



THE ROLE OF SOME INFLAMMATORY BIOMARKERS IN ASSESSING THE SEVERITY AND COURSE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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SUMMARY:

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease with pulmonary and extrapulmonary involvement. The inflammatory process plays a role in the pathogenesis of COPD. Inflammation is local and systemic, involving many inflammatory biomarkers, mediators and cytokines.

Objective: To determine the relationship between the severity and course of COPD with the levels of some inflammatory biomarkers.

Materials and methods: Retrospective study in 85 outpatients with COPD for a six-month period in 2023. Patients were stratified by disease severity according to GOLD 2019 criteria.

COPD exacerbations in the previous year were tracked.

The levels of the main markers of inflammation in COPD - leukocytes, neutrophils, CRP and uric acid were studied, and those that were less frequently monitored in medical practice - IL-6, IL-8 and vitamin D. We studied their relationship with the severity and the course of the disease.

The survey data were processed using STAT GRAPHICS PLUS and EXCELL for Windows.

Results: We established: positive correlations between: the severity of COPD and high values of leukocytes ($p=0.002$) and uric acid (Pearsson $p<0.05$); exacerbations and high leukocyte values ($p=0.01$); the higher point score of CAT and high values of leukocytes ($p=0.008$) and IL ($p<0.05$); leukocyte levels and mMRC score ($p=0.0005$), there is a negative correlation between vitamin D and mMRC ($p=0.02$).

Conclusion: Elevated levels of inflammatory biomarkers are associated with systemic inflammation in COPD, but there is no proven specific biomarker for the severity and course of the disease.

Keywords: COPD, inflammation, biomarkers, exacerbations

INTRODUCTION:

Knowledge about the etiology and pathogenesis of the chronic obstructive pulmonary disease (COPD) has significantly deepened in recent years. It is known that it is not only pulmonary, but a rather complex disease with a heterogeneous nature. It is defined as a complex syndrome with pulmonary and extrapulmonary involvement [1].

The fact that smoking is one of the main risk factors for the development and progression of the disease is indisputable. Along with various external damaging agents, it contributes to the progression of tissue inflammation involving cells and mediators of innate and adaptive immunity [2]. Inflammation in COPD is both local and systemic. Local inflammation is found in both large and small airways.

Several types of cells are involved in the inflammatory process in COPD, which affects the peripheral airways. Epithelial cells producing mucus, antioxidants, antiproteases, and defensins are responsible for a large part of the lung's protection against cigarette smoke, harmful gases, bacteria, fungi, and viruses. Epithelial cells activated by cigarette smoke produce inflammatory mediators such as TNF- α , IL-1 β , IL-6, GM-CSF IL-8. Macrophages are of primary importance for the inflammatory process, which is proven by the correlation between their number in the parenchyma and the severity of emphysema [3]. Because COPD increases the redistribution of monocytes from the circulation in response to the action of selective chemokines, an increased number of macrophages in the lungs is found precisely in patients with COPD and in smokers. Activation of macrophages by cigarette smoke leads to the release of reactive oxygen radicals, TNF- α , IL-1, IL-8, LTB 4 and the secretion of various enzymes such as cathepsins and metalloproteinases [4]. Their main function is to phagocytose clear bacteria by apoptosis, but in COPD, it is somewhat limited, which is related to the colonization of microorganisms in the airways in the disease. Neutrophils mainly play a role in the inflammatory proc-

ess by stimulating mucus hypersecretion through the secretion of serine proteases – cathepsin, neutrophil elastase, proteinase metalloproteinases [1, 5]. Their number correlates with the severity of the disease, and they also increase during exacerbations. The link between innate and adaptive immunity is mediated by dendritic cells. They protect the lungs in contact with external irritants by activating other cells involved in the inflammatory response [6]. Another type of inflammatory cell is T lymphocytes, found in increased amounts in the peripheral airways, mainly at the expense of CD8+. Their number correlates with the degree of alveolar destruction and airway obstruction.

In addition to the local inflammatory effects, a systemic inflammatory response has been established, including a direct effect on the endothelial function of peripheral vessels, stimulation of the hematopoietic system with the release of polymorphonuclear leukocytes, activation of coagulation factors, systemic oxidative stress, eosinophilic inflammation [7]. Many studies demonstrate the association of COPD with systemic inflammation. It is associated with activation of circulating inflammatory cells - such as leukocytes, neutrophils, eosinophils; with increased levels of inflammatory mediators - CRP, uric acid and pro-inflammatory cytokines such as IL-6 IL-8 [8, 9, 10].

Pulmonary and systemic inflammation in COPD is associated with disease progression and mortality. Celli and co-authors investigated the associations between mortality and levels of a broad set of biomarkers in a large cohort of COPD patients over 3 years, concluding that the addition of a panel of selected biomarkers to establish clinical signs increased the capacity to predict mortality in COPD [5].

The aim of our study was to determine the relationship between the severity and course of the disease and some inflammatory biomarkers, both routinely used in clinical practice and those that are not used daily.

MATERIALS AND METHODS:

Retrospective study in patients with COPD diagnosed more than 1 year ago. 85 patients from an outpatient practice in the city of Pleven were monitored for a six-month period in 2023. The patients had no evidence of exacerbation of the disease during the last four weeks of the examinations. 60 men and 25 women with a mean age of 66.73 years were included. All of them signed an informed consent. A medical history was taken, and a physical examination was performed, along with an assessment of accompanying diseases, medications, and risk factors. Patients were divided into groups according to the severity of the disease, to the GOLD 19 criteria. The COPD Assessment Test (CAT) and the Modified Medical Research Council Dyspnea Scale (mMRC) were administered. They were followed for COPD exacerbations in the previous year.

To study the levels of biomarkers, 10 ml of blood was taken from each patient by venipuncture by qualified personnel, following all the rules of the procedure. The widely used inflammatory markers - leukocytes, neutrophils, CRP and uric acid, as well as the less frequently monitored in routine practice - IL-6, IL-8 and vitamin D

were studied.

A correlation of the inflammatory markers with the severity and course of the disease was sought. Statistical methods were used to determine the significance of the results using the software packages Statgraphics Plus, version 2.1, and EXCEL for Windows. Parametric and non-parametric tests were used: chi-square, Pearson, ANOVA, with a value of $p < 0.05$ considered statistically significant.

RESULTS:

Elevated values of leukocytes were registered in 14 of the patients (16.5%). We found leucocytosis in 28,5% of patients – I and II stages of COPD and in 71,5% of patients – III and IV stage. We established a relationship between high values of leukocytes and the severity of COPD (Pearsson $p = 0.002$, Fig. 1). The exacerbations and hospitalisation were more frequent in patients with leucocytosis (42,8%/57,2%, $p = 0.01$, fig. 2), and they had more pronounced symptoms, confirmed by a higher point score of mMRC ($p = 0.0005$) and CAT ($p = 0.008$).

Fig. 1. Stages of COPD severity and leukocytes

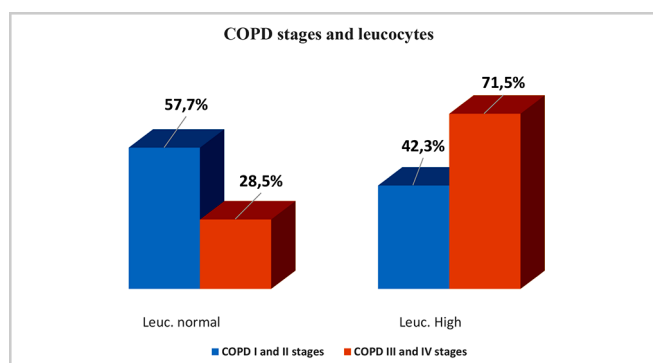
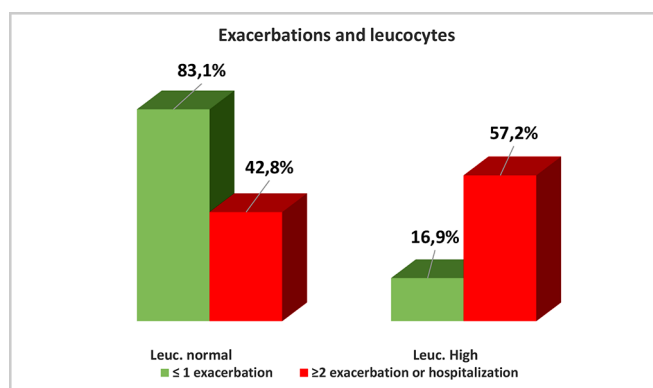


Fig. 2. Exacerbations and leukocytes

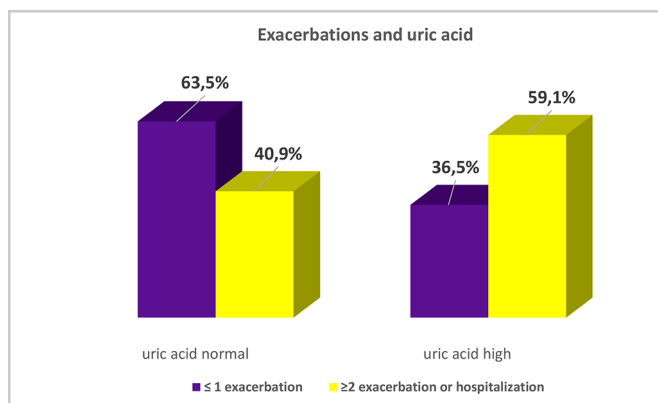


Increased neutrophils were detected in 2 (2.35%) of the subjects. The small number of these patients did not allow us to make conclusions about statistical dependencies.

Higher levels of CRP were found in 31 patients (36.5%), but there was no correlation with the severity and course of COPD.

In patients with ≥ 2 exacerbations or hospitalization, uric acid levels are elevated compared to patients with less exacerbations. (59.1%/40,9% Pearson $p < 0.05$, fig. 3)

Fig. 3.Exacerbations of COPD and uric acid



Increased values of IL-6 were present in all studied patients, but we did not find a correlation between the severity of COPD and the course of the disease. A correlation was detected between higher IL-6 values and CAT-test results, $p < 0.05$. IL-8 studies in all patients showed no abnormalities. Regarding Vitamin “D”, no correlations were found with the severity of COPD, exacerbations and CAT-test, but there was a statistically significant relationship between its lower levels and the higher point score of the mMRC scale ($p = 0.02$)

DISCUSSION:

Inflammatory biomarkers - both those routinely investigated in medical practice and those less commonly used - are widely discussed as factors that play an important role in the systemic inflammation of COPD. Many studies present undisputed data that neutrophils are an important factor in the pathology of COPD. This includes not only their activation but also changes in cellular functions that favor lung tissue damage. There is no definitive evidence that elevated leukocyte counts are related to the severity and course of the disease, rather, it is a response to the inflammatory process itself in COPD [11].

We found a relationship between higher leukocyte values with severity and exacerbations in COPD and as well as more expressed symptoms.

An inflammatory marker of important clinical importance is CRP. There are numerous reports on the role of CRP in the severity and course of COPD. In a study done at Shifa Islamabad Hospital on 104 patients with COPD, a correlation was found between high CRP levels and COPD severity [12].

Other authors observed high levels of CRP in bacterial exacerbations but not in COPD exacerbations caused by other factors [13]

Although there are many reports in the literature about an association between high CRP levels and severity and exacerbation in COPD, we did not find a correlation.

Uric acid is another inflammatory biomarker that has been studied in COPD. A meta-analysis including seven studies from countries in Europe, Asia and Africa reported higher uric acid levels in patients with COPD compared to healthy controls. Differences in its values have also been

established according to the stage of the disease [14]. Our study found a correlation between high uric acid levels and exacerbations but not with COPD severity.

Interleukin 6 (IL-6) is involved as an inflammatory marker in the earliest stages of the inflammatory process. Although not widely used in medical practice, its role in the inflammatory process of COPD has been proven in many studies. An observational study conducted at Beni Suef University Hospital, Egypt, in patients with COPD found a relationship between high levels of IL-6 with disease severity and exacerbations [15]. In a study of hospitalized COPD patients in Huizhou, China, higher levels of IL-6 were found to be associated with the frequency of exacerbations [16]. There are reports in which patients with COPD were followed for several years without the relationship between elevated IL-6 and the severity of the disease, as well as the nature of its course [17,18].

In conformation of these data we did not find association between elevated IL-6 levels and COPD severity.

In research from Shanghai, China, high IL-8 values were reported during COPD exacerbation but not at a steady state. They correlate with an increase in the levels of other inflammatory biomarkers [19].

The anti-inflammatory effect of vitamin D on the lungs is known. Lower values are associated with an increase in inflammatory biomarkers in patients with COPD. An inverse relationship between vitamin D levels and inflammatory markers correlates with COPD severity [20]. Although there are many reports of elevated levels of various inflammatory biomarkers in patients with COPD, there is no definitive evidence that any of them as an independent indicator has a determining role in the severity and course of COPD. There are publications regarding patients with COPD, mainly smokers, in whom elevated values of more than two inflammatory biomarkers may be associated with a more severe course of the disease.

High levels of leukocytes, uric acid, CRP and IL-6 were found in the patients studied by us. A correlation was obtained between the severity of COPD and high levels of leukocytes and uric acid, but not with the other indicators. A large number of participants in our study had a low vitamin D levels, but we did not find a correlation between low vitamin D values and COPD severity. A relationship between the frequency of exacerbations and high levels of inflammatory indicators was established only in relation to leukocytes.

CONCLUSION:

Elevated values of inflammatory biomarkers in patients with COPD are evidence of a systemic inflammatory nature of the disease. Leukocytosis and elevated value of uric acid as biomarkers of inflammation in COPD, correlate with frequency of exacerbations and hospitalizations.

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