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Assessment of Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) as Markers of Severity in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Abstract: ***Background: Chronic Obstructive Pulmonary Disease (COPD) is a major global health burden. Acute exacerbations (AECOPD) are primary causes of hospitalization and mortality. This study evaluates the Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) as accessible, cost-effective markers of systemic inflammation and disease severity during these acute events. Methodology: A cross-sectional observational study was conducted on 100 AECOPD patients over 18 months at NMCH & RC, Raichur. Patients were staged using Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. NLR and PLR were calculated from routine complete blood counts. Results: The mean age of the cohort was was 67.14±8.03 years, with a 9:1 male predominance. Mean NLR significantly correlated with disease stage: Stage 1: 3.73±0.18, Stage 2: 6.07±1.27, Stage 3: 6.02±1.14, and Stage 4: 8.19±2.66 ($p < 0.05$). Mean PLR also showed significant variation ($p < 0.05$), peaking at Stage 2 (22219.93 ± 7797.9). NLR and PLR were significantly higher in females compared to males ($p < 0.05$). Conclusion: Both NLR and PLR are useful tools for evaluating inflammation and severity in AECOPD, though NLR demonstrates higher specificity for disease progression.***

Keywords: COPD, Gold criteria, Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte ratio (PLR), Spirometry, Pulmonary function test

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is currently the third leading cause of death worldwide, affecting over 200 million individuals[1]. It is characterised by a progressive destruction of the pulmonary tissue, often the result of an inflammatory response to external stimuli (i.e. long-term exposure to cigarette smoking, environmental pollution), which culminates in a non-fully reversible airflow limitation. [2]

1.1 The Impact of Acute Exacerbations

Acute exacerbations (AECOPD) are defined as an acute worsening of respiratory symptoms that results in additional therapy. These events are associated with:

- Increased risk of subsequent exacerbations.
- Deterioration of respiratory function.
- High healthcare costs due to frequent hospitalization.
- Increased mortality rates.[3]

1.2 The Role of Inflammatory Markers

Inflammation is a central pathogenic mechanism in COPD, involving neutrophils, macrophages, and T-lymphocytes. While biomarkers like CRP, IL-6, and fibrinogen are associated with the disease, they are often time-consuming, costly, or not readily available in peripheral clinical settings.

The **Neutrophil-to-Lymphocyte Ratio (NLR)** and **Platelet-to-Lymphocyte Ratio (PLR)** have emerged as "effortless and basic parameters" obtained from a simple complete blood count (CBC). NLR reflects the balance between active inflammation (neutrophilia) and immune competence (lymphopenia), while PLR reflects roles in damage and repair processes during inflammation.

2. Objectives

1) To study the blood neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte count ratios as markers of acute exacerbation of chronic obstructive pulmonary disease.
2) To compare these ratios as markers of severity of COPD.

3. Review of Literature

3.1 Historical Context

The description of COPD dates back to Hippocrates, who noted breathlessness associated with cough. The term "voluminous lungs" was used by Bonet in 1679.[4] Laennec, the inventor of the stethoscope, provided foundational clinical work on emphysema and chronic bronchitis in the 19th century.[5] Spirometry, the cornerstone of modern diagnosis, was invented by John Hutchinson in 1846.[6]

3.2 Epidemiology and Burden

- **Global Burden:** COPD kills approximately 3 million people annually and is expected to reach the 3rd leading cause of death by 2030 [7]
- **Economic Impact:** In the US and Europe, estimated costs exceed 38 billion US dollars each.[8]
- **India:** India accounts for over half a million deaths annually, with a high prevalence linked to smoking and biomass fuel exposure.

3.3 Pathophysiology

COPD involves an imbalance between proteases and antiproteases, and oxidants and antioxidants. The inflammatory and structural changes in the airways increase

with disease severity and persist even after smoking cessation.

Result is physiological abnormalities- mucous hypersecretion and ciliary dysfunction, airflow obstruction and hyperinflation, gas exchange abnormalities, pulmonary hypertension, and systemic effects.

4. Methodology

4.1 Study Setting and Design

This cross-sectional observational study was conducted at Navodaya Medical College Hospital & Research Centre (NMCH & RC), Raichur, from October 2019 to October 2021.

4.2 Sample Size Estimation

The sample size of 100 was calculated using the formula : $n=Z2\cdot\sigma 2d2.$, based on a population mean (M) of 2.24 and standard deviation (S) of 0.56 from existing literature [9]

4.3 Inclusion and Exclusion Criteria

- **Inclusion:** Confirmed COPD diagnosis via spirometry based on GOLD criteria (FEV_1/FVC < 0.70).
- **Exclusion:** Patients with bronchial asthma, bronchiectasis, active TB, malignancy, pneumonia, or those on systemic corticosteroids/antibiotics.

4.4 Data Collection

NLR and PLR were calculated from absolute counts in the CBC. Severity was graded by post-bronchodilator FEV_1:

- **GOLD 1 (Mild):** FEV_1\geq 80\% predicted.
- **GOLD 2 (Moderate):** 50\% \leq FEV_1 < 80\% predicted.
- **GOLD 3 (Severe):** 30\% \leq FEV_1 < 50\% predicted.
- **GOLD 4 (Very Severe):** FEV_1 < 30\% predicted.

5. Results

5.1 Demographic Data

- **Age:** Mean age was 67.14 ± 8.03 years.
- **Gender:** 90% were male; 10% were female.
- **Residence:** 69% were from rural areas.
- **Smoking:** Prevalence was 80%.

5.2 Clinical Presentation

Common symptoms included increased sputum volume (96%), cough (92%), and increased sputum purulence (82%). Most patients presented with Stage 3 disease (39%).

5.3 Biomarker Analysis by Severity

Variable	Stage 1 (Mean ± SD)	Stage 2 (Mean ± SD)	Stage 3 (Mean ± SD)	Stage 4 (Mean ± SD)	p-value
NLR	3.73 ± 0.18	6.07 ± 1.27	6.02 ± 1.14	8.19 ± 2.66	< 0.0001
PLR	12690.48 ± 3978.45	22219.93 ± 7797.9	19158.73 ± 5070.88	19544.87 ± 10207.59	0.029

NLR Observations: Mean NLR was significantly higher in Stage 4 compared to other groups ($p < 0.01$). **PLR Observations:** Mean PLR was highest in Stage 2, followed by Stage 4.

5.4 Gender-Based Comparison

- **Mean NLR:** Males (3.73 ± 0.18) vs Females (6.07 ± 1.27), $p < 0.01$.
- **Mean PLR:** Males (12690.48 ± 3978.45) vs Females (22219.93 ± 7797.9), $p < 0.01$.

6. Discussion

Our study confirms that NLR and PLR are significantly associated with COPD severity during acute exacerbations.

6.1 NLR as a Severity Marker

The highly significant increase in NLR with GOLD stages ($p < 0.0001$) suggests it effectively reflects the intensification of systemic inflammation as airflow limitation worsens. This aligns with Sakurai et al., who found NLR correlated with FEV_1 decline and exacerbation risk. Our mean NLR of 6.46 is consistent with findings by Farah et al. (6.3) and Taylan et al. (7.1).

6.2 PLR and Prognosis

While PLR also showed statistical significance ($p = 0.029$), its progression across stages was less linear than NLR. This supports the conclusion that NLR may be more specific to disease severity. However, previous studies (e.g., Karadeniz et al.) have highlighted PLR as a useful tool for evaluating ongoing inflammation during stable periods and exacerbations.

6.3 Clinical Implications

Because these markers are low-cost and derived from routine tests, they provide critical diagnostic value in low-resource or peripheral hospital settings. NLR values > 6.90 have been noted as valuable markers for predicting in-hospital mortality in AECOPD.

7. Conclusion

NLR and PLR serve as valuable, easily accessible markers for assessing systemic inflammation and disease severity in AECOPD. In this cohort, NLR exhibited a more direct correlation with GOLD staging than PLR. These biomarkers can help clinicians identify high-risk patients and monitor the inflammatory status during acute events without the need for expensive or complex testing.

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