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Neutrophil to Lymphocyte Ratio and Clinical Outcomes in COPD

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a disabling condition that is characterised by poorly reversible airflow limitation and inflammation. Acute exacerbations of COPD are a common cause of hospitalisation and death among COPD patients. Several biochemical markers have been studied as outcome predictors in COPD; however, their measurement often requires significant time and resources. Relatively simple biomarkers of inflammation calculated from routine complete blood count tests, such as the neutrophil to lymphocyte ratio (NLR), might also predict COPD progression and outcomes. This review discusses the available evidence from studies investigating the associations between the NLR, COPD exacerbations and death in this patient group.

Keywords: COPD, NLR.

Introduction

COPD 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 (Lozano *et al.*, 2012). Typical clinical manifestations include chronic bronchitis, caused by large-airway inflammation and remodelling, and emphysema, a disease of the distal airways and the lung parenchyma, characterised by loss of alveolar respiratory surface. Shortness of breath and chronic productive cough can progress over time to chronic hypoxaemic and/or hypercapnic respiratory failure (Mannino and Buist, 2007). Moreover, COPD is often characterised by extrapulmonary manifestations, such as systemic inflammation, cardiovascular comorbidities, cancer, cachexia and muscle dysfunction, osteoporosis, anaemia, depression and anxiety, which also contribute to disability and premature mortality (Burney *et al.*, 2015).

Acute exacerbations of COPD (AECOPD), defined as worsening of the patient's baseline dyspnoea, cough and/or sputum are an essential component of the natural history of the disease. AECOPD are associated with increased risk of subsequent exacerbations, worsening of coexisting pathological conditions, poor performance status and physical activity, deterioration of respiratory function and, ultimately, death. About half of AECOPD are triggered by bacterial and viral infections; however, non-infective factors such as environmental pollution can also contribute. It is possible that bacterial colonisation itself, or repetitive and intermittent exacerbation caused by recurrent infections, may contribute to the chronic inflammatory state and progression of COPD. Inflammation encompasses a complex network of interactions involving various immune-related cells, including neutrophils and lymphocytes, which can lead to persistent respiratory tissue injury and damage (Rycroft *et al.*, 2014). Moreover, it is likely that an excessive inflammatory response against bacteria contributes to chronic inflammation. It has been reported that the absolute counts of key immune-related cell populations in the peripheral blood, and their ratios, can adequately reflect chronic inflammatory conditions.

In particular, the neutrophil to lymphocyte ratio (NLR) in peripheral blood is being

increasingly studied as a systemic inflammatory marker, particularly considering its rapid, widely available, and relatively inexpensive assessment through routine blood count analysis. NLR has been shown to be an independent prognostic factor in various solid tumours, including lung, colorectal, pancreatic, breast, ovarian and gastric cancer (Agusti *et al.*, 2010). Furthermore, it has been associated with disease severity, hospitalisation, malnutrition, recurrences and mortality in various chronic diseases, including cardiovascular and kidney diseases. In recent years, the NLR has also been investigated as diagnostic and prognostic marker in COPD. Chronic inflammation in COPD causes the recruitment of both the main white blood cell populations, lymphocytes and neutrophils. The latter, once activated, release neutrophil elastase, cathepsin G, proteinase-3, matrix metalloproteinase (MMP)-8 and MMP-9, myeloperoxidase (MPO) and human neutrophil lipocalin, which participate actively in the pathophysiological mechanisms of emphysema and COPD. For example, neutrophil elastase is able to degrade insoluble elastin and MPO mediates the bactericidal effects of neutrophils. Furthermore, both neutrophil elastase and MPO favour tissue destruction in COPD. Therefore, NLR has been investigated as a putative marker of disease severity and prognosis. In this review, we discuss the results of published studies on the association between NLR, disease exacerbation and mortality in COPD.

NLR in stable COPD and exacerbations

The use of NLR as a marker in patients with stable COPD or during AECOPD has only been evaluated in the past few years (table 1). In 2014, GÜNAY *et al.* [36] investigated the hospital records of 269 COPD patients with stable disease and acute exacerbations, as well as 50 sex- and age-matched healthy controls. There was a significant difference in NLR values between healthy controls (mean \pm SD 1.71 \pm 0.65), stable COPD (2.59 \pm 1.79) and AECOPD (4.28 \pm 4.12). However, there were no significant differences in relation to disease severity, both in stable and AECOPD patients. By contrast, there were significant positive correlations between NLR, C-reactive protein (CRP), and red cell distribution width (RDW), as well as a negative association between NLR and the mean platelet volume (MPV), both in stable COPD and AECOPD. Systemic inflammation reduces the survival of erythrocytes and platelets and deforms their membranes. High RDW and MPV have been associated with increased inflammatory activity in several diseases.

The associations remained significant after adjusting for age, sex, Charlson co-morbidity index and smoking status, and suggest the potential role of the NLR to predict features of COPD severity. In this study, a significant association was also observed.

NLR and infections in COPD exacerbations

The authors enrolled 77 patients with AECOPD and carried out cultures from tracheal aspirates or sputum on admission. Bacteria were isolated in 37.4% of patients and the procalcitonin (PCT), CRP and NLR values between them and the remaining cases were compared. NLR values were significantly higher in patients with bacterial exacerbation. The cut-off NLR value for predicting bacterial infections was 11.5 (sensitivity 61%, specificity was 58%, AUC 0.58); the AUC of PCT was significantly better in predicting bacterial exacerbation.

NLR as a prognostic marker in COPD

The association between NLR and inflammation in COPD patients was investigated in other studies that focused on its ability to predict in-hospital and post-discharge mortality. NLR values were higher in patients who died in hospital than in those discharged alive. In addition, mortality rates were higher in patients with $\text{NLR} \geq 4$ than those in patients with $\text{NLR} < 4$. After adjusting for age, sex, anaemia and thrombocytopenia, a binary logistic regression showed that NLR independently predicted in-hospital mortality. ROC analysis indicated that a NLR with a cut-off value of 4 predicts in-hospital mortality with 87% sensitivity and 40% specificity (AUC 0.717).

In a recent retrospective study, Yao *et al.* [52] enrolled 303 patients with AECOPD. NLR values were significantly higher in patients who died in hospital than in those who survived. ROC analysis for using NLR to predict in-hospital mortality indicated an optimal cut-off of 6.24 (AUC 0.803), with 81.1% sensitivity and 69.2% specificity. In the entire cohort NLR values correlated positively with serum CRP levels, while the predictive capacity of NLR exceeded that of CRP and platelet to lymphocyte ratio (PLR) individually or in combination.

The baseline NLR values were significantly higher in COPD patients than in controls (2.98 ± 1.89 versus 2.02 ± 1.92). The mean NLR values of the 272 patients who survived

during the follow-up were lower than those who died. Both univariate and multivariate analysis showed that NLR independently predicted death. ROC analysis (AUC 0.91) indicated that a NLR cut-off value of 3.3 predicted mortality with sensitivity of 85.8% and specificity of 89.7%. According to this cut-off point, COPD subjects were divided into a high NLR group and a low NLR group; exacerbations and mortality were significantly lower in the latter group. The same cut-off value was found to predict AECOPD in other studies, as previously discussed.

The mean NLR values in patients who died were higher than those of survivors (13 ± 10 versus 7 ± 8). Nevertheless, in this study multivariable logistic regression analysis showed that NLR was not significantly associated with mortality at 90 days from discharge, after adjusting for age, haemoglobin, neutrophil count, PLR and urea.

Some studies assessed the prognostic role of NLR in relation to eosinophilic state. In the retrospective study of SALTÜRK *et al.* [55], 647 COPD subjects requiring intensive care unit (ICU) admission were divided into two groups according to their peripheral eosinophil count: 62 in the eosinophilic group (eosinophils $>2\%$) and 585 in the non-eosinophilic group (eosinophils $<2\%$). Blood NLR on ICU admission was significantly lower in the eosinophilic group (median (interquartile range) 4.6 (3.2–6.8)), compared to the non-eosinophilic group (13.0 (17.3–23.1)). Similar findings were observed on discharge and the difference in NLR between admission and discharge was significantly higher in the non-eosinophilic group. Logistic regression analysis, after adjusting for age, sex, BMI, peripheral eosinophilia, long-term oxygen or noninvasive mechanical ventilation applications use, APACHE (Acute Physiology and Chronic Health Evaluation) II score on admission, presence of arrhythmia, septic shock, resistant pathogen and CRP $>50 \text{ mg} \cdot \text{mL}^{-1}$ showed that a NLR >16 independently predicted mortality. This value is consistently higher than other cut-offs reported in other studies and might reflect the severity of the patients evaluated (figure 1).

NLR in patients with COPD and other comorbidities

Three studies evaluated the role of NLR in patients with COPD and other comorbidities. VAGULIENE *et al.*[46] compared NLR values between 139 patients with lung cancer, 55 with lung cancer and stable COPD, 40 with stable COPD and 33 healthy individuals. The NLR was significantly higher in lung cancer patients with COPD (2.92 (0.93–13.42)) or

without COPD (3.08 (1.18–8.84)) when compared to non-cancer patients with COPD (2.35 (1.13–4.25)) or healthy individuals (1.86 (1.16–3.21)). However, the difference between COPD patients and healthy subjects was not statistically significant in this study. YASAR *et al.* [47] recruited 140 patients with COPD, of whom 63 had metabolic syndrome, and 50 sex- and age-matched healthy controls. Among patients with COPD, the NLR was significantly higher in patients with metabolic syndrome than those without (3.40 ± 0.93 versus 2.07 ± 0.43). ARISOU *et al.* [48] studied the relationship of NLR with atrial conduction time in a case–control study including 40 stable COPD patients and 40 controls. The authors evidenced that tricuspid atrial conduction time was significantly longer in COPD patients than in controls (26.4 ± 11.4 ms versus 17.7 ± 7.7 ms), and a significant positive correlation was identified between tricuspid atrial conduction time and NLR ($r=0.38$, $p<0.001$). These findings, as opposed to those of which suggest that specific comorbidities can influence the kinetics of NLR (Vestbo *et al.*, 2014).

NLR and steroid therapy in COPD

Glucocorticoid therapy is not the mainstay COPD treatment! It is the dual bronchodilation which is the pivotal treatment of COPD. Inhaled corticoids are only recommended when frequent exacerbations occur according to GOLD. Nevertheless, this is also questionable and likely that inhaled corticosteroids are essentially useful in eosinophilic COPD [61]. In most of the studies examined to date detailed data about the type, dose and regimen used are lacking. An evaluation of NLR temporal changes in relation to Significant correlations with CRP, WBC and ESR. High NLR values in AECOPD patients with low CRP, WBC or ESR levels RDW, CRP and CD64 significantly elevated in AECOPD.

Conclusions

Blood NLR is a simple, inexpensive, widely available index which has been intensively evaluated in recent years in several clinical applications and in various diseases, including COPD. The studies reviewed showed that the NLR is a valuable predictor of AECOPD and mortality. Furthermore, it correlates well, and in some studies is even more accurate, than other traditional inflammatory indexes (WBC counts alone) or more complex and expensive markers (CRP and calprotectin). Additionally, several NLR cut-off values have been identified in several clinical situations (stable COPD, exacerbations and ICU patients), and with different prediction purposes (COPD itself, exacerbation, infection,

and in hospital and general mortality). The routine use of the NLR in clinical practice should be further assessed in large, well-designed, prospective studies.

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Study significance: NLR is a valuable predictor of AECOPD and mortality. Furthermore, it correlates well, and in some studies is even more accurate, than other traditional inflammatory indexes (WBC counts alone) or more complex and expensive markers (CRP and calprotectin).

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