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Original Article

The relationship between acute exacerbation of chronic obstructive pulmonary disease and neutrophile-to-lymphocyte ratio, serum uric acid and gamma-glutamyl transferase levels

Kronik obstrüktif akciğer hastalığının akut alevlenmesi ile nötrofil-lenfosit oranı ve serum ürik asit düzeyleri arasındaki ilişki

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ABSTRACT

Aim: Chronic inflammation plays a pathogenic role in chronic obstructive pulmonary disease. Increase in the ratio of circulating neutrophil to lymphocyte ratio (NLR), serum uric acid and gamma-glutamyl transferase (GGT) levels may serve as a marker of systemic inflammation. The aim of this study is to evaluate the potential predictive value of blood neutrophil-to- lymphocyte NLR and possible role of serum uric acid and gamma-glutamyl transferase levels as biomarkers in chronic obstructive pulmonary disease patients.

Material and Methods: The sample was derived from a population of 276 patients admitted for acute exacerbation of chronic obstructive pulmonary disease to our respiratory medicine department.

Results: Higher N/L ratios, uric acid and GGT levels were detected in chronic obstructive pulmonary disease patients than in the controls ($P < 0.001$). Positive correlations between smoking (pack-years) and NLR, serum GGT, uric acid, and C-reactive protein levels were found ($P < 0.001$; $r = 0.339$, $P < 0.001$; $r = 0.224$, $P < 0.001$; $r = 0.242$, and $P < 0.001$; $r = 0.563$, respectively).

Conclusion: Our study demonstrated that NLR, serum GGT and uric acid levels are significantly higher in patients with chronic obstructive pulmonary disease. With regard to the associations between chronic obstructive pulmonary disease and these parameters, they can be used to determine disease burden besides other risk factors in routine clinical practice.

Keywords: chronic obstructive pulmonary disease, neutrophil to lymphocyte ratio, uric acid, gamma-glutamyl transferase, C- reactive protein, inflammation

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ÖZ

Amaç: Kronik inflamasyon, kronik obstrüktif akciğer hastalığında (KOAH) patojenik bir rol oynamaktadır. Dolaşımdaki nötrofil-lenfosit oranı (N / L oranı), serum ürik asit ve gama-glutamil transferaz (GGT) düzeylerindeki artış, sistemik bir iltihabın göstergesi olabilir.

Bu çalışmanın amaı KOAH'lı hastalarda biyolojik belirteç olarak kan nötrofil-lenfosit (N / L) oranı ile serum ürik asit ve gama-glutamil transferaz (GGT) düzeylerinin muhtemel rolü üzerindeki olası değerini değerlendirmektir.

Gereç ve Yöntemler: Retrospektif bir çalışma.Gereç ve Yöntem: Örneklem, KOAH'ın stabil ve akut alevlenmesi için göğüs hastalıkları bölümümüze başvuran 260 hastadan (stabil KOAH, n = 68, KOAH'ın akut alevlenişi, n = 192) oluşturuldu.

Bulgular: KOAH hastalarının akut alevlenmesinde yüksek N / L oranları ve serum ürik asit seviyeleri tespit edildi (p <0.01). Sigara (paket-yıllar) ile N / L oranı ve C-reaktif protein düzeyleri arasında pozitif korelasyon bulundu (sırasıyla P = 0.014; r = 0.153 ve P = 0.001; r = 0.252).

Sonuçlar: Çalışmamız, akut KOAH alevlenmesi olan hastalarda N / L oranı ve serum ürik asit düzeylerinin belirgin olarak daha yüksek olduğunu göstermiştir. Kronik obstrüktif akciğer hastalığı ile bu parametreler arasındaki ilişkilerle ilgili olarak, rutin klinik uygulamada diğer risk faktörlerinin yanında hastalık yükünü belirlemek için kullanılabilirler.

Anahtar Kelimeler: kronik obstriktif akciğer hastalığı, nötrofil lenfosit oranı inflamasyon, C reaktif protein, serum ürik asit, inflamasyon

Introduction

Chronic obstructive pulmonary disease (COPD), is a type of obstructive lung disease characterized by chronically poor airflow. Acute exacerbation of COPD was defined as " a sustained worsening of the patient' s condition, from the stable state and beyond normal day-to- day variations, and necessitates a change in regular medication [1]. Exacerbations of respiratory symptoms are important because of their profound and long – lasting adverse effects on patients [2]. During the acute episode, levels of circulating acute phase proteins and inflammatory cells are elevated [3]. Biomarkers are any clinical features, imaging quantification or laboratory-based test markers that characterize disease activity, which are useful for diagnosing and monitoring disease processes and response to therapy [4]. Providing reliable evidence to validate biomarkers remains an important challenge to be addressed include the accuracy and reliability of clinical utility and cost- effectiveness [5].

Blood neutrophil to lymphocyte ratio (NLR) is a simple marker of subclinical inflammation that can be easily obtained from the record of a patient's blood cells. Also, serum uric acid (sUA) and gamma-glutamyl transferase (GGT) levels have been associated with increased levels of inflammatory markers that may be important in the outcomes of COPD patients [6,7]. The aim of the study was to evaluate the predictive value of the NLR and possible roles of sUAand GGT as biomarkers in COPD patients.

Material and Methods

The sample was derived from a population of 357 consecutive patients admitted for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) to the respiratory medicine department of Ufuk University Faculty of Medicine (Ankara, Turkey) between December 2012 and September 2015. The study was conducted in accordance with the principles of The Declaration of Helsinki. In total, 81 of them were excluded because they met the exclusion criteria (n = 56) and did not fulfill the inclusion criteria (n = 25). Finally, 276 patients were enrolled, including 135 male (48.9%) and 141 female subjects (51.1%). All subjects were current or ex-smokers (35.76 ± 30.19 pack - years). The inclusion criteria were age above 40 years, current smoker or ex-smoker, a spirometry clear enough to enable evaluation of the respiratory function, and the patient's consent. The exclusion criteria were current bronchial asthma, bronchiectasis, pregnancy, cardiomyopathy, coronary artery disease, congestive heart failure, history of any inflammatory disease (infection, malignancy, rheumatic disorders etc.), gout disease, and any hepatobiliary disorders. Blood samples were collected for complete blood count (CBC), CRP, GGT and sUA. The tubes containing EDTA were used for automatic blood count; the others were measured using conventional methods. Spirometry was performed using a VMAX Encore system (Germany). Staging of airflow limitation

was made according to GOLD guidelines (GOLD stage I [FEV1 ≥ 80%], Stage II [50 ≤ FEV1 < 80], Stage III [30% ≤ FEV1 < 50%] and Stage IV [FEV1 < 30%] [8]. Also, severity of dispnea was evaluated with the COPD Assessment Test (CAT) [9]. The case definition of an exacerbation was a functional one, based on the decision by a patient's primary clinician or by study personnel to prescribe antibiotics or systemic corticosteroids, alone or in combination.

Statistical Analysis

The data were analyzed with the IBM SPSS Statistics 21 for Windows. The normal distribution of variables was verified with the Kolmogorov-Smirnov test. Degrees of association between continuous variables were evaluated by Spearman's Rank Correlation analyses. Comparisons between the groups were made with the Kruskal Wallis test and Mann-Whitney U test. When needed, binary comparisons among the groups were made using the Conover-Inman test ($p<0.05$ was considered statistically significant). A chi square (X2) test was used to investigate whether distributions of categorical variables differed within groups. Optimal cut-off values to predict the severe COPD by sUA and GGT were determined by receiver operating characteristics (ROC) analysis, and area under the curve (AUC) values were determined. To determine the independent risk factors (age, sex, smoking, and NLR) for the presence of COPD, binary logistic regression analysis was performed. The data were shown as mean ± SD for continuous variables and absolute numbers (%) for dichotomous variables. All analyses were stratified by presence of COPD. A P value less than 0.05 was considered statistically significant.

Results

The mean age of the study population was 65.9 ± 11.7 years and 48.9 % of them were male. Baseline characteristics and biochemical examinations are shown in Table 1.

Table 1. Baseline Characteristics of the Individuals

	Control Group	AECOPD Group	p value
Age (years)	59.33±10.28	70.99±10.14	<0.001
Smoking (pack-years)	0.50±5.47	35.76±30.19	<0.001
Uric acid (mg/dL)	5.23±1.65	8.80±28.92	<0.001
GGT (U/L)	26.76±16.81	46.95±51.15	<0.001
LDL (mg/dL)	126.21±34.67	100.90±36.29	<0.001
HDL (mg/dL)	47.03±13.17	43.35±13.81	0.024
TC (mg/dL)	195.71±41.15	176.08±49.10	<0.001
Triglyceride (mg/dL)	138.62±71.34	120.14±56.02	0.038
TC/HDL	4.40±1.32	4.38±1.68	0.433
Hemoglobin (g/dL)	13.50±1.72	13.47±2.18	0.698
MPV (fL)	8.43±1.03	7.94±1.45	<0.001
Platelet count (x103/µL)	262.25±71.49	234.84±91.87	0.006
Creatinine (mg/dL)	0.80±0.38	1.09±1.13	<0.001
Neutrophil (x103/mm3)	4.76±1.81	7.25±3.53	<0.001
Lymphocyte (x103/mm3)	1.88±0.62	1.55±0.74	<0.001
NLR	2.82±1.66	6.37±7.09	<0.001
CRP (mg/L)	5.77±11.27	93.00±87.25	<0.001

Of the 276 patients, 56.5% had COPD, 23.6% had diabetes mellitus, 51.4% had hypertension, 41.3% had hyperlipidemia, and 42.4% had history of smoking. Mean NLR were 2.8 ± 1.7 and 6.4 ± 7.1in the control and COPD groups, respectively ($P < 0.001$).

There are positive correlations between CRP and GGT, NLR ($P = 0.001$; $r = 0.213$, $P < 0.001$; $r = 0.403$, respectively). There are negative correlations between CRP and FEV1, FEV1 / FVC. ($P < 0.001$; $r = -0.286$, $P = 0.002$; $r = -0.241$, respectively) Also, negative correlations between smoking (pack-years) and FEV1, FEV1 / FVC, and HDL levels were found ($P = 0.017$; $r = -0.183$, $P < 0.001$; $r = -0.274$, and $P < 0.001$; $r = -0.245$, respectively). Differently, positive correlations between smoking (pack-years) and NLR, Cr levels, hemoglobin, GGT, sUA and CRP levels were found ($P < 0.001$; $r = 0.339$, $P < 0.001$; $r = 0.216$, $P = 0.039$; $r = 0.125$, $P < 0.001$; $r = 0.224$, $P < 0.001$; $r = 0.242$,and $P < 0.001$; $r = 0.563$, respectively). CATS and MPV, sUA, serum creatinine levels showed statistically significant positive correlations ($P = 0.001$; $r = 0.291$, $P = 0.032$; $r = 0.190$, $P = 0.004$; $r = 0.240$) (Figure 1).

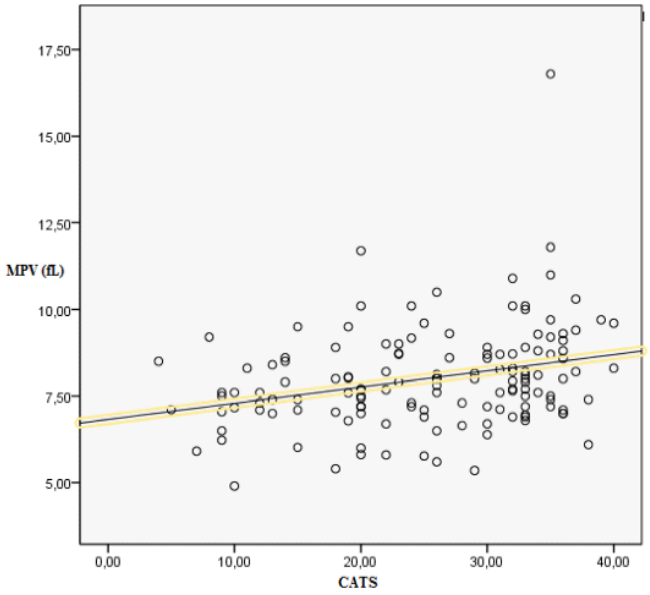

Figure 1. There is a positive correlation between MPV and CATS (P = 0.001; r = 0.291)

Higher levels of NLR were found in the AECOPD patients than in the controls (P < 0.001) (Figure 2).

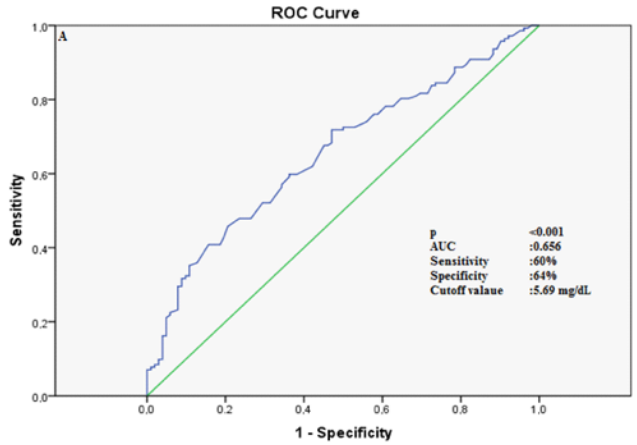

Figure 2. NLR were higher in the COPD patients than in the controls (P < 0.001)

Also, higher levels of GGT and sUA levels were detected in AECOPD group (Table 1) After adjustment for age, sex, and smoking status, the relationship of AECOPD to NLR maintained its significance [P < 0.001; adjusted OR = 1.418 (95 % CI, 1.177 - 1.708)]. Cut off values of sUA (A) and GGT (B) levels for predicting the AECOPD are shown in Figure 3.

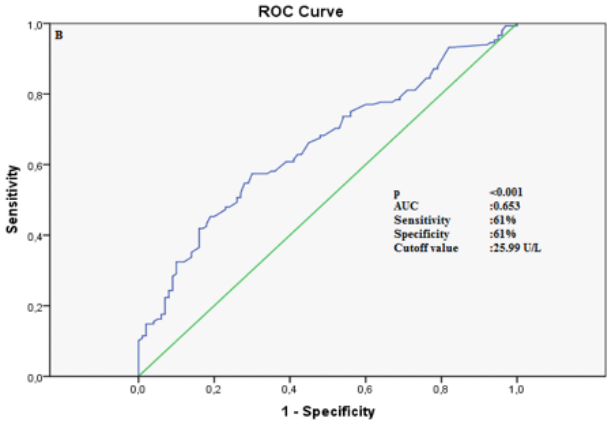

Figure 3. Cut-off values of uric acid (A) and GGT (B) for predicting the AECOPD. AUC, area under the curve; COPD, chronic obstructive pulmonary disease; GGT, gamma-glutamyl transferase; ROC, receiver-operating characteristic.

Discussion

A range of blood biomarkers have been related with severity of airflow limitation. The current study manifested that there was a significant association between GGT, sUA levels and AECOPD. The study also showed that NLR was higher in AECOPD patients than in the control group. All of them were readily available and cost-effective biomarkers.

Exacerbations are associated with the quality of life and disease progression in COPD and therefore early detection of disease activity could significantly reduce the mortality. Elevations of CRP during exacerbation are associated with worsening of COPD [10-12] study from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort found elevated levels of CRP and fibrinogen and leukocyte count to be associated with the exacerbations in the first year of follow-up in univariate analyses [13]. In our study, we found a negative correlation between CRP and FEV1.

The pathogenesis of COPD is complex. The neutrophil is an important cell in the pathogenesis of COPD [14]. Although the underlying mechanism associated between the NLR and COPD has not been clearly established neutrophils, one of the most important mediators of innate immunity, are professional phagocytes which mount the acute inflammatory response and act as the first line of defense against invading pathogens

[15]. The systemic inflammation is reflected by an increase number of neutrophil granulocytes in the circulation and neutrophil granulocyte count is associated with progression of COPD. Previous epidemiological studies have shown an inverse relationship between circulating neutrophil numbers and the forced expiratory volume in one second (FEV1) [16,17]. Activation may be even more pronounced in neutrophils which are sequestered in the pulmonary microcirculation in smokers and in patients with COPD [18]. Smoking induces oxidative stress and lung inflammation in COPD [19]. As a result of damage to lung tissues induced by oxidants and inflammation, pulmonary function declines with long-term exposure to smoke [8,20]. Likewise, we found a positive correlation between NLR and smoking in our study.

NLR also has been examined as a measure of inflammation in different groups of patients such as those with chronic kidney disease [21,22] cardiovascular disease [23,24], or ulcerative colitis [25]. Previous studies have shown that NLR associated with disease severity and exacerbation in COPD patients that can be used as a new inflammatory marker. This ratio has also been useful to evaluate the adverse clinical outcomes and mortality in various cancer types [26,27]. Previous studies have shown that NLR associated with disease severity and exacerbation in COPD patients that can be used as a new inflammatory marker [28-30]. Gürol et al. [31] found NLR to have higher sensitivity than CRP and WBC. This marker showed a significant increase not only exacerbation but also in stabil COPD patients [32]. In our study, the NLR level was higher in patients with exacerbated COPD than control group. Therefore, NLR may be useful as a diagnostic tool like CRP to show the inflammation and confirm exacerbation COPD and identify patients with the severity of AECOPD.

Oxidative stress appears to be a key component of many reactions associated with chronic inflammation. Gamma-glutamyl transferase (GGT) is a clinical marker of biliary disease, but is also of importance in anti-oxidant metabolic pathways and, consequently, is a potential biomarker of oxidative stress which increases in inflammation because of leukotriene-induced inflammation in COPD [33]. It is imperative for a cell to maintain this level of activate glutathione (GSH) for normal functioning. Cells, in particular within the lungs, have evolved elaborate mechanisms that ensure proper balance between the pro-oxidant and antioxidant molecules as a defense against constant oxidative challenge. GSH is the most important non-protein sulphydryl in the cells and plays a key role in the maintenance of the cellular redox status. The redox potential is defined as the ratio of the concentration of oxidizing equivalents to that of reducing equivalents [34]. As the only enzyme of the cycle located on the outer surface of plasma membrane, gamma-glutamyl transpeptidase (GGT) plays key roles in GSH homeostasis by breaking down extracellular GSH and providing cysteine, the rate-limiting substrate, for intracellular de novo synthesis of GSH. GGT also initiates the metabolism of glutathione S-conjugates to mercapturic acids by transferring the gamma-glutamyl moiety to an acceptor amino acid and releasing cysteinylglycine. In Holme's study, GGT correlated with airflow obstruction and, it was independently related to FEV(1), mortality, smoking history and male gender [35] Lim et al [36] examined association between serum GGT and concentrations of serum C-reactive protein (CRP) among 12,110 adult participants. After adjustment for race, sex, age, cigarette smoking, alcohol intake, and body mass index (BMI), serum concentration of GGT across all deciles was positively associated with serum concentrations of CRP. A strong clinical relationship between CRP and GGT was described [37] In our study we also found positive correlation between GGT levels and CRP as Ermiş et al did [7]. GGT levels are also correlated with smoking status.

Tissue hypoxia has been reported to induce the degradation of adenosine. This results in the release of purine intermediates and end products of purine catabolism, such as uric acid [38]. Elevation of sUA levels has been observed in hypoxic subjects, including patients with COPD [39]. Uric acid is the end-product of purine degradation [40] and it is a biomarker of xanthine oxidase activity, which is known to be an important source of reactive oxygen species [41]. High levels of lung oxidative stress and inflammation, circulating UA levels may be elevated as a result of lung tissue damage. Therefore, several investigators have reported that elevated sUA levels were associated with worsening of cardiovascular disease, heart failure and COPD [42,43]. Positive associations were demonstrated between sUA and inflammatory markers such as CRP and interleukin - 6 (IL-6) [44]. A Spanish study reported associations between sUA / creatinine ratio and FEV 1 [37]. Similarly, Kocak et al found [45], both sUA levels and sUA/creatinine ratios were significantly higher in COPD patients than in healthy controls. According to a Japanese study, hypoxia, pulmonary hypertension, oxidative stress and inflammation, which eventually results in impairment of pulmonary function are possible explanations for the association between sUA levels and pulmonary

function [46] Bartziokas et al [6] have shown that patients with increased sUA levels had increased 30-day mortality rates, and increased risk of AECOPD and hospitalization in the 1- year follow up. Similarly we found positive correlation between sUA levels and smoking (pack-years). Multiple logistic analysis revealed that FVC % predicted in females and FEV1 % predicted in both genders were significant predictive for hyperuricemia. In our study, sUA levels were significantly higher in COPD patients than in controls and there were significant associations between spirometric measures, smoking pack / year and sUA levels. It has been suggested that sUA levels increase in the presence of persistent systemic inflammation caused by COPD.

Our study has some limitations. First, the study population was relatively small and our study was retrospective A larger study population would provide a higher statistical power. Another limitation was that neutrophils and lymphocytes count was not determined visually by peripheral blood smear. Large scale prospective studies are needed to obtain further information.

As a conclusion although there is no ideal single serum marker for predicting disease severity, white blood cell count, CRP and ESR are the most commonly used inflammatory indices in routine clinical practice. Our study demonstrates that in patients with AECOPD, NLR, serum GGT and sUA, which are widely and rapidly available, simple, low-cost biomarkers could be used as marker of inflammation in AECOPD. Large scale prospective, randomized clinical trials are needed to see whether the N / L ratio, GGT, and sUA levels obtained during routine testing are of greater value in terms of diagnosis, risk stratification, and treatment evaluation in patients with COPD.

Declaration of conflicting interests

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