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Review Article

Neutrophil-to-Lymphocyte Ratio as a Predictor of COPD Exacerbations: A Comprehensive Literature Review

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Abstract

Aim: To evaluate the role of the Neutrophil-to-Lymphocyte Ratio (NLR) as a biomarker for predicting acute exacerbations in COPD (AECOPD) based on current literature. ***Background:*** Chronic obstructive pulmonary disease (COPD) is one of the leading cause of morbidity and mortality worldwide. Acute exacerbations (AECOPD) have led to a major impact on patient health, which in turn lead to hospitalizations and also an increased risk to disease burden. Thus in order to optimize treatment stratergies, one have to identify those reliable biomarkers that help predict exacerbations. The neutrophil-to-lymphocyte ratio (NLR) has been a potential indicator to assess inflammation in COPD patients [1-6]. ***Review Results:*** This review critically examines six key studies on NLR and COPD exacerbations, assessing both its clinical utility as well as its limitations. Several studies have found a link between higher NLR and an increased risk of COPD exacerbations. However, changes in cutoff values, study designs and confounding factors like corticosteroid use may have an impact on prediction accuracy [1-6]. ***Conclusion:*** The NLR is a promising biomarker for determining AECOPD risk. However, consistent cutoff values and multi marker techniques are necessary for clinical use.

Keywords: COPD, Exacerbation, Neutrophil-to-Lymphocyte Ratio, Biomarkers, Systemic Inflammation, Risk Stratification.

1. BACKGROUND

COPD is a progressive inflammatory lung disease which is characterized by recurrent exacerbations, which lead to increased morbidity as well as an increase in healthcare expenditure [1]. Recent researches have focused on inflammatory biomarkers such as NLR in order to predict the exacerbation risks. NLR is a simple yet cost-effective marker that is derived from routine blood tests, making it an easier option for clinical use [2]. However, there is also an ongoing debate regarding its accuracy to predict AECOPD across different populations and clinical settings [3]. This review analyzes current evidence on role of NLR in exacerbation prediction and highlighting key findings from all the six major studies.

2. REVIEW RESULTS

A systematic literature search was conducted in PubMed, Scopus, and Google Scholar using the keywords 'neutrophil-to-lymphocyte ratio,' 'COPD exacerbations,' and 'biomarkers in COPD.' Studies were included if they met the following criteria:

1. Studies those examined the relationship between NLR and COPD exacerbations.
2. Studies those were published in the last 10 years with a defined patient population.
3. Studies having a statistical association such as odds ratios (OR) and confidence intervals (CI).

Those studies with incomplete statistical data or lacking defined methodologies were excluded.

Table 1: Association of NLR with Exacerbation Risk in COPD Patients

Study	Sample Size	NLR Cutoff	Exacerbation Risk (OR, CI, p-value)	Limitations
Ellingsen *et al*., (2021)	466	≥3.0	OR 1.20 (95% CI 1.04–1.38), p=0.002 [1]	Self-reported AECOPD with limited severe cases
Chen *et al*., (2023)	340	Not defined	1.372-fold increase per unit NLR ($p<0.05$) [2]	Small sample but confounders not adjusted

Cai *et al*., (2024)	264	≥3.5	NLR linked to higher exacerbation severity [3]	Single-center study and retrospective bias
Alupo *et al*., (2024)	312	≥1.17	Higher NLR associated with hospitalization [4]	Confounders not fully adjusted
Chis *et al*., (2019)	60	Not reported	NLR higher in active smokers, linked to inflammation [5]	Small sample and lack of exacerbation-specific data
Xu *et al*., (2023)	2625 COPD patients	Not defined, include SII(Systemic immune inflammation index)	OR 1.35 (95% CI 1.03–1.76), p=0.031 High SII associated with higher COPD prevalence [6]	SII is nonspecific, can be affected by various inflammatory conditions

2.1. *Detailed Comparative Analysis of Studies*

From comparing the assessment of the studies, it shows a significant difference in methodology, sample populations and findings. While it can be noted that five studies have a positive association between NLR and COPD exacerbation, there are few differences in NLR cutoff values and prediction strength [1-6].

Studies conducted by Ellingsen *et al*. (2021) and Chen *et al*. (2023) shows that an increased NLR level is associated with an increased risk of exacerbation. Studies done by Ellingsen *et al*. (2021), could identify a cutoff value of (≥3.0), [1] however studies of Chen *et al*. (2023) could not identify such a specific threshold value [2]. In contrast, a much lower cutoff value of (≥1.17), was shown in studies conducted by Alupo *et al*. (2024), [4] and all of this indicates a population-based differences in predictive accuracy. Studies of Cai *et al*. (2024) indicated the association of NLR in severity of exacerbation, linking its values to a greater level in ICU admissions [3]. Chis *et al*. (2019) highlighted that, smokers tend to have an increased levels of NLR but it could not assess it to a direct risk of exacerbation.[5] Xu *et al*. (2023) used systemic immune inflammation index (SII) as a marker and found a significant association between increased SII levels and the presence of COPD in a large US cohort population [6].

One of the major limitations of all these studies is its variations in sample size as well as the study designs used. While Ellingsen *et al*. (2021) and Chen *et al*. (2023) conducted large-scale cohortstudies, [1-2] the others did single-center retrospective study designs, thus increasing the risk of selection bias [3-6]. Also, most of the studies could not determine on corticosteroid use, a confounder that affects the lymphocyte count.

3. DISCUSSION

All studies except for Xu *et al*. (2023), indicated a positive association between an increased level of NLR and COPD exacerbations [1-5]. However in all of these studies there exist differences in the cut off values, threshold ranging from ≥1.17 to ≥3.5. These variations occur due to the differences in demographics, severity of disease, also due to different methodologies used [1-6]. For example, studies of Ellingsen *et al*. (2021) showed an NLR cutoff ≥3.0 in a Swedish cohort,[1] while that of Alupo *et al*. (2024) showed that the threshold was much lower of ≥1.17 in an African population [4].

Also, as some researches highlight the importance of predictive strength of NLR, but other studies highlight its drawbacks. Chen *et al*. (2023) revealed that NLR as a marker is more reliable in patients with eosinophilic COPD.[2] However studies conducted by Chis *et al*. (2019) examined the relationship between NLR and eosinophils and revealed that sometimes the eosinophilic counts may affect the predictive accuracy of NLR [5]. The studies of Xu *et al*. (2023) showed the scope of immune-inflammatory biomarkers in COPD diagnosis, thus suggesting multi marker approaches that can improve its accuracy [6].

4. CONCLUSION & FUTURE DIRECTIONS

Although there is no uniform way in order to detect neutrophil to lymphocyte ratio (NLR) across different population, still it shows as a potential biomarker for COPD exacerbations. The accuracy may be affected by differences in demographics and threshold values. Future studies may focus on:

1. Creating uniform NLR cutoff levels to evaluate the risk of COPD
2. Investigating multi marker models that combine NLR with C-reactive protein (CRP), SII and eosinophilic counts.
3. Implementing into practice prospective, multi centered research with a variety of patient populations.

5. ACKNOWLEDGMENTS

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Clinical Significance

- NLR is a low cost and easily accessible biomarker for assessing COPD exacerbation risk.
- It may help with early intervention measures, lowering hospitalizations and increasing patient outcomes.
- Additional study is required to establish standardized NLR levels for various COPD populations.

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