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Evaluation of The Prognostic Values with Neutrophil-Lymphocyte Ratio in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Aging is an important risk factor for most chronic diseases. Patients with COPD develop more comorbidities than non-COPD subjects. We hypothesized that the development of comorbidities characteristically affecting the elderly occurs at an earlier age in subjects diagnosed with COPD.

Keywords: chronic diseases, pulmonary disease, exacerbation

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized with the presence of air flow limitation and exacerbations caused by inflammation. COPD is the third leading cause of mortality worldwide, and approximately 3 million patients died for COPD in 2012. The severity of COPD is generally assessed by lung function, especially forced expiratory volume in 1 second (FEV_1). However, the severity of inflammation could not be reflected by the measurements and lung function is not routinely applied in the status of exacerbation (Vogelmeier et al., 2017). Previous studies demonstrated the severity of inflammation and exacerbation could be identified by various biomarkers, such as C-reactive protein, IL-6, erythrocyte sedimentation rate, procalcitonin, and platelet to lymphocyte ratio.[14] Recently, neutrophil to lymphocyte ratio (NLR) in peripheral blood has drawn more attention as an inflammatory biomarker. NLR has been considered as a predictor for clinical outcomes various tumors, the ratio of neutrophil and lymphocyte, which represent innate and adaptive immune, respectively (Hoyert, Xu , 2011). The variation of NLR reflects the change of immune system and the inflammation response. Gunay et al. firstly used the NLR as a quick, cheap, and easily measurable biomarker for the severity of inflammation in patients with COPD. Later, many studies showed that the NLR was an independent predictor for COPD exacerbation and mortality.

However, the prognostic value of NLR for COPD remains controversial. NLR was an effective predictor for respiratory hospitalization, while another study showed the NLR had no significant association with COPD exacerbation (Thomsen et al., 2003). In addition, higher NLR was associated with higher mortality in COPD, while Sorensen et al showed the NLR was not a biomarker for mortality in the COPD patients treated by systemic glucocorticoids. Thus, we conducted a meta-analysis to evaluate the prognostic values of NLR for exacerbation and mortality in patient with COPD (Jones, Agusti, 200).

Review Methodology

1.1. Search strategy

This meta-analysis was conducted following the PRISMA flow diagram. A literature search was conducted using the search engines on the database of Cochrane Central Register of Controlled Trials, EMBASE, and PubMed, before April 2019. The eligible articles were searched using the keywords “neutrophil lymphocyte ratio” or “NLR” and “chronic obstructive pulmonary disease” or “COPD.” References in the eligible studies

were checked to find additional related articles. This is a meta-analysis and ethical approval was not necessary.

1.2. *Study selection*

After reviewing the titles and abstracts of all available articles, two reviewers retrieved the related articles independently with the inclusion criteria: articles reporting the COPD were diagnosed as the FEV_1 lower than 70% of forced vital capacity (FVC) after bronchodilation[27,31]; articles reporting the odds ratios (ORs) and 95% confidence intervals [CIs] of NLR for the mortality or the exacerbation, which were defined as aggravation of respiratory symptoms and needed additional treatments (corticosteroids or antibiotics)[24,27]; case–control studies and cohort studies were included. Letters, case reports, reviews, or nonclinical articles were excluded.

1.3. *Data* ***extraction***

2 authors extracted the following data with a standard data form: year of publication, country, study design, number of patients, sex, mean age of patients, mean of FEV_1/FVC, study period, mean NLR, follow-up time, ORs, and 95% CIs for mortality or exacerbation. The ORs and 95% CIs of multiple regression analysis would be the first choice; if not available, the ORs and 95% CIs of univariate regression analysis would be used. The Quality In Prognosis Studies (QUIPS) tool was used to assess the risk of bias. [32,33]

1.4. *Data analysis*

The pooled ORs of were used to evaluate the association of NLR with mortality and exacerbation. We used the Review Manager Version 5.3 (Cochrane collaboration, Oxford, UK) to pool the results. The random-effects model was used for all analyses. When there was a considerable heterogeneity with I^2 >50% or P <.10, the sensitivity analysis would be used to make the results more conservative. The subgroup analysis also would be used to analyze the heterogeneity between the included studies. Using the STATA 13.0 (STATA Corporation, College Station, TX), the publication bias of included articles was evaluated by funnel plot with Begg rank correlation. There was a statistical significance if $P < .05$.

Search outcome

1.5. *Literature research*

The initial research retrieved 63 articles, and two authors screened the title and abstracts of all articles independently. One record was identified after checking the references of eligible articles. Seventeen articles were retrieved after excluding the unrelated articles, and the full text of these eligible articles were inspected for meeting the inclusion criteria.

After assessing the full text of eligible articles, nine articles were left and included in our analysis, and six records were excluded for exclusion criteria and without the available data for OR and 95% CIs. Based on the QUIPS tool, two studies were rated as moderate risk, and six studies were rated as high quality. The supplemental Figure 1 showed the assessment of the risk of bias of the studies included, http://links.lww.com/MD/D121.

1.6. Study characteristics

The characteristics of included studies were showed in the Table 1. Nine articles with 5140 patients, including three prospective studies and five retrospective studies, were included in this meta- analysis. Three studies were conducted in Eurasia and the rest of studies were conducted in Asia. The mean age of patients ranged from 61 to 72 years, and most of mean FEV_1/FVC in included articles were about 50% (Figs. 1–3).

Discussion

The present study aimed to identify the prognostic value of NLR for the exacerbation and mortality in patients with COPD by a meta-analysis. This study, including 9 articles of 5140 patients, suggested that the higher NLR was associated with COPD exacerbation. In addition, NLR was a positive prognostic marker for mortality, especially for the Asian and the patients older than 70. To our best knowledge, this is the first study to systematically evaluate the prognostic role of NLR in COPD by a meta-analysis.

The NLR was an inflammation biomarker for clinical outcomes in patients with COPD, which were caused by systemic inflammation and enhanced airway. Higher NLR was reflected by increased neutrophils and decreased lymphocytes. The activated neutrophils could release the inflammatory cytokines and proteolytic enzymes (such as matrix metal-proteinase, calprotectin, and elastase), which resulted in the emphysema and decreased FEV_1. In addition, lymphocytes played an important role in immune system, and lymphopenia was associated with a high risk of infection and mortality. Thus, increase of inflammatory response (neutrophil) and reduction of immune function (lymphocytes) might explain that higher NLR was associated with poor clinical outcomes in patients with COPD.

Previous studies showed that the higher NLR was negatively associated with exacerbation in COPD, while another study showed no significant association by multiple regression analysis. We found the NLR was associated with COPD exacerbation; however, there was significant heterogeneity attributed to the study by Taylan et al. After excluding the study, the result was consistent with the pooling results of 3 studies. In addition, there were many factors to influence the incidence of exacerbation, such as age,

smoking status, and use of inhaled corticosteroid .he results with body mass index, FEV_1 (% predicted), and exacerbation during the previous year. Also, multiple regression analysis suggested that the NLR was an independent predictor for the exacerbation in patients with COPD. Thus, higher NLR increased the risk of exacerbation.

The prediction ability of NLR for mortality in patients with COPD was still on debate. Some previous studies showed NLR could predict the mortality in patients with COPD, while 1 study suggested the NLR was not a predictor for mortality using glucocorticoid. Several studies demonstrated that the use of glucocorticoid would result in lymphopenia and neutrophilocytosis, which increased the values of NLR and influenced the prediction of NLR for mortality. However, it showed that the NLR could predict mortality independently after adjusting by using the steroid. Our pooled results showed that NLR was a predictor of mortality in patients with COPD. After subgroup analysis (Table 3), we found the heterogeneity decreased in Asia group and Eurasia group, respectively, and the pooled ORs were higher in the Asia group (OR: 4.48) than the Eurasia group (OR: 1.82). Some studies also reported that the higher predictive ability of NLR for various diseases was found in Asia.

In addition, we found that NLR had a higher prognostic value in Asian patients. The cutoff values of NLR were different, and most of studies reported a cutoff from 3 to 7. Previous studies [46showed the higher cutoff would have a stronger predictive ability for clinical outcomes in tumors. The results in one prospective article and four retrospective articles also suggested NLR was a predictor for mortality, which was consistent with the results of included articles. Moreover, we found the pooled OR was higher in high mean NLR group (OR: 3.83) than low mean NLR group (OR: 2.61). This suggested that the predictive ability might increase in the patients with a high mean NLR. The incidence of mortality could also be affected by other factors, such as age, CRP, and steroid use. After adjusting by other factors, the pooled results showed the NLR was an independent predictor for mortality, consistent with the results of 5 included articles. Thus, the NLR was an independent predictor for mortality in patients with COPD. Moreover, NLR had a higher prognostic value in Asian patients than Eurasian patients with COPD or patients with higher mean NLR.

The analysis of exacerbation presented significant heterogeneity, and we found the heterogeneity was attributed to the study. This study only provided the OR of univariate regression analysis without considering other confounding factors, which might affect the results. After subgroup analysis of mortality, we found the different races resulted in the heterogeneity. After grouping by country, there was no significant heterogeneity in Asia group and Eurasia group (Table 3).

Conclusion

Higher NLR may be an independent predictor for the higher incidence of exacerbation and mortality in patients with COPD. In addition, NLR may have a various predictive abilities for mortality in different races and a higher predictive ability for mortality in Asian and COPD patients with higher mean NLR. Nevertheless, due to the heterogeneity, more studies were needed to verify these results.

Author contribution

Manimekalai P, Suresh Kanna S, Vijaykumar Edward, and Anandan P encouraged and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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Conflict of interest: Nil

Study significance: The prognostic value of NLR for COPD remains controversial. The NLR was an effective predictor for respiratory hospitalization, while another study showed the NLR had no significant association with COPD exacerbation.

REFERENCES

Hoyert DL, Xu J. Deaths: preliminary data for 2011. Natl Vital Stat Rep 2012;61:1-51.

Jones PW, Agusti AG. Outcomes and markers in the assessment of chronic obstructive pulmonary disease. Eur Respir J 2006;27:822-32. https://doi.org/10.1183/09031936.06.00145104

Thomsen M, Ingebrigtsen TS, Marott JL, et al. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. JAMA 2013;309:2353-61. https://doi.org/10.1001/jama.2013.5732

Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 Report. GOLD executive summary. Am J Respir Crit Care Med 2017;195:557-82. https://doi.org/10.1164/rccm.201701-0218PP

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