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Is an elevated neutrophil-to-lymphocyte ratio a predictor of metabolic syndrome in patients with chronic obstructive pulmonary disease?

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Abstract. – OBJECTIVE: This study aimed to evaluate the diagnostic value of the neutrophil-to-lymphocyte ratio (NLR) in early detection of metabolic syndrome (MetS) in patients with chronic obstructive pulmonary disease (COPD).

PATIENTS AND METHODS: We retrospectively enrolled hospital records of 140 COPD patients and 50 sex and age-matched healthy controls. The diagnostic values of NLR were estimated using the sensitivity, specificity, and area under the receiver operating characteristic curve (AUC).

RESULTS: In total, 140 patients with COPD of which 63 patients had MetS and 50 healthy subjects were included in the study. We found that the NLR values of the stable COPD patients were significantly higher than those of the controls ($p < 0.001$). Among patients with COPD, the NLR was significantly higher in patients with than without MetS ($p < 0.001$). The AUC of the NLR was 0.898 in patients with MetS. The optimal NLR cut-off was 2.56 and was validated in the testing set. For evaluation of MetS, the sensitivity and specificity were 84.1% and 84.4% in patients with COPD under the suggested cut-offs.

CONCLUSIONS: The NLR is a simple, effective, and practical predictor of MetS in patients with stable COPD. It has potential value in public health practice for management of patients with COPD.

Key Words:
Chronic obstructive pulmonary disease, Metabolic syndrome, Chronic systemic inflammatory syndrome, Neutrophil-to-lymphocyte ratio.

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by poorly reversible airflow limitation. It is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, particularly cigarette smoke. Significant extrapulmonary effects may contribute to its severity in individual patients[1]. Comorbidities associated with an increased risk of mortality, such as cardiovascular diseases, are frequently seen in patients with COPD[2,3]. The pathophysiological mechanisms linking COPD and extrapulmonary manifestations remain incompletely described. Smoking causes not only airway and local inflammation but also induces a systemic cellular and humoral inflammatory state involving systemic oxidative stress, changes in endothelial function, and enhanced circulating concentrations of several procoagulant factors[4,5]. Advanced age, certain medications, systemic inflammation, and metabolic disturbances may also contribute to comorbidities.

Metabolic syndrome (MetS) is defined by the presence of abdominal obesity, atherogenic dyslipidemia, high blood pressure, and insulin resistance, which are associated with an increased risk of diabetes mellitus and coronary artery disease[6]. Previous studies have reported an increased prevalence of MetS in patients with COPD[7,8].

Chronic systemic inflammatory syndrome has been proposed to be responsible for the inflammatory nature common to COPD and its comorbidities[9]. To be diagnosed with this syndrome, a patient must meet three of the following diagnostic criteria: age > 40 years, a smoking history > 1 0 pack-years, lung function and symptoms compatible with COPD, chronic heart failure, MetS, and a high C-reactive protein (CRP) level. These

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criteria are based on the systemic inflammation related to the pathogenesis of both COPD and MetS[6,10]. Chronic inflammation involves activation and recruitment of leukocytes, especially neutrophils[11-14]. Leukocyte subtype ratios in patients with various chronic diseases were investigated in recent studies[15-17]. An increase in the neutrophil-to-lymphocyte ratio (NLR) has been described in patients with COPD[18]. Life-threatening risk factors such as cardiovascular disease sometimes cluster, and it is important for clinicians to diagnose patients early and take a broad approach to the management of such patients.

In this study, we aimed to evaluate the clinical value of the NLR for detecting MetS and to clarify whether it can serve as a predictor for MetS in patients with COPD.

Patients and Methods

Study Population

Data were retrospectively collected from the hospital records of all patients diagnosed as stable COPD (n=196) admitted to our outpatient clinic during six months period. We enrolled 140 stable COPD patients with different levels of severity whose complete data including laboratory records (complete blood count, CRP, biochemical parameters and pulmonary function tests at the first admission) on admission for diagnosis could be accessed. The same day datas for assessing both MetS and NLR. The diagnosis of COPD was based on GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria[19]. 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[20]. The criteria for exclusion were having an acute exacerbation (increase in cough, sputum production, worsening dyspnea, sputum purulence within three weeks), having any infectious or inflammatory diseases, any kind of oncologic pathology less than 5 years prior to the study and missing one or more data on admission mentioned above. Forty-six (23.4%) patients were excluded from the study. Fifty subject who were selected for control group were age and sex matched with patient group, with normal spirometry and without any infectious or inflammatory diseases who admitted to our outpatient clinics for routine check-up. The study was approved by the Ethics Committee of our hospital.

Lung Function Status

Lung function parameters were collected using standardized spirometry (V max 20 Pulmonary Spirometry Instrument, Germany). At least three manoeuvres were performed and the best measure of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/ FVC was recorded. The degree of severity of airflow limitation was classified according to the GOLD guidelines[19].

Measurements

Each enrolled participant underwent a physical examination and a detailed medical interview. Relevant to this study, blood pressure were taken according to the American Heart Association's recommendations[20]. Blood pressure was taken from both arms and the higher measurement was used for analysis. Waist circumference was measured horizontally around the narrowest part of the torso, between the lowest rib and the iliac crest[21]. Body mass index (BMI), calculated from weight divided by height squared, was grouped in accordance with World Health Organization recommendations for Asian populations[22]. Cumulative cigarette consumption in pack-years was calculated to quantify the exposure, where 1 pack-yr is equivalent to smoking a mean of 20 cigarettes-day-1 for 1 yr. Dyspnea assessment was carried out using the MMRC scales. The MMRC is an ordinal five-point scale (grades I to V) based on degrees of various physical activities that precipitate dyspnea[23]. Grade V represents the most severe category. Blood samples were collected for fasting glucose, triglyceride and high-density lipoprotein (HDL)-cholesterol were determined using an automated clinical chemical analyser (Olympus Auto analyzer AU 2700, Bayer Health Care Systems, USA) and CBC counts were performed with ABX Pentra DX 120 device in the biochemistry laboratory of our hospital. High sensitivity serum CRP levels were assessed by chemiluminescent immunoassay. The analytical sensitivity of this CRP assay is 0.1 mg/L. NLR was calculated as a simple ratio between the absolute neutrophil and the absolute lymphocyte counts.

Metabolic Syndrome

Metabolic syndrome was classified according to the International Diabetes Federation (IDF) as follows[24].

Waist circumference (WC ≥ 94 cm in European men or ≥ 80 cm in European women) plus two of the following:

1. Glucose 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes;
2. Triglyceride ≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality;
3. High density lipoprotein (HDL), 40 mg/dL (1.03 mmol/L) in men or, 50 mg/dL (1.29 mmol/L) in women or specific treatment for this lipid abnormality;
4. Systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg or treatment of previously diagnosed hypertension.

Statistical Analysis

Data analysis was performed by using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, United States). While, the continuous and ordinal data were shown as mean ± standard deviation, otherwise, number of cases or percentages was used for categorical variables. Whether the differences among groups regarding for continuous and ordinal variables were statistically significant or not was evaluated by Kruskal Wallis test. When the p value from the Kruskal Wallis test statistics are statistically significant Conover's non-parametric multiple comparison test was used to know which group differ from which others. Categorical data were analyzed by Pearson's Chi-square or Fisher's exact test, where applicable. A *p* value less than 0.05 was considered statistically significant. But, all possible multiple comparisons, the Bonferroni Correction was applied for controlling type I error."

Results

A hundred and forty COPD patients with a stable period and 50 healty control subjects were evaluated. 2 (1.4%) patients were classified as Stage 2, 102 (72.9) patients were Stage 3 and 2 (1.4%) patients were Stage 4 COPD. The clinical characteristics of the study population with stable COPD and controls are described in Table I. The groups were well matched with respect to age

Table I. Characteristics, laboratory findings and pulmonary function tests of study groups.

	COPD (n=140)	Control (n=50)	$p^{\#}$
Age (year), mean (SD)	65.12 (10.04)	62.46 (7.44)	0.0486
Sex (male)	74%	64%	0.167
Smoking history	88.6%	64%	< 0.001#
Pack-year, mean (SD)	50.21 ± 34.44	20.42 ± 17.19	< 0.001#
BMI, mean (SD)	26.46 ± 5.06	27.52 ± 3.19	0.090
Waist circumference (cm)	99.11 ± 12.82	97.26 ± 7.09	0.213
SBP (mmHg)	138.43 ± 21.57	124.66 ± 10.65	< 0.001#
DBP (mmHg)	83.00 ± 11.64	78.80 ± 7.25	0.004
Laboratory findings			
Triglycerides (mg/dL)	138.17 ± 90.19	118.04 ± 40.0	0.035
LDL cholesterol (mg/dL)	121.30 ± 29.97	113.20 ± 22.39	0.048
HDL cholesterol (mg/dL)	51.16 ± 12.57	50.94 ± 6.50	0.873
Fasting plasma glucose (mg/dL)	116.49 ± 54.88	90.80 ± 6.76	< 0.001#
Leukocyte ($\times 10^3$ µl)	8.74 ± 2.57	6.56 ± 0.91	< 0.001#
Lymphocyte ($\times 10^3$ µl)	2.29 ± 0.57	2.57 ± 0.51	< 0.001#
Neutrophil-to-lymphocyte ratio	2.67 ± 0.96	1.50 ± 0.24	< 0.001#
Hemoglobin (g/dl)	14.20 ± 1.32	12.89 ± 0.75	< 0.001#
RDW (%)	14.30 ± 1.39	11.93 ± 0.98	0.005
Platelets ($\times 10^3$ µl)	293.61 ± 79.43	300.10 ± 77.80	0.616
MPV (fl)	8.49 ± 0.93	10.64 ±1.04	< 0.001#
PDW (fl)	15.77 ± 1.28	16.51 ± 0.52	< 0.001#
CRP (mg/dl)	3.86 ± 2.05	0.69 ± 0.56	< 0.001#
Pulmonary function test			
FEV_1 (%)	1.22 ± 0.45	2.61 ± 0.47	< 0.001#
FEV_1/FVC (%)	57.22 ± 10.77	81.92 ± 6.34	< 0.001#

BMI: Body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL: high-density lipoprotein, LDL: light-density lipoprotein, CRP: C-reactive protein, FEV_1: forced expiratory volume in the first second, FVC: forced vital capacity, MPV: mean platelet volume, PDW: platelet distribution width, RDW: red cell distribution width. Data are Median (interquartile range) unless otherwise indicated. #Where the *p* value is significant, values within a row with the same superscript letter are significantly different.

and gender. Compared to control group, COPD patients were older and had high number of pack years. Prevelance of high systolic and diastolic BP, the criterias of metabolic syndrome was more prevalent in patients than healty group. There was a significant difference in results of all parameters of CBC among COPD patient and control group. The levels of NLR, CRP, RDW, and PDW were higher while MPV was lower in patients. There was no significant difference in Hgb and Htc levels between two groups.

Metabolic syndrome was detected in 45% of COPD patients. The clinical characteristics of the study population with MetS and without MetS in stable COPD patients are described in Table II. NLR, CRP, RDW and PDW levels were higher and MPV was lower in patients who had MetS than the ones without MetS. NLR levels in patients with MetS was significantly higher when compared with the patients without MetS ($p < 0.001$). The number of MetS parameters was evaluated in COPD patients. There was a significant positive correlation between NLR and parameter number (≥ 3 criteria) of MetS. (R = 0.798, $p < 001$). And also there was a significant negative correlation between NLR and FEV_1 (R = – 0.043, $p < 0.0001$) (Figure 1) and positive correlation between NLR and dyspnea scores. (R = 0.0631, $p < 0.001$).

ROC analysis showed that if the chosen cutt-off point for NLR is 2.56 the specificity and sensitivity are 84.4%, 84.1%, respectively (Figure 2). These was statistically significant ($p < 0.001$, AUC 0.898, 95% CI 0.845-0.951).

Discussion

The main findings of our study are as follows. Patients with stable COPD have higher NLR and CRP level than healthy controls. Additionally, patients with MetS have higher NLR levels than patients with COPD but without MetS. Furthermore, while NLR is positively correlated with dyspnea scores, there is a negative correlation between FEV_1 levels. We revealed a significant association between MetS and NLR in patients with stable COPD. To the best of our knowledge, there are no existing reports regarding the relationship between the NLR and MetS in patients with COPD.

A new advanced approach to management of COPD takes into account the frequent comorbidities observed in COPD and suggests the addition of the term chronic systemic inflammatory syndrome[9]. In recent studies, the levels of several inflammatory proteins are elevated in the systemic circulation of patients with COPD, even during the stable phase[18,25-27]. Similarly, we found higher CRP and NLR levels in patients with COPD than in the control group in the present study.

Table II. Characteristics, laboratory findings and pulmonary function tests of COPD patients with and without metabolic syndrome.

COPD patients	MetS + (n=63)	MetS – (n=77)	p#
Age (year), mean (SD)	64.79 (9.09)	65.47 (10.81)	0.689
Sex (male)	76%	72%	0.642
Labaratory findings			
Leukocyte, ($\times 10^3$ µl)	10.96 ± 1.68	6.93 ± 1.55	< 0.001#
Lymphocyte, (×103 µl)	2.49 ± 0.46	2.14 ± 0.60	< 0.001#
Neutrophil-to-lymphocyte ratio	3.40 ± 0.93	2.07 ± 0.43	< 0.001#
Haemoglobin, (g/dl)	14.30 ± 1.13	14.12 ± 1.47	< 0.001#
RDW, (%)	15.60 ± 0.76	13.24 ± 0.75	0.424
Platelets, ($\times 10^3$ µl)	321.31 ± 71.70	270.94 ± 78.66	< 0.001#
MPV, (fl)	4.83 ± 1.83	9.15 ± 0.60	< 0.001#
PDW, (fl)	15.21 ± 1.34	15.98 ± 0.78	< 0.001#
CRP, (mg/dl)	4.83 ± 1.83	3.06 ± 1.87	< 0.001#
Pulmonary function test			
FEV_1, (%)	1.17 ± 0.36	1.26 ± 0.51	0.226
FEV_1/FVC, (%)	58.38 ± 9.41	56.27 ± 11.75	0.241

CRP: C-reactive protein, FEV1: forced expiratory volume in the first second, FVC: forced vital capacity, MPV: mean platelet volume, PDW: platelet distribution width, RDW: red cell distribution width. Data are Median (interquartile range) unless otherwise indicated. #Where the p value is significant, values within a row with the same superscript letter are significantly different.

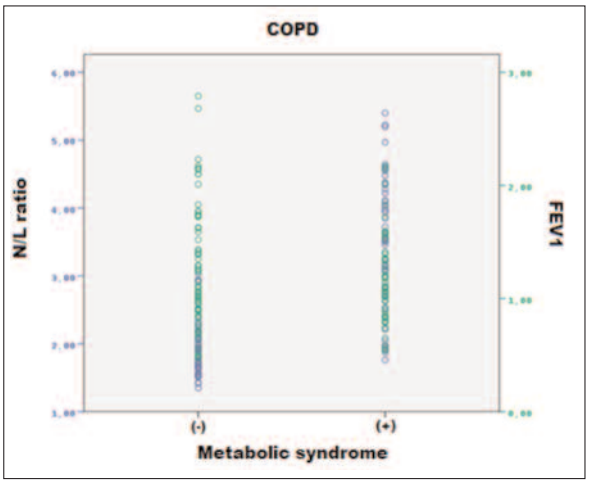

Figure 1. Correlation between NLR and FEV_1.

MetS has been recognized as one of the most relevant clinical components associated with COPD. These two diseases are regarded as two poles of the same pathophysiological mechanism of bronchial and systematic inflammation[7,8]. The estimated prevalence of MetS in patients with COPD is 21% to 53%[28,29]. The prevelance of MetS in our study is 45%. Studies comparing COPD in patients with and without MetS have found a significant increase in the levels of some systemic inflammatory mediators including CRP, IL6, TNF , and adiponectin in patients with concurrent COPD and MetS[8,30-32]. In the present study, we found that inflammatory markers such as the NLR, CRP level, and RDW were higher in patients with than without MetS. This result suggests that the presence of MetS in patients with COPD is associated with more intense systemic inflammation.

In recent studies, it has been reported that decline in pulmonary function has been linked to increased inflammatory markers[27]. In consistent, we found significantly negative correlation between NLR and FEV_1 and positive correlation between the NLR and dyspnea score. And dyspnea was also significantly associated with MetS in our study consistent with that reported by Diez-Manglano et al[33]. Ongoing inflammation in stable COPD might be responsible for increased date of co-morbidities.

The importance of comorbidities in patients with COPD places emphasis on developing a new global strategy for management of COPD. In particular, these comorbidities have a significant impact on the prognosis of COPD, and some of them have been found to be the most frequent cause of death in patients with mild COPD (e.g., cardiovascular diseases and type 2 diabetes)[1]. Moreover, previous studies have indicated that MetS increases the comorbidity index[8,30]. Therefore, MetS must be identified and treated appropriately in patients with COPD. The leukocyte count, ESR, and CRP level have been investigated in terms of their diagnostic performance in several diseases[14-17]. Additionally, the NLR was introduced as a potential cost-effective inflammatory marker that has prognostic and predictive values in patients with systemic inflammatory diseases such as cardiovascular disease, kidney disease, inflammatory bowel disease, febrile seizure and familial Mediterranean fever[16,34-38]. We found a high diagnostic sensitivity and specificity of NLR in the present study. The significantly higher NLR among patients with COPD and its independence as a predictor of MetS suggests that the NLR can be used in future revisions of COPD management protocols. In line with this, an NRL cutoff of 2.56 mg/L enhanced the prognostic information for COPD, especially in terms of differentiating patients with and without MetS. The identification of easily accessible predictors of MetS such as NLR may be helpful for clinicians in formulating a comprehensive ap-

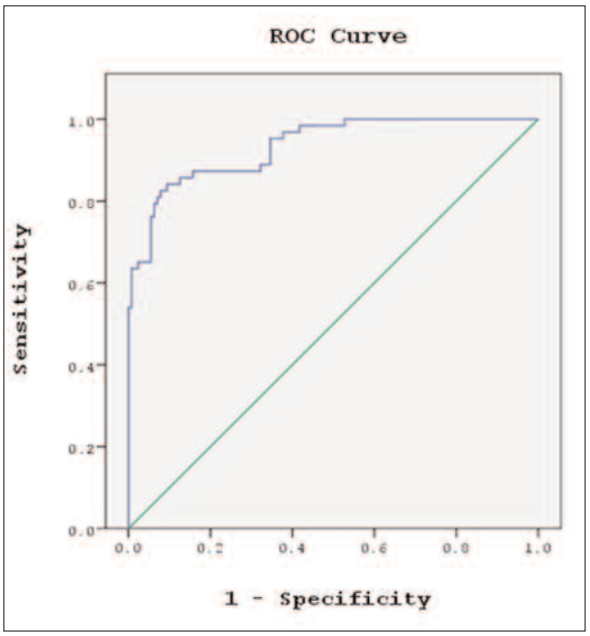

Figure 2. Cut-off value of neutrophil-to-lymphocyte ratio was estimated by receiver-operating curve analysis yielding the area under curve as 0.89 and cut-off level of 2.56 at the sensitivity and specificity of 84 and 84%.

proach to COPD management, which may include smoking prevention and cessation, weight control, exercise, and rehabilitation.

Longitudinal studies are warranted to investigate the long-term effects of MetS on other morbidities in patients with COPD. Most of our participants had mild-to-moderate COPD, and the disease severity was not well distributed.

Conclusions

We found that the NLR is closely associated with MetS in patients with COPD. This finding suggests that the NLR may be a useful marker in the management of COPD with respect to identifying new therapies, modifying lifestyles, and preventing the development of comorbidities.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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