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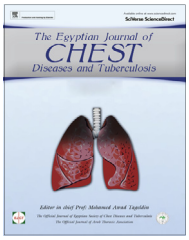

ORIGINAL ARTICLE

Role of neutrophil to lymphocyte ratio in prediction of acute exacerbation of chronic obstructive pulmonary disease

Aida M. Yousef [a,*], **Wael Alkhiary** [b]

[a] *Mansoura University, Faculty of medicine, Department of chest medicine, Egypt*
[b] *Lecturer of Clinical Pathology, Faculty of Medicine, Mansoura University, Egypt*

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KEYWORDS

Chronic obstructive pulmonary disease;
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Abstract Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the lung. Some of the inflammatory markers such as C-reactive protein (CRP), leukocyte count are associated with COPD. The aim of this study is to evaluate the role of neutrophil-to-lymphocyte ratio (NLR) as new inflammatory marker in COPD patients in comparison with the other well-known inflammatory markers. We prospectively evaluated neutrophil-to-lymphocyte ratio, CRP and ESR in 60 patients with stable COPD and 68 COPD patients during acute exacerbation and 60 sex- and age-matched healthy controls. We found that NLR values during acute exacerbation of the disease were significantly higher than those during stable period ($P < 0.001$). NRL values of the stable COPD patients were significantly higher than those of the controls ($P < 0.001$). NLR values were also positively correlated with serum CRP levels, ESR, and WBC.

Conclusion: NLR can be used as a new inflammatory marker for assessment of inflammation in COPD patients. It is a good predictor for exacerbation of COPD. It is a quick, cheap, easily measurable marker with no need for a special request.

Introduction

One of the characteristic features of COPD is acute exacerbations, which usually are associated with increased inflammation due to infections (bacterial, viral and combined viral/bacteria) and or environmental factors. There is a positive relationship between exacerbations of COPD and hospitalization, decline in quality of life and mortality rate. Early detection of acute exacerbation of COPD is essential to avoid these major complications [1].

Inflammation in COPD may be contributed to many cell-types such as the macrophages, the neutrophils and the lymphocytes [2–4].

Neutrophils play an important role in inflammatory conditions more than macrophages. Neutrophils are an important source of proteases, especially reactive oxygen species and

* Corresponding author.
E-mail address: aymanhusen2002@yahoo.com (A.M. Yousef).
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neutrophil elastase. They are the hallmark of acute inflammation [5] .

Unlike other inflammatory biomarkers e.g., ESR and CRP, the Neutrophil–lymphocyte ratio (NLR) is derived from routine complete blood count (CBC) tests. It does not need a special request. It is also a rapid, easy method, and cost-effective. Many studies have reported an increase of NLR during the inflammatory conditions in different diseases such as pancreatitis, inflammatory bowel diseases, and acute coronary syndrome [6–10].

To our knowledge few number of studies have been published about the relationship between neutrophil lymphocyte ratio and respiratory diseases.

Our hypothesis is that NLR could be a useful important inflammatory marker that detects the inflammatory status during acute exacerbations of COPD (AE-COPD) and could identify early acute exacerbations for early management.

The aim of this study is to evaluate the potential for NLR to be used as a biomarker of COPD exacerbation.

Study patients

Between February 2014 and November 2015, patients admitted to our department with acute exacerbated COPD were prospectively enrolled into this study.

The study included 68 COPD patients with exacerbation (mean age was 49.5 years), 60 patients during stable COPD (mean age was 48.9 years) and 60 control subjects(mean age was 48.3 years). The subjects in all groups were males.

Complete blood count (CBC), Erythrocyte sedimentation rate (ESR), and C Reactive protein (CRP) were measured from blood samples taken from patients with AE-COPD (68 patients) within 2 h of admission to the hospital. Three months later on after an acute exacerbation, CBC, ESR, and CRP were measured again from the same patients during the stable period of COPD (60 patients). Eight patients were lost during the follow up. The same investigations were done for the control group. The control group included 60 ex-smokers normal persons. They were matched to patients regarding age and sex. NLR, CRP and ESR values were compared among the three groups of the study. NLR was calculated from the CBC.

Pulmonary function tests were done and both groups of COPD were staged according to the severity criteria of GOLD [7]; stage I [FEV1 $\geqslant$ 80%,], stage II [50% $\leqslant$ FEV1 $<$ 80%], stage III [30% $\leqslant$ FEV1 $<$ 50%] and stage IV [FEV1 $<$ 30%].

Inclusion criteria

Patients with acute exacerbation of COPD, stable COPD patients with no history of acute exacerbation during the past 3 months.

Exclusion criteria

Exclusion criteria for subject enrollment included: (1) severe structural lung disease such as tuberculosis; bronchiectasis (2) a concurrent active inflammatory disease other than COPD; (3) bronchial asthma; (4) having any infectious, inflammatory diseases or malignancy.

COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease guidelines if the ratio of post-bronchodilator forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC) was <0.7. An exacerbation of COPD was defined if there was acute deterioration of the patient's respiratory symptoms beyond normal day-today variations, and there was a need for additional steroids or antibiotics.

Stable COPD was defined as the absence of significant changes in symptom along with no further requirements to additional treatment or doses of daily inhaler treatment for 3 months.

Statistical analysis

Statistical analyses were performed using SPSS version 15 01. Independent-samples t-test, paired t-test and Mann–Whitney U tests were used for the comparison of continuous variables. Pearson's correlation was used between NLR and other inflammatory markers. Receiver operating characteristic (ROC) curves were constructed for the WBC, NLR, CRP, and ESR variables, and the areas under the ROC curve values with 95% CIs were calculated and compared with each other. Optimal cut-off values were determined; sensitivity, and specificity were calculated with (95% CI). P value $\leqslant 0.05$ was considered statistically significant.

Results

The characteristics and laboratory findings of involved subjects in the three groups are outlined in Table 1. There was no statistical difference among the groups with respect to age and sex.

NLR, ESR, and CRP were significantly higher in the exacerbated COPD group compared to stable COPD group and control group. The mean NLR values of exacerbated COPD patients, stable and controls were 4.44, 2.36, and 1.45, respectively ($P = 0.000$) (Table 2). Mean NLR of exacerbated COPD group was significantly higher than those of stable group and control group (respectively $P = 0.000$ and $P = 0.000$). Pearson correlation analysis indicated a significant correlation of NLR with WBC (r 0.694, $P < 0.000$), CRP (r 0.609, $P < 0.000$), and ESR (r 0.714, $P < 0.000$) (Figs. 1 and 2)

The cutoff for NLR was 3.12. it has 86.7% sensitivity for detection of COPD exacerbation and 76.7% specificity (AUC 0.878, $P < 0.001$).

The cutoff for CRP was 3.15. It has 80% sensitivity for detection of COPD exacerbation. and 87% specificity (AUC 0.825, $P < 0.001$) (Fig. 3).

The cutoff for ESR was 17.5. it has 60% sensitivity for detection of COPD exacerbation of COPD and 80% specificity (AUC 0.677, P $<$ 0.001).

The cutoff for WBC was 9.5. It has 76.1% sensitivity for detection of COPD exacerbation and 83.3% specificity (AUC 0.781, $P < 0.001$) (Table 3).

CRP levels were lower than the optimal cut-off value (CRP $<$ 3.15) in twelve patients who were present during AE-COPD, six of them (50%) had higher NLR values than the optimal cutoff NLR (NLR $>$ 3.12). ESR levels were lower

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