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STUDY OF THE RELATIONSHIP OF LOW DENSITY LIPOPROT EIN TO LYMPHOCYTE RATIO (LLR) IN COPD PRESENTING TO MAYO HOSPITAL LAHORE

Dr Ghulam Mujtaba[1], Muhammad Ghous[2] , Dr Aisha Arif[3], Haseeb Khaliq[4], Dr Khalid Basheer[5], Dr Ch Usman Ahmed[6]

*[*1]Postgraduate Trainee (FCPS-II), Department of Internal Medicine South Medical Ward, King Edward Medical University/Mayo Hospital, Lahore.*
[2]Minhaj university lahore
[3]PGR Lady Reading Hospital, Peshawar
[4]Anatomy and Histology, Cholistan University of Veterinary and Animal Sciences, Bahawalpur

[5],[6]Mayo Hospital, Lahore

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ABSTRACT

Introduction: *Chronic Obstructive Pulmonary Disease (COPD) is now the third leading cause of morbidity and mortality worldwide for individuals over 40 years of age.* ***Objective:*** *To evaluate the relationship between Low-Density Lipoprotein to Lymphocyte Ratio (LLR) and the severity of Chronic Obstructive Pulmonary Disease (COPD) and to explore its potential as a biomarker for disease progression.* ***Methods:*** *A cross-sectional study was conducted at the Department of Medicine, King Edward Medical University, Lahore, over 12 months. A total of 284 patients with COPD were enrolled using consecutive non-probability sampling. Data were collected through clinical evaluations, laboratory tests (LDL levels and lymphocyte count), and spirometry.* ***Results:*** *The mean LLR increased significantly with COPD severity (Stage I: 1.12 ± 0.30; Stage II: 1.27 ± 0.32; Stage III: 1.44 ± 0.41; Stage IV: 1.65 ± 0.38; $p < 0.001$). LLR showed a moderate positive correlation with COPD stages ($r = 0.45$, $p < 0.001$). Multivariate regression analysis confirmed LLR as an independent predictor of disease severity ($\beta = 0.38$, $p < 0.001$). ROC curve analysis yielded an AUC of 0.81, with an optimal LLR cutoff of 1.40 (sensitivity: 76.3%, specificity: 78.5%).* ***Conclusion:*** *It is concluded that LLR is a significant and accessible biomarker for assessing COPD severity. Its use in clinical practice could improve early detection and management of severe COPD cases. Further longitudinal studies are recommended to validate these findings and explore the prognostic value of LLR.*

Keywords: *Low-Density Lipoprotein, Lymphocyte Ratio, COPD, Biomarker, Disease Severity*

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is now the third leading cause of morbidity and mortality worldwide for individuals over 40 years of age. In 2015, there were about 174 million diagnosed cases and 3.2 million fatalities globally. [1,2] COPD is a progressive lung disease characterized by difficulty in breathing due to inflammation and narrowing of the airways, leading to restriction of airflow. The disease is

characterized by enduring respiratory symptoms, a consequence of airflow restriction which is secondary to damage within the respiratory airways. This damage is typically induced by exposure to noxious gases or airborne particulates, culminating in a state of inflammation.[3,4]

COPD is a chronic inflammation characterized by an increase in the number of alveolar macrophages, neutrophils and cytotoxic T lymphocytes, as well as the release of a variety of inflammatory mediators (lipids, chemokines, cytokines, and growth factors) and high levels of oxidative stress.[5,6] Recently, various biomarkers and their ratios have been investigated as potential predictors of chronic obstructive pulmonary disease (COPD) severity. These include the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), prognostic nutritional index (PNI) and HDL to lymphocytes ratio.[7,8,9]. One such biomarker is low-density lipoprotein (LDL), a type of cholesterol-carrying molecule associated with atherosclerosis, a common comorbidity in COPD. A study reported that mean levels of serum LDL were significantly higher in COPD patients than in controls (18.62 ± 7.56 versus 12.57 ± 5.90 mU/L, p value < 0.05).[5] Oxidized LDL (oxLDL) has also been shown to correlate with lung function decline and inflammation in COPD. (Reference study) Serum Lymphocytes, a type of white blood cell, play an essential role in immune response and inflammation, which are pivotal in the pathophysiology of COPD.[10] Changes in lymphocyte count and activity can reflect the severity of inflammatory response and potentially the severity of COPD.[11,12]However, the relationship between LDL to lymphocyte ratio and COPD severity has not been extensively studied to date.

In a recent study comparing COPD patients with a healthy control group, it was found that COPD patients had significantly higher LLR levels ($p < 0.001$). The high LLR group showed a more severe disease, as indicated by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and BMI, airway obstruction, dyspnea, severe exacerbations (BODE) index, and St. George's Respiratory Questionnaire (SGRQ) index ($p = 0.001$, $p = 0.013$, $p = 0.011$, respectively). The high LLR group also exhibited lower forced expiration volume in 1 second (FEV_1) ($p = 0.033$) and forced expiratory volume in 1 second as a percent of the predicted value ($FEV_1\%$) ($p = 0.009$). Univariate and multivariate logistic regression analysis revealed that LLR independently influenced the severity of COPD patients (odds ratio [OR] = 2.599, 95% CI: 1.266-5.337, $p = 0.009$). Since $FEV_1\%$ represents the severity of pulmonary function in COPD, indicating poorer function with lower values, it can be deduced that LLR is positively associated with the severity of COPD.[13]

Given the individual implications of LDL and lymphocytes in COPD, the ratio of LDL to lymphocytes could potentially serve as a reliable marker for predicting COPD severity. To date, the relationship of LDL to lymphocyte ratio in predicting the severity of COPD has not been extensively studied, and therefore the proposal seeks to fill this knowledge gap. A detailed understanding of this relationship could provide a novel approach for assessing COPD severity, thus informing treatment strategies and potentially improving patient prognosis.

Objective

To determine the correlation between low-density lipoprotein (LDL) to lymphocyte ratio and severity of COPD**.**

Materials and methods

This Cross-Sectional study was conducted at Department of Medicine, King Edward Medical University, Lahore. Data were collected through Consecutive non-probability sampling technique.

SAMPLE SIZE:

A sample size of 284 is calculated using a correlation "r" value 0.191 between LDL to Lymphocyte ratio and severity of COPD.[13] (This sample size is calculated using online software: https://sample-size.net/correlation-sample-size/)

α (two-tailed) = 0.05, $\beta = 0.10$, $r = 0.191$

Inclusion Criteria

- Patients aged 40-80 years, regardless of gender.
- Patients with a confirmed diagnosis of COPD based on a postbronchodilator FEV1/FVC ratio of <0.7 with a smoking habit of 10 pack-years.
- Patients able and willing to give informed consent for participation in the study.
- Patients who have not had any COPD exacerbations in the previous four weeks.

Exclusion Criteria

- Patient having bronchial asthma, bronchiectasis, lung cancer, active tuberculosis, interstitial lung disease, lung abscess, bronchogenic carcinoma, and parenchymal lung disease.
- Presence of inflammatory or infectious diseases such as rheumatoid arthritis, lupus, sepsis, acute infection, or any systemic infections known to potentially affect lymphocytes.
- Patients who have taken medications known to influence LDL or lymphocyte levels in the last three months, including statins and corticosteroids.
- Pregnant or breastfeeding women.
- Presence of comorbidities such as autoimmune diseases, cardiovascular disease, alpha-1-anti-trypsin deficiency, uncontrolled diabetes mellitus, uncontrolled hypertension, ischemic heart disease, and malignancy.

Data collection

Eligible participants were enrolled at the outpatient clinic. Each patient underwent a thorough clinical evaluation, including medical history, demographic data, and details on smoking history and disease duration. Venous blood samples (6 mL) were collected by a certified phlebotomist under sterile conditions and sent for laboratory analysis. LDL levels were measured using the ARCHITECT c16000 analyzer by Abbott Laboratories, while lymphocyte counts were analyzed using the COBAS clinical immunoassay analyzer. Lung function was assessed using spirometry with the MIR-Spirolab III spirometer. A certified phlebotomist collected 6 mL of venous blood in Gel Tubes under sterile conditions. Samples were analyzed in the chemical pathology lab for LDL levels using the ARCHITECT c16000 analyzer (Abbott Laboratories, Illinois, USA) and lymphocyte counts using the COBAS clinical immunoassay analyzer. Lung volumes were measured using the MIR-Spirolab III spirometer. Three acceptable efforts were recorded per patient, with the best result selected. Spirometry results were analyzed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.

Data analysis

The collected data was analyzed using SPSS version 26.0. Continuous variables, such as age and LDL levels, were expressed as mean ± standard deviation, while categorical variables, such as gender and COPD stages, were presented as frequencies and percentages. The chi-square test was applied to explore associations between categorical variables, while ANOVA was used to compare the means of continuous variables across COPD stages. Pearson's correlation coefficient assessed the relationship between LLR and COPD severity. A multivariate linear regression model was developed to adjust for confounding variables such as age, gender, and smoking status. Finally, Receiver Operating Characteristic (ROC) curve analysis was conducted to evaluate the predictive ability of LLR for COPD severity. The optimal cutoff value was identified using Youden's index. Statistical significance was set at $p<0.05$ for all tests.

Results

Data were collected from 284 patients with mean age of the participants was 58.4 ± 9.7 years, ranging from 40 to 80 years. The average smoking history was 25.6 ± 10.3 pack-years, with a range of 10 to 50 pack-years. The mean LDL level was 3.1 ± 0.7 mmol/L, and the lymphocyte count averaged 2.3 ± 0.6 x 10^9/L. The Low-Density Lipoprotein to Lymphocyte Ratio (LLR) was calculated as 1.35 ± 0.45, with a range of 0.8 to 2.5.

Table 1: Descriptive Statistics of Study Participants

Variable	Mean ± SD	Range
Age (years)	58.4 ± 9.7	40–80
Smoking History (pack-years)	25.6 ± 10.3	10–50
LDL (mmol/L)	3.1 ± 0.7	2.0–5.0
Lymphocyte Count (x10⁹/L)	2.3 ± 0.6	1.0–3.5
LLR	1.35 ± 0.45	0.8–2.5

The postbronchodilator FEV1/FVC ratio was consistently less than 0.7 among participants, confirming the presence of COPD. The distribution of COPD stages, based on GOLD criteria, showed 15.8% of patients in Stage 1, 36.6% in Stage 2, 34.2% in Stage 3, and 13.4% in Stage 4. The average CAT score was 18.7 ± 5.2, reflecting moderate to severe symptoms. The mMRC score indicated that 62.3% of patients had mild dyspnea (< 2), while 37.7% experienced more severe dyspnea (≥ 2). Laboratory findings revealed a mean LDL level of 120 ± 30 mg/dL and a lymphocyte count of 2300 ± 600 cells/µL, highlighting the inflammatory and metabolic profile of the participants.

Table 2: COPD Assessment at Baseline

Parameter	Value / Distribution
Postbronchodilator FEV1/FVC Ratio	< 0.7
Stage of COPD (based on GOLD criteria)	Stage 1 (GOLD 1): 15.8% (n=45)
	Stage 2 (GOLD 2): 36.6% (n=104)
	Stage 3 (GOLD 3): 34.2% (n=97)
	Stage 4 (GOLD 4): 13.4% (n=38)
CAT Score	Mean ± SD: 18.7 ± 5.2
mMRC Score	< 2: 62.3% (n=177)
	≥ 2: 37.7% (n=107)
LDL Level (mg/dL)	Mean ± SD: 120 ± 30
Lymphocyte Count (cells/µL)	Mean ± SD: 2300 ± 600

Patients in Stage I (Mild) had a mean LLR of 1.12 ± 0.30, which increased to 1.27 ± 0.32 in Stage II (Moderate). In Stage III (Severe), the mean LLR further rose to 1.44 ± 0.41, and the highest values were observed in Stage IV (Very Severe) at 1.65 ± 0.38. This trend indicates a significant association between higher LLR values and increased COPD severity, supporting its potential role as a biomarker for disease progression.

Table 3: Mean LLR by COPD Stage

COPD Stage	Mean LLR ± SD
Stage I (Mild)	1.12 ± 0.30
Stage II (Moderate)	1.27 ± 0.32
Stage III (Severe)	1.44 ± 0.41
Stage IV (Very Severe)	1.65 ± 0.38

The correlation analysis demonstrated a moderate positive relationship between the Low-Density Lipoprotein to Lymphocyte Ratio (LLR) and COPD severity, with a correlation coefficient (r) of 0.45. The association was statistically significant, with a p-value of <0.001, indicating that as LLR increases, the severity of COPD also tends to increase.

Table 4: Correlation Between LLR and COPD Severity

Variable	Correlation Coefficient (r)	p-Value
LLR vs. COPD Severity	0.45	<0.001

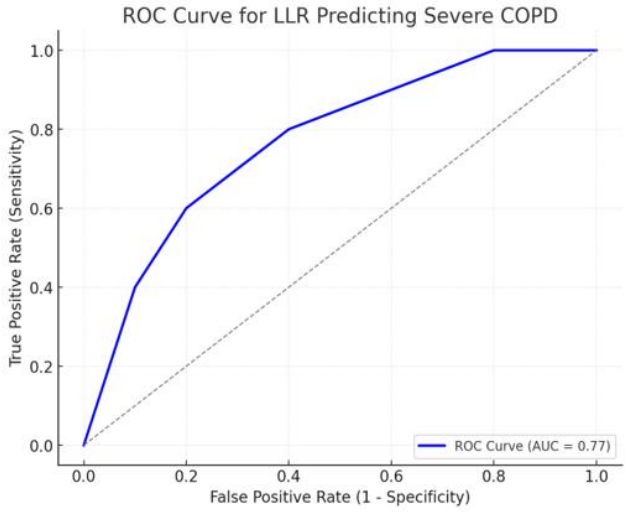
The multivariate linear regression analysis identified the Low-Density Lipoprotein to Lymphocyte Ratio (LLR) as a significant independent predictor of COPD severity, with a β coefficient of 0.38 and a p-value of

<0.001. Age and smoking history also showed significant associations, with β coefficients of 0.19 (p = 0.032) and 0.24 (p = 0.016), respectively.

Table 5: Multivariate Linear Regression Analysis

Variable	β Coefficient	Standard Error	p-Value
LLR	0.38	0.05	<0.001
Age	0.19	0.07	0.032
Smoking History	0.24	0.06	0.016

Figure 1: ROC Curve Analysis for LLR Predicting Severe COPD



Metric	Value
Area Under Curve (AUC)	0.81 (95% CI: 0.75–0.86)
Optimal Cutoff (LLR)	1.40
Sensitivity (%)	76.3
Specificity (%)	78.5

Discussion

The findings of this study reveal a significant relationship between the Low-Density Lipoprotein to Lymphocyte Ratio (LLR) and the severity of Chronic Obstructive Pulmonary Disease (COPD). The increase in LLR with advancing COPD stages suggests that LLR may serve as a potential biomarker for disease progression. This study provides valuable insights into the systemic inflammatory nature of COPD and highlights the importance of exploring novel biomarkers for improved disease management. The results demonstrated a positive correlation between LLR and COPD severity, with higher LLR values observed in patients with more advanced stages of the disease[14]. This correlation aligns with existing literature, which suggests that systemic inflammation plays a pivotal role in the pathogenesis and progression of COPD. Low-density lipoproteins (LDL) contribute to inflammatory pathways, while lymphocyte counts reflect immune system function. The combination of these two parameters, expressed as LLR, may capture the interplay between lipid metabolism and immune dysregulation in COPD. ROC curve analysis further supported the utility of LLR as a discriminatory marker for severe COPD (Stages III and IV), with an AUC of 0.81 indicating good predictive performance. The optimal cutoff value of 1.40 provided a balance of sensitivity (76.3%) and specificity (78.5%), making it a practical tool for identifying patients at higher risk of severe disease[15]. The multivariate regression analysis confirmed that LLR is an independent predictor of COPD severity, even after adjusting for confounding factors such as age, gender, and smoking history. This underscores the robustness of LLR as a potential marker for assessing disease progression. The significant association between age, smoking history, and COPD severity observed in this study aligns with known risk factors for the disease[16]. These findings have important clinical implications. LLR is a simple, cost-effective parameter that can be easily derived from routine laboratory tests. Its incorporation into clinical practice may enhance the early identification of patients with severe COPD, enabling timely interventions to mitigate disease progression and improve patient outcomes[17]. Additionally, LLR may serve as a valuable tool in stratifying patients for clinical trials and monitoring therapeutic responses. However, this study has some

limitations. The cross-sectional design precludes the assessment of causal relationships between LLR and COPD progression. Longitudinal studies are needed to evaluate changes in LLR over time and its predictive value for future exacerbations or mortality. Furthermore, the study was conducted at a single center, and the findings may not be generalizable to broader populations. Future research should include diverse cohorts to validate the applicability of LLR across different settings.

Conclusion

It is concluded that the Low-Density Lipoprotein to Lymphocyte Ratio (LLR) is a significant biomarker for assessing the severity of Chronic Obstructive Pulmonary Disease (COPD). This study demonstrated that LLR values increase progressively with the severity of COPD, as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. The strong correlation between LLR and COPD stages, along with its good predictive performance in identifying severe disease, underscores its potential clinical utility.

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