023; 28: 127.
[26] Ding YH, Qian LY, Pang J, Lin JY, Xu Q, Wang LH, Huang DS and Zou H. The regulation of immune cells by Lactobacilli: a potential therapeutic target for anti-atherosclerosis therapy. Oncotarget 2017; 8: 59915-59928.
[27] Xu F, Lin J, Cui W, Kong Q, Li Q, Li L, Wei Y and Dong J. Scutellaria baicalensis attenuates airway remodeling via PI3K/Akt/NF-kappaB pathway in cigarette smoke mediated-COPD rats model. Evid Based Complement Alternat Med 2018; 2018: 1281420.
[28] Pokharel MD, Garcia-Flores A, Marciano D, Franco MC, Fineman JR, Aggarwal S, Wang T and Black SM. Mitochondrial network dynamics in pulmonary disease: bridging the gap between inflammation, oxidative stress, and bioenergetics. Redox Biol 2024; 70: 103049.
[29] Yalcinsoy M, Beykumul A, Gulbas G, Arslan AK and Neselioglu S. DO disease stages affect oxidative stress in stable COPD? Heliyon 2024; 10: e31188.