# PREDICTION OF THE COURSE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE BY BLOOD BIOMARKERS

***D.I. Murashka[1]*, A.D. Tahanovich[1], M.M. Kauhanka[1], I.A. Nikitina[1], A.V. Kolb[1], L.S. Bogush[2], E.I. Davidovskaya[2], O.A. Budnik[2]***

[1]Belarusian State Medical University,
83 Dzerzhinsky ave., Minsk, 220116 Belarus; *e-mail: dashamurashka@mail.ru
[2]Republican Scientific and Practical Center of Pulmonology and Phthisiatry,
157 Dolginovsky tract, Minsk, 220080 Belarus

Chronic obstructive pulmonary disease (COPD) is one of the most common pathologies of the respiratory system; it is characterized by increasing airflow limitation. The course of COPD is unstable and is often accompanied by periods of exacerbation, when respiratory symptoms of the disease significantly increase. The frequency of COPD exacerbations is an important predictor of its course, allowing to predict the decline in lung tissue function and the outcome of the disease. Currently, the risk of future COPD exacerbations in a patient is assessed based on the history of previous exacerbations, and the improvement of his condition is evaluated on the basis of the weakening of COPD symptoms. However, the lack of objective criteria complicates unambiguous verdict on the probability of acute condition development and the effectiveness of treatment of COPD patients. Based on the analysis of literature data we propose determination of the levels of chemokines (CXCL5, CXCL8, CXCR1/2, CD44v6), HIF-1α, procalcitonin, albumin and C-reactive protein, leukocyte cells, as well as their possible combination in the peripheral blood as an informative tool for evaluation in COPD patients.

**Keywords:** COPD; biomarkers; CXCL5; CXCL8; CXCR1/2; CD44v6; HIF-1α; acute phase proteins; blood cells

**DOI:** 10.18097/PBMCR1579

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a respiratory disease characterized by progressive airflow limitation and connective tissue destruction [1]. In 2024, COPD ranked fourth in the global structure of adult mortality [2]. In addition, the incidence of COPD continues to increase due to the constant impact of the main risk factors for its development: urbanization, smoking, air pollution [3]. According to expert forecasts, in the period up to 2050, global costs for the COPD treatment will be as high as 326 trillion USD [3]. By 2030, current costs for the diagnostics and treatment of this disease will more than double and exceed the costs of treating cardiovascular pathology [4].

In clinical practice, criteria for the air flow rate limitation are determined to establish a diagnosis of COPD using spirometry. The main criterion is the ratio of the forced expiratory volume in the first second (FEV1) to the forced vital capacity of the lungs (FVC), measured after a test with a bronchodilator. In COPD, the FEV1/FVC ratio does not exceed 0.7 [5]. The severity of the disease is also evaluated during selection of a treatment plan. According to the Global Initiative for COPD (GOLD) criteria, the degree of airflow limitation is determined based on the post-bronchodilator FEV1 value (in % of predicted). Mild COPD is diagnosed (GOLD 1) when this value exceeds 80%. FEV1 from 50% to 79% of the reference values corresponds to moderate severity (GOLD 2). In case of FEV1 of 30–49% and less than 30%, severe and extremely severe degrees are diagnosed, respectively (GOLD 3 and 4).

The course of COPD is unstable: a stable course of the disease is often interrupted by exacerbations. COPD exacerbations are conditions that are characterized by a sharp deterioration in disease symptoms, an increase in local and systemic inflammatory response, which require additional therapy [6]. As a rule, they are typical for patients whose spirometry results correspond to the GOLD 3 and 4 criteria [7]. Exacerbations leading to progressive decline in lung functioning often require hospitalization [8]. The five-year survival rate of patients hospitalized due to COPD exacerbation does not exceed 40%, so the frequency and severity of COPD exacerbations are the key criteria for assessing the severity, prognosis, and outcome of this disease. They also play a major role in making decisions about prescribing pharmacological agents to patients [6, 8]. The ability to predict COPD exacerbations helps doctors to create a treatment plan, and patients to adjust their lifestyle to minimize the risk of subsequent exacerbations [9].

The COPD exacerbation risk assessment in patients is currently evaluated based on the history of previous exacerbations [10]. A history of at least two mild or moderate exacerbations in the past year, or one severe exacerbation leading to hospitalization, indicates a high risk of future exacerbations and requires preventive measures [11]. However, assessing the risk of exacerbations solely based on the patient's history is informative mainly in case of repeated medical care, while data on the frequency of COPD exacerbations in patients undergoing treatment for the first time are lacking [12].

An important parameter influencing the tactics of COPD treatment is the severity of exacerbations, assessed mainly on the basis of the patient's subjective sensations of increased shortness of breath, cough, or sputum production. At the same time, patients often underestimate the severity of these symptoms [13, 14]. The effectiveness of treatment of exacerbations is usually assessed on the basis of FEV1 parameter monitoring, as it is closely correlates with mortality due to this disease. At the same time, it has been shown that FEV1 is not associated with COPD symptoms and for this reason is not informative enough to distinguish COPD exacerbations from a stable course of this disease [14, 15]. As researchers indicate, there is still a need for objective criteria that could be used to assess the treatment effectiveness and prediction of COPD exacerbations in patients during the period of disease remission [14].

Despite intensive studies of COPD, data on molecular events in the pathogenesis of this disease are quite ambiguous and scarce. For example, it has been shown that the pathogenesis of COPD is closely associated with the development of oxidative stress in lung tissue [15]. First of all, it is caused by the prooxidant effect of chemical agents of polluted air and cigarette smoke [15]. There is information on a decrease in the activity of the antioxidant system in COPD. For example, COPD patients had an increased concentration of blood malondialdehyde and decreased levels of reduced glutathione and catalase activity compared to healthy individuals [16]. Oxidative stress is recognized in the lung tissue even in former smokers, thus indicating that it is partly endogenous [17].

There is much more information about the blood cell response to chronic inflammation. In the lungs of COPD patients, especially during exacerbations, the number of alveolar macrophages and neutrophils significantly increased. They produce superoxide anion radical and hydrogen peroxide, contributing to tissue damage [17].

## 1. BLOOD CELLS

Lung tissue damage due to oxidative stress leads to the development of an inflammatory response. The number of macrophages, T-lymphocytes and B-lymphocytes, as well as granulocytes, increases in the lung tissue. They produce cytokines, chemokines, and growth factors that increase and maintain the inflammatory process [18, 19]. Inhalation of cigarette smoke particles and polluted air causes neutrophil activation. Neutrophils secrete proteases that catalyze the breakdown of connective tissue proteins [20] and release of proinflammatory mediators.

### *1.1. Neutrophils and Eosinophils*

During COPD exacerbation, the number of neutrophils in the blood of patients is significantly higher than in patients with a stable course of this disease. This sign is even proposed to be considered as a risk factor for the exacerbation development [21]. Other studies provide arguments that an increased number of neutrophils in the blood of COPD patients not only indicates an increased risk of exacerbations, but is also associated with the development of complications (particularly, pneumonia) and also with higher mortality [22]. Despite the unambiguity of the literature data on the changes in the level of these cells in the blood of COPD patients, the determination of the neutrophil content as a biomarker of this disease is limited by its low specificity and high variability, especially in acute conditions [23].

In addition to neutrophilic granulocytes, eosinophils play an important role in the development of inflammation in COPD. It has been shown that although most COPD patients are characterized by neutrophilic inflammation of the lung tissue, eosinophilic infiltration occurs in 20–40% of cases [24]. Producing proinflammatory cytokines, these cells promote activation of matrix metalloproteinases and thus mediate lung tissue remodeling [25]. Certain evidence exists in the literature that COPD patients have increased levels of eosinophils (especially during exacerbation) compared to healthy people [24, 26]. The results of cohort studies involving 1481 COPD patients indicate that patients with a blood eosinophil content of >2% had higher FEV1 values [27]. Another large retrospective study showed that high levels of eosinophils in the blood of patients during an exacerbation of COPD were associated with a shorter hospital stay and lower in-hospital mortality [28]. At the same time, the researchers indicate that the blood concentration of these cells is not associated with the risk of subsequent exacerbations [28]. In contrast, the results of some studies, including more recent ones, indicate a relationship between an increased number of blood eosinophils and a higher frequency of COPD exacerbations and also a higher risk of rehospitalization [21].

Despite the contradictory data presented in the literature on association of the blood eosinophil level with the severity and prognosis of COPD,

the opinions of researchers regarding the effectiveness of COPD therapy accompanied by eosinophilic inflammation converge. Most of the available reports indicate that patients with a high content of these cells in the blood respond better to treatment with glucocorticoids [27, 29–33]. For this reason, attempts are being undertaken to identify these cells as a COPD biomarker in order to monitor the course of the disease and evaluate the treatment effectiveness. However, the importance of their determination in COPD is still a matter of debates [34].

*1.2. Monocytes and Lymphocytes*

Lymphocytes also play a significant role in the inflammatory process accompanying COPD. The effect of toxins and allergens on the respiratory tract epithelium leads to excessive activation of CD8+ T-lymphocytes, increased secretion of inflammatory mediators and the development of lymphocyte resistance to apoptosis, which is also one of the factors in the development of steroid resistance in COPD. Lymphocytes also secrete proinflammatory chemokines, prostaglandins, cytotoxic enzymes and generate reactive oxygen species, thus increasing tissue damage and inflammation [35].

Blood lymphocyte number was lower in COPD patients compared to healthy people [36] and this correlated with higher mortality and an increased risk of lung cancer [36]. A reduced relative number of blood lymphocytes (less than 20%) was found to be associated with lower FEV1 values [37, 38] (Table 1). However, the authors [37] could not find a relationship between the number of lymphocytes in the blood serum and either mortality or the frequency of COPD exacerbations. Moreover, it has been reported that despite the increased number of CD8+ T-lymphocytes in the lung tissue, their number in the blood of COPD patients was not higher than in healthy people, regardless of their smoking status [39].

The activation of alveolar macrophages derived from monocytes is an integral part of the inflammatory response in COPD. The mechanisms of the monocyte impact on the development of COPD are not fully known [40]. However, during COPD exacerbation, the absolute number of these cells in the blood is higher than outside of exacerbations [41].

There is no consensus among researchers on the relationship between the blood monocyte number and the frequency and risk of COPD exacerbations. It has been shown that the risk of exacerbations of this disease increases in COPD patients with both low (7.4%) and high (>10%) relative content of blood monocytes. At the same time, the absolute number of monocytes in the blood of patients with a high risk of exacerbations in both cases was $<(0.62\times10^{9})$/l [41].

*1.3. Blood Leukocyte Ratio*

In addition to absolute blood cell counts, blood cell ratios are often calculated for assessment of the severity of the inflammatory response. They reflect the balance between the intensity of chronic inflammation and the activity of the adaptive immune system and are considered more stable and reliable indicators [23, 42]. It is reasonable to assume that their values also change as the inflammatory response progresses, including in COPD, and reflect its intensity. The blood neutrophil to lymphocyte ratio (NLR) and neutrophil to monocyte ratio (NMR) increased in COPD patients who had exacerbations over the past three years, compared to patients who had COPD remission during this period [21, 32]. However, according to the authors, none of these parameters could be considered a reliable risk factor for the development of exacerbations of the disease. Other researchers, on the contrary, report that the increased NLR values were not only associated with future COPD exacerbations, but could also be predictors of mortality due to this disease [21]. For example, high NLR values were noted in 33.5% of patients with a history of COPD exacerbations, and only in 20.4% of patients without a history of exacerbations.

Certain attempts have been undertaken to evaluate a role of the blood monocyte to eosinophil ratio (MER) in COPD [43]. There is evidence that high values of this indicator are associated with an increased risk of obstructive sleep apnea in COPD patients [43]. It has been shown that the risk of recurrent exacerbation of the disease in patients with COPD-asthma overlap syndrome doubles with an increase in blood MER by one unit [43]. The results of the ROC analysis presented in this work indicate a high prognostic value of this parameter in assessing the risk of recurrent exacerbation (area under the curve was 0.830). In addition, the researchers report that the values of blood MER in COPD without asthma were significantly lower than during the exacerbation of the overlap syndrome, and it was possible to differentiate these pathologies with significant efficiency (the area under the ROC curve was 0.7) [43]. The results of assessing the blood MER of patients with COPD compared to healthy people, as well as the data on its determination for the purpose of predicting the course of COPD without asthma are not presented in the literature.

The ratios of the number of platelets to lymphocytes (PLR), as well as monocytes and lymphocytes (MLR) are increased in the blood of patients during COPD exacerbation compared to patients outside of exacerbations. It has been noted that high levels of these blood parameters, along with NLR are associated with more significant airway obstruction and in-hospital mortality [44, 45]. However, data on the assessment of these relationships for the prediction of COPD exacerbations are currently lacking.

*Table 1.* Results of determination of potentially informative biomarkers of COPD in the blood of patients

| Potential biomarker | Association with COPD | Reference |
|---|---|---|
| **BLOOD CELLS** | | |
| ↑Neutrophils | ↑pneumonia risk<br>↑mortality | [22] |
| ↑Eosinophils | ↑during exacerbation period[1]<br>↑exacerbation frequency<br>↑risk of hospitalization | [24, 25, 26]<br>[24] |
| ↑Monocytes | ↑during exacerbation period[1] | [41] |
| ↑Lymphocytes | ↑FEV1 | [37, 38] |
| **LEUKOCYTE RATIOS** | | |
| ↑NLR | ↑exacerbation frequency<br>↑mortality | [21] |
| ↑PLR | ↓FEV1<br>↑mortality | [45] |
| **PLASMA PROTEINS** | | |
| ↓Albumins | ↓in COPD[1]<br>↑mortality | [47]<br>[46] |
| ↑CRP | ↑mortality | [52] |
| ↑PCT | ↑duration of antibacterial therapy<br>↑duration of hospitalization | [60] |
| ↑Fibrinogen | ↑mortality<br>↑exacerbation frequency | [15] |
| **CHEMOKINES** | | |
| ↑CXCL9 | ↑in COPD[1]<br>Does not differ between exacerbations and non-exacerbations | [79] |
| ↑CXCL10 | ↑during exacerbation period[1] | [80] |
| ↑CXCL12 | ↑in COPD[1] | [81] |
| ↑CXCL8 | ↑during exacerbation period[1,2]<br>↓FEV1<br>↑exacerbation frequency<br>↓exacerbation frequency | [87]<br>[89, 90]<br>[91]<br>[78] |
| ↑CXCL5 | ↑in COPD[1]<br>↓FEV1/FVC | [73]<br>[80] |
| **CELL RECEPTORS** | | |
| ↑CXCR3 | ↑in COPD[1] | [97] |
| ↑CXCR1 | ↑in COPD[1]<br>↓FEV1 | [102]<br>[105] |
| ↑CXCR2 | ↑in COPD[1]<br>↑during exacerbation period[1,2] | [102]<br>[101] |
| ↓CD44 | ↓in COPD[1] | [68] |
| **TRANSCRIPTION FACTORS** | | |
| ↑HIF-1 | ↑in COPD[1]<br>↓FEV1/FVC | [75] |

1 – compared with individuals without COPD; 2 – compared with stable COPD.

## 2. BLOOD PROTEINS: PRESENT AND POTENTIAL BIOMARKERS IN COPD

### *2.1. Albumins*

Literature data indicate significant changes in protein metabolism parameters in blood of COPD patients [46]. In this context special attention is paid to the plasma albumin fraction. In the blood, albumin exists mainly in a reduced state containing a free cysteine residue (Cys34) crucial for its antioxidant function [46]. The plasma albumin concentration decreases during the acute phase of the inflammatory response. In addition, albumin is one of the key markers of malnutrition, which is common among COPD patients and negatively affects the quality of life, the risk of exacerbations, the duration of hospitalization of patients and increases the costs of treating the disease [46]. Hypoalbuminemia is associated with a longer hospital stay during exacerbations, acute respiratory failure and increased mortality in COPD patients [46, 47]. The plasma albumin concentration in patients with stable COPD decreased compared to individuals without COPD [47]. However, results of other studies indicate no association between the serum albumin concentration and mortality due to this disease [48].

### *2.2. C-Reactive Protein*

Levels of some acute phase proteins, first of all C-reactive protein (CRP) [49], were evaluated in the context of possible association with the severity of the course and the effectiveness of COPD therapy. CRP activates the classical pathway of the complement system and induces phagocytosis, mediating a non-specific immune response. The blood CRP concentration directly proportional to the intensity of inflammation was elevated in patients with COPD exacerbations. In addition, it has been shown that increased levels of blood CRP in COPD patients persist even outside of exacerbations and can be a predictor of its worse prognosis [49].

High plasma CRP is associated with higher mortality but not with the risk of COPD exacerbations in patients treated with inhaled glucocorticosteroids [50–52] (Table 1). No relationship was found between the blood CRP concentration and the FEV1 parameters [53]. In order to assess CRP informativeness as a COPD biomarker, GOLD recommends conducting additional studies of its level in the blood of patients due to the inconsistency of study results and the non-specificity of this indicator [54].

In addition to absolute values, attempts are undertaken to determine their ratio for prognostic purposes [55]. Higher CRP/albumin ratios in the blood of COPD patients are associated with higher mortality due to this disease [55, 56]. Increased blood CRP/albumin values upon admission to hospital of a patient with an exacerbation of COPD are associated with a high frequency of subsequent exacerbations and the development of COPD complications [57, 58].

According to results of our study, the CRP/albumin ratio increased in blood of patients during COPD exacerbation compared to healthy individuals [59]. It demonstrated a 9.4-fold increase, mainly due to an increase in the CRP level and decreased to control values after the exacerbation.

### *2.3. Procalcitonin (PCT)*

Numerous literature data indicate a higher PCT level in the blood of patients with exacerbations of COPD than in patients with a stable course of COPD [60]. Apparently, this explains, why the treatment of patients with high blood PCT levels requires more financial costs, which are associated with their more frequent hospitalization and a longer duration of hospital stay (Table 1) [60].

Acute COPD is often accompanied by bacterial infections. For this reason, acute pneumonia is the most common comorbid pathology in patients with an exacerbation of COPD [61]. One of the proteins whose synthesis is activated in response to the addition of a bacterial infection in COPD is PCT, a precursor of the hormone calcitonin, which also belongs to the acute phase proteins [54, 62]. Normally, its synthesis and post-translational modification are carried out in the C-cells of the thyroid gland, but in the presence of a bacterial infection, the expression of its gene increases sharply in all parenchymal organs [54]. Parenchymal tissues are not able to convert PCT into active calcitonin and this leads to an increase in its level in the blood [54].

Currently, serum PCT levels are actively studied in patients as a putative criterion for antibiotic therapy prescription. However, up to 20% of COPD exacerbations are not accompanied by a bacterial infection [60]. Despite this, systemic antibiotic therapy is prescribed to all patients during this period [54]. However, monitoring the concentration of PCT in the blood it is possible to reduce the use of antibiotics in COPD patients by 50% and shorten the duration of antibiotic therapy for this disease [54]. For example, antibiotic therapy is not recommended if the blood PCT level in patients is less than 0.1 μg/l [54].

### *2.4. Fibrinogen*

Fibrinogen is another acute phase protein determined in COPD. During the acute inflammatory reaction, the blood level of fibrinogen increases significantly [15]. A relationship between its increased concentration and the frequency of future exacerbations and higher mortality due to this disease has been demonstrated [15] (Table 1). At the same time, no relationship has been recognized between high fibrinogen concentration and a decrease in FEV1. Therefore, it is believed that this parameter cannot be used to assess COPD progression [15].

There is also no consensus on the advisability of determining fibrinogen concentrations for monitoring the course and assessing the effectiveness of COPD treatment. For example, it has been reported that the level of this protein in the blood of patients with stabilized COPD normalized within 4–6 weeks after exacerbation [63, 64]. Other researchers have not found a relationship between blood fibrinogen in COPD patients and the weakening of disease symptoms during recovery [65].

### *2.5. Connective Tissue Components*

The role of cell adhesion molecules in the pathogenesis of various inflammatory diseases is discussed in the literature [66]. One of these molecules is the CD44 receptor, which is actively expressed by lung tissue macrophages. Its main ligand is hyaluronic acid (HA). High molecular weight HA polymers are normal components of connective tissue. Smaller HA molecules (MM<$10^6$ Da) accumulate in areas of inflammation and tissue damage. Their interaction with the CD44 receptor mediates the activation of signaling pathways that promote attraction of leukocytes, especially T-lymphocytes, to the inflammatory focus [66]. It has been reported that this may lead to T-cell-mediated endothelial injury and increased inflammatory response [67].

CD44 is involved in lung tissue regeneration [66]. It is suggested that this receptor participates in apoptotic cell phagocytosis by macrophages [68]. This prevents release of proinflammatory mediators and subsequent stimulation and propagation of the inflammatory process [68]. CD44 loss in murine lung interstitial cells is associated with persistent inflammation. Murine lung macrophages lacking CD44 were more susceptible to oxidative stress and transformation into foam cells, which deteriorated inflammatory reactions and lung tissue injury [69].

Besides standard isoforms of the CD44 receptor, connective tissue and blood leukocytes contain isoform variants originated from pre-mRNA alternative splicing. CD44v6 is the most studied form; in contrast to the standard glycoprotein it contains an amino acid sequence encoded by the variable sixth exon of the primary transcript of the *CD44* gene [70].

Studies of the structure and function of CD44v6 are mainly focused on elucidation of its role in oncogenesis [71]. Nevertheless, it is also known that CD44v6 is involved in lymphocyte migration [71]. The CD44v6 level increased in enterocytes in blood lymphocytes during inflammatory bowel disease [71, 72]. CD44v6 is also involved in the lung fibrosis development [73].

*CD44* expression was significantly lower in tissue macrophages from COPD patients as compared with healthy individuals [68]. Decreased expression of *CD44* was also found in the group of COPD patients who quitted smoking. At the same time, the smoking status had an insignificant impact on the level of this receptor in macrophages of healthy individuals. Other researchers found a high level of *CD44v6* expression in circulating pulmonary cells of 35.2% COPD patients, while for COPD-free patients this was not typical [72]. Evaluation of CD44 and CD44v6 levels in blood of COPD patients has not performed yet.

Lung tissue remodeling, which accompanies the inflammatory process in COPD, is associated with transcription factor synthesis in cells. Hypoxia-inducible factor 1α (HIF-1α) is one of them. It regulates the development and propagation of COPD related inflammatory process, mainly due to induction of vascular endothelium growth factor (VEGF) synthesis; VEGF overexpression is associated with a more intense inflammatory reaction in this disease [73, 74]. In lung tissue of COPD patients expression of genes encoding HIF-1α, VEGF and its receptors was higher than in healthy people [73]. The levels of these proteins negatively correlated with FEV1 and FVC [73].

ELISA-based assays of these proteins in blood are generally consistent with results of histological studies. For example, the blood HIF-1α concentration in COPD patients exceeded control values even during the stable course of the disease; it correlated with disease severity (by the GOLD classification) and lower FEV1/FVC values [75]. However, data on possible use of HIF-1α concentrations for monitoring of treatment efficiency and prediction of COPD exacerbation are still absent in the literature.

### *2.6. Chemokines*

For realization of the immune response leukocytes secrete proinflammatory cytokines and also chemoattractants, promoting further cell attraction to the inflammatory area. Cytokines play a key role in regulation of chronic inflammation in COPD by attracting cells, the major participants of the inflammatory reactions, and maintaining their survival. Thus, chemokines are considered not only as potential diagnostic markers, but also as targets for pharmacological agents [76].

Many cytokines and chemokines are involved in the development of COPD-related chronic progressive inflammation of lung tissue. However, despite their importance as key players of inflammation information about their concentration in blood of COPD patients is very limited (or even absent). Current interest is focused not only on their levels in blood but their receptor mediated signaling in blood cells. This significantly extends the list of potential participants and consequently possibilities to find some quantitative changes associated with symptoms and prognosis of COPD.

The attention of most researchers studying the role of chemokines in the pathogenesis of COPD is focused on the CXC chemokine subfamily, which has received

its name because its members are characterized by the presence of two adjacent cysteine residues near the N-terminus of the molecule and the residue of any other amino acid between them [77].

**2.6.1. CXCL9 and CXCL10.** Proinflammatory chemokines CXCL9 and CXCL10 are produced by alveolar macrophages, smooth muscle, and bronchial epithelial cells [78]. By interacting with the CXCR3 receptor, these chemokines trigger signaling pathways that mediate attraction of activated T-lymphocytes to the inflammation site.

These cytokines have been determined in the sputum of patients. The level of both cytokines increased in COPD patients and correlated with the number of neutrophils in it [78]. The other study has shown that the level of CXCL9 was higher in COPD patients than in healthy people, but no differences were found between groups of patients with stable COPD and during its exacerbation [79]. The level of CXCL10, on the contrary, increased in sputum only during COPD exacerbation and did not differ from control during a stable course of the disease. Data on determining the concentration of these proteins in the blood of COPD patients are scarce. There are indications of an increase in the concentration of CXCL10 in the blood of COPD patients during exacerbation associated with rhinovirus infections [80]; however, the results of measuring its blood level in patients with stable COPD for the prognosis of this disease are still absent.

**2.6.2. CXCL12.** The proinflammatory chemokine CXCL12 acts via a similar mechanism. It plays an important role in the maturation and movement of lymphocytes, as well as the migration of granulocytes to the inflammation site [81, 82]. In COPD patients the blood CXCL12 concentration is not only higher than in the control group, but it exhibited moderate negative correlation with lung tissue function parameters ($r = -0.551$) [81]. The results of the ROC analysis presented in the study indicate a fairly high diagnostic efficiency of determining the of CXCL12 concentration in differentiating patients with COPD and healthy people (the area under the ROC curve was more than 0.7) [81]. However, there is no information on determining the concentration of CXCL12 in the blood of COPD patients during an exacerbation of the disease. An assessment of the feasibility of using this cytokine to predict the course of COPD has also not been conducted yet.

**2.6.3. CXCL8 (Interleukin-8, IL-8).** CXCL8 is another chemokine identified as a player involved in the COPD-related inflammatory process [78]. CXCL8 is synthesized primarily by leukocytes (monocytes, T-lymphocytes, neutrophils, NK cells), epithelial cells and fibroblasts. Expression of the *CXCL8* gene is activated only during the inflammation development [83]. Its secretion is stimulated by bacterial lipopolysaccharides, leading to the release of the contents of neutrophil granules and a respiratory burst [78]. In vitro studies have shown that bronchial epithelial cells exposed to exhaust gases and small particulate matter also secrete IL-8 [84, 85]. This leads to stimulation of the airway epithelium, airway narrowing and increased permeability to inflammatory cells [86]. It has been shown that the CXCL8 concentration in the sputum of patients with stable COPD is higher than in healthy non-smokers, and is associated with the number of neutrophils in the sputum (in other words with the inflammation intensity) [86]. The level of this chemokine in the sputum of patients is higher than in the group of smokers with preserved lung function [86].

It has been repeatedly demonstrated that the blood CXCL8 concentration is higher in COPD patients than in healthy people even during the stable course of the disease [87–89]. Although there are indications in the literature on the involvement of IL-8 in the development of COPD exacerbations, researchers still have not come to a common viewpoint on its role in this process [78]. For example, some studies have shown that IL-8 levels in the sputum of patients with a COPD exacerbation is higher than in a stable course [90]. High concentrations of IL-8 have been found in the blood of patients who have suffered more than one COPD exacerbation over the past three years [91]. In another study, on the contrary, it was noted that, despite the relationship with a decrease in FEV1 parameters and the progression of pulmonary emphysema, the level of blood IL-8 negatively correlated with COPD exacerbation frequency [78].

**2.6.4. CXCL5.** CXCL5 is another chemokine secreted by leukocytes and involved in the pathogenesis of COPD [92]. Traditionally, this chemokine is considered a powerful inducer of neutrophil chemotaxis to the inflammatory site. It has been shown that CXCL5 is secreted primarily by T-lymphocytes of the lung tissue in response to stimulation with cigarette smoke. The level of this chemokine in the bronchoalveolar lavage of COPD patients is higher than that of healthy individuals [93]. The *CXCL5* gene expression in lung epithelial cells is increased during a COPD exacerbation [94]. There are quite a few studies devoted to assessing the blood CXCL5 concentrations in COPD patients. However, there are results indicating that the serum level of this chemokine is higher in smoking and non-smoking COPD patients than in healthy individuals [95]. According to ROC-analysis data it is possible to use the CXCL5 concentration to differentiate COPD patients from healthy individuals (area under the ROC curve of 0.882) [95]. It has been shown that the CXCL5 level in the blood of COPD patients remains high even after smoking cessation; however, no significant differences in its concentration in the blood of smoking and non-smoking patients were found.

High concentrations of CXCL5 in the blood plasma of patients are associated with lower FEV1/FVC values, i.e., its determination can be informative in predicting a decrease in lung function in patients [95]. However, prognostic importance of this chemokine level for predicting COPD exacerbation frequency has not been yet examined.

### *2.7. CXC Chemokine Receptors*

Realization of metabolic effects of the cytokines CXCL9 and CXCL10 requires their interaction with the membrane receptor CXCR3. The number of CXCR3 expressing cells increased in the epithelium and submucosa of the respiratory tract of smokers with COPD compared to non-smoking patients [81, 96]. Previously, we also noted an increased level of this receptor in the population of B-lymphocytes in the blood of COPD patients compared to healthy people [97]; however the analysis of the blood concentration of this protein to assess the severity and effectiveness of treatment of the disease was not performed.

Another receptor of proinflammatory cytokines involved in cell migration to the inflammation site is CXCR4. The main ligand for this receptor is the chemokine CXCL12. Synthesis of this receptor in fibrocytes of COPD patients increased during exacerbation; this increased the chemotactic capacity of these cells [98]. In this regard, the CXCL12/CXCR4 axis has attracted attention as a target for drugs [99]. For example, certain evidence exists that the use of CXCR4 inhibitors improved lung function [100]. Determination of the CXCR4 level in the blood of patients with COPD for prediction of its course has not been previously carried out.

CXCR1 and CXCR2 receptors also interact with a number of CXC chemokines. IL-6 and IL-8 are ligands for CXCR1, while CXCR2 can also bind other CXC chemokines (CXCL1, 2, 3, 5, 6, 7) [78]. It was shown that the level of CXCR2 receptor mRNA in the bronchial epithelium of patients with COPD exacerbations was higher than in the stable course of this disease, while *CXCR1* gene expression in these cells did not differ from the control group and did not differ in dependence on the phase of the COPD course [101, 102]. In a later study, it was found that the level of gene expression of both receptors in the bronchial epithelium of patients with COPD significantly increased compared to healthy people (but regardless of the exacerbation stage) [102].

Most of the currently available literature data is devoted to the analysis of the concentration of cytokine receptors in the lung tissue of COPD patients. At the same time, it is known that cytokine receptors are also present on the leukocytes membranes. Interacting with them, cytokines activate signaling pathways necessary for the activation and chemotaxis of cells, as well as further synthesis of inflammatory mediators [103, 104].

There are a few reports on evaluation of cytokine receptor concentrations in blood of COPD patients. They mainly describe results of the determination of the blood level of CXCR1 and CXCR2 receptors. Some researchers report that the concentration of CXCR1 in blood neutrophils from COPD patients is significantly higher than in healthy people, and it correlates with a decrease in FEV1 parameters in patients, while the level of CXCR2 in the same cells does not differ in COPD patients compared to the control group [105]. Other researchers obtained opposite results. It was shown that the fluorescence intensity of antibody-CXCR1 complexes, characterizing the membrane receptor density was significantly lower in blood neutrophils from COPD patients than in healthy people [106]. As in the previous study, it was shown that the concentration of CXCR2 in neutrophils in COPD did not differ from that in healthy individuals [106]. It should be noted that in both studies, the analysis of the receptor level in patients' blood cells was carried out outside of exacerbation periods.

Previously, we published the results of determination of CXCR1 and CXCR2 in blood cells from patients with in acute pulmonary inflammatory diseases. We found a three-fold increase in the proportion of lymphocytes equipped with the CXCR1 receptor in the total population of blood lymphocytes in patients with an exacerbation of COPD and in patients with pneumonia compared to healthy people. The CXCR2 receptor density in lymphocytes also demonstrated significant changes. In COPD and pneumonia, it increased by 20.5% and 60.0%, respectively, compared to the control group. At the same time, the CXCR1 receptor density in granulocytes increased by 2.0 and 2.1 times, respectively. The level of these parameters stabilized as the acute inflammatory process was relieved and decreased to the control level by the time of discharge from the hospital [59].

Table 1 summarizes the data on blood components that have been found to be associated with the COPD and its course.

## CONCLUSIONS

Thus, using currently available results of the search for potential biomarkers of COPD, it is not possible yet to come to an unambiguous opinion regarding the assessment of the severity of the course and the effectiveness of COPD therapy based on laboratory parameters of intra- and extracellular metabolism in the blood. At the same time, researchers have demonstrated the involvement of blood cells, acute phase proteins, chemokines and their receptors in the formation and course of the inflammatory response in this disease. First of all, this includes blood leukocytes; this is quite logical, due to their immunocompetence. The secretion of proinflammatory mediators, including chemoattractants and reactive

oxygen species increases. In this context bacterial infections are not always the trigger. Acute phase proteins and chemokines, affecting lung cells, contribute to the progression of the inflammatory response and, ultimately, tissue remodeling. Lung function decreases, the frequency of COPD exacerbations increases. At the same time, basically all of the above-considered studies do not provide results of determination of parameters characterizing their prognostic value in this pathology. This does not allow us to make an unambiguous conclusion and even to compare the informativeness of potential biomarkers. Therefore, further research in this direction is clearly needed.

Criteria are urgently needed for prediction of exacerbations not only on the basis of the patient's medical history, but also on objective data. This will help to justify the appropriateness of including corticosteroids, antibiotics, and other drugs in the treatment regimen for exacerbations. Such criteria should be accessible (and inexpensive for evaluation) and they should be characterized by a high degree of probability in detecting the severity of the course and the risk of exacerbations of COPD. During an exacerbation of the disease, treatment should be rational. Therefore, the selected criteria should be monitored during the therapy.

At the same time, the analysis of literature data reviewed suggests the potential informativeness of determining the concentration of leukocytes, albumins, and acute phase proteins (procalcitonin, fibrinogen, CRP), a number of CXC chemokines (CXCL5, 8, 9, 12), cellular receptors (CXCR1, 2, CD44v6) and transcription factors (HIF-1α) in the blood of COPD patients. These indicators of intra- and extracellular metabolism are significant for the pathogenesis of the disease and undergo quantitative changes in the blood of COPD patients. Some of them respond to an exacerbation of this disease. At the same time, much remains to be studied, especially during the exacerbation, since the data presented in the literature are still fragmentary and their results are ambiguous.

In addition to determining the level of individual markers, their informativeness can be increased by creating diagnostic panels including a combined assay of several markers. Using a model that includes several markers it is possible to achieve more than 90% diagnostic sensitivity at high specificity of tests, while initial sensitivity/specificity characteristics of individual markers included in the model were low [107]. Currently, there are no data on the development of such models for COPD in the literature.

## FUNDING

The work was performed within the framework of SPSR 4 “Translational Medicine” (subprogram 4.2 “Fundamental Aspects of Medical Science”) for 2021–2025, task 4.2.44 “To determine the dynamics of changes in the blood levels of proinflammatory proteins, cytokines, their receptors and cells in patients with chronic obstructive pulmonary disease”.

## COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## REFERENCES

1. *Agarwal A.K., Raja A., Brown B.D.* (2025) Chronic obstructive pulmonary disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Retrieved April 9, 2025, from: https://pubmed.ncbi.nlm.nih.gov/32644707/
2. WHO: the top 10 causes of death. Retrieved April 9, 2025, from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
3. S*imiao C., Kuhn M., Prettner K., Yu F., Yang T., Bärnighausen T., Bloom D., Wang C.* (2023) The global economic burden of chronic obstructive pulmonary disease for 204 countries and territories in 2020–50: a health-augmented macroeconomic modelling study. Lancet Global Health, **11**(8), e1183–e1193. DOI: 10.1016/S2214-109X(23)00217-6
4. *Adeloye D., Agarwal D., Barnes P.J., Bonay M., van Boven J.F., Bryant J., Caramori G., Dockrell D., d'Urzo A., Ekström M., Erhabor G., Esteban C., Greene C.M., Hurst J., Juvekar S., Khoo E.M., Ko F.W., Lipworth B., López-Campos J.L., Maddocks M., Mannino D.M., Martinez F.J., Martinez-Garcia M.A., McNamara R.J., Miravitlles M., Pinnock H., Pooler A., Quint J.K., Schwarz P., Slavich G.M., Song P., Tai A., Watz H., Wedzicha J.A., Williams M.C., Campbell H., Sheikh A., Rudan I.* (2021) Research priorities to address the global burden of chronic obstructive pulmonary disease (COPD) in the next decade. J. Global Health, **11**, 15003. DOI: 10.7189/jogh.11.15003
5. *Agusti A., Celli B.R., Criner G.J., Halpin D., Anzueto A., Barnes P., Bourbeau J., Han M.K., Martinez F.J., Montes de Oca M., Mortimer K., Papi A., Pavord I., Roche N., Salvi S., Sin D.D., Singh D., Stockley R., López Varela M.V., Wedzicha J.A., Vogelmeier C.F.* (2023) Global initiative for chronic obstructive lung disease 2023 report: GOLD executive summary. Eur. Respir. J., **61**(4), 2300239. DOI: 10.1183/13993003.00239-2023
6. *MacLeod M., Papi A., Contoli M., Beghé B., Celli B.R., Wedzicha J.A., Fabbri L.M.* (2021) Chronic obstructive pulmonary disease exacerbation fundamentals: diagnosis, treatment, prevention and disease impact. Respirology, **26**(6), 532–551. DOI: 10.1111/resp.14041
7. COPD Stages and the GOLD Criteria. Retrieved April 9, 2025, from: https://www.webmd.com/lung/copd/gold-criteria-for-copd

8. *Celli B.R., Fabbri L.M., Aaron S.D., Agusti A., Brook R.D., Criner G.J., Franssen F.M.E., Humbert M., Hurst J.R., Montes de Oca M., Pantoni L., Papi A., Rodriguez-Roisin R., Sethi S., Stolz D., Torres A., Vogelmeier C.F., Wedzicha J.A.* (2023) Differential diagnosis of suspected chronic obstructive pulmonary disease exacerbations in the acute care setting: best practice. Am. J. Respir. Crit. Care Med., **207**(9), 1134–1144. DOI: 10.1164/rccm.202209-1795CI
9. *Barnes P.J.* (2009) The cytokine network in chronic obstructive pulmonary disease. Am. J. Respir. Cells Mol. Biol., **41**(6), 631–638. DOI: 10.1165/rcmb.2009-0220TR
10. *Hurst J.R., Han M.K, Singh B., Sharma S., Kaur G., de Nigris E., Holmgren U., Siddiqui M.K.* (2022) Prognostic risk factors for moderate-to-severe exacerbations in patients with chronic obstructive pulmonary disease: a systematic literature review. Respir. Res., **23**(1), 213. DOI: 10.1186/s12931-022-02123-5
11. *Barnes P.J.* (2016) Inflammatory mechanisms in COPD. J. Allergy Clin. Immunol., **138**(1), 40. DOI: 10.1016/j.jaci.2016.05.011
12. *Müllerová H., Shukla A., Hawkins A., Quint J.* (2014) Risk factors for acute exacerbations of COPD in a primary care population: a retrospective observational cohort study. BMJ Open, **4**(12), e006171. DOI: 10.1136/bmjopen-2014-006171
13. *Kim V., Aaron S.D.* (2018) What is a COPD exacerbation? Current definitions, pitfalls, challenges and opportunities for improvement. Eur. Respir. J., **52**(5), 1801261. DOI: 10.1183/13993003.01261-2018
14. *Franciosi L.G., Page C.P., Celli B.R., Cazzola M., Walker M.J., Danhof M., Rabe K.F., Della Pasqua O.E.* (2006) Markers of exacerbation severity in chronic obstructive pulmonary disease. Respir. Res., **7**(1), 74. DOI: 10.1186/1465-9921-7-74
15. *Duvoix A., Dickens J., Haq I., Mannino D., Miller B., Tal-Singer R., Lomas D.A.* (2013) Blood fibrinogen as a biomarker of chronic obstructive pulmonary disease. Thorax, **68**(7), 670–676. DOI: 10.1136/thoraxjnl-2012-201871
16. *Altuntaş E., Turgut T., İlhan N., Deveci F., Muz M.H., Çelik İ.* (2003) The levels of oxidant and antioxidant in patients with COPD. Tüberküloz ve Toraks, **51**(4), 373–379.
17. *Barnes P.J.* (2020) Oxidative stress-based therapeutics in COPD. Redox Biol, **2020**, 101544. DOI: 10.1016/j.redox.2020.101544
18. *Donnelly L.E., Barnes P.J. (2006)* Chemokine receptors as therapeutic targets in chronic obstructive pulmonary disease. Trends Pharmacol. Sci., **27**(10), 546–553. DOI: 10.1016/j.tips.2006.08.001
19. *Barnes P.J.* (2022) Oxidative stress in chronic obstructive pulmonary disease. Antioxidants (Basel), **11**(5), 965. DOI: 10.3390/antiox11050965
20. *Singh D.* (2015) Chronic obstructive pulmonary disease, neutrophils and bacterial infection: a complex web involving IL-17 and IL-22 unravels. EBioMedicine, **2**(11), 1580–1581. DOI: 10.1016/j.ebiom.2015.10.021
21. *Yoon E.C., Koo S.-M., Park H.Y., Kim H.C., Kim W.J., Kim K.U., Jung K.-S., Yoo K.H., Yoon H.K., Yoon H.-Y.* (2024) Predictive role of white blood cell differential count for the development of acute exacerbation in Korean chronic obstructive pulmonary disease. Int. J. Chron. Obstruct. Pulmon. Dis., **19**, 17–31. DOI: 10.2147/COPD.S435921
22. *Lonergan M., Dicker A.J., Crichton M.L., Keir H.R., van Dyke M.K., Mullerova H., Miller B.E., Tal-Singer R., Chalmers J.D.* (2020) Blood neutrophil counts are associated with exacerbation frequency and mortality in COPD. Respir. Res., **21**(1), 166. DOI: 10.1186/s12931-020-01436-7
23. *Song M., Graubard B.I., Loftfield E., Rabkin C.S., Engels E.A.* (2024) White blood cell count, neutrophil-to-lymphocyte ratio, and incident cancer in the UK Biobank. Cancer Epidemiol. Biomarkers Prev., **33**(6), 821–829. DOI: 10.1158/1055-9965.EPI-23-1145
24. *David B., Bafadhel M., Koenderman L., de Soyza A.* (2021) Eosinophilic inflammation in COPD: from an inflammatory marker to a treatable trait. Thorax, **76**(2), 188–195. DOI: 10.1136/thoraxjnl-2020-215167
25. *Higham A., Beech A., Singh D.* (2024) The relevance of eosinophils in chronic obstructive pulmonary disease: inflammation, microbiome, and clinical outcomes. J. Leukoc. Biol., **116**(5), 927–946. DOI: 10.1093/jleuko/qiae153
26. *Kolsum U., Southworth T., Jackson N., Singh D.* (2019) Blood eosinophil counts in COPD patients compared to controls. Eur. Respir. J., **54**(4), 1900633. DOI: 10.1183/13993003.00633-2019
27. *Singh D., Kolsum U., Brightling C.E., Locantore N., Agusti A., Tal-Singer R.* (2014) Eosinophilic inflammation in COPD: prevalence and clinical characteristics. Eur. Respir. J., **44**(6), 1697–1700. DOI: 10.1183/09031936.00162414
28. *Jabarkhil A., Moberg M., Janner J., Petersen M.N., Jensen C.B., Henrik Äangquist L., Vestbo J., Jess T., Porsbjerg C.* (2020) Elevated blood eosinophils in acute COPD exacerbations: better short- and long-term prognosis. Eur. Clin. Respir. J., **7**(1), 1757274. DOI: 10.1080/20018525.2020.1757274
29. *Singh D.* (2020) Blood eosinophil counts in chronic obstructive pulmonary disease: a biomarker of inhaled corticosteroid effects Tuberc. Respir. Dis. (Seoul), **83**(3), 185–194. DOI: 10.4046/trd.2020.0026
30. *Chapman K.R., Hurst J.R., Frent S.-M., Larbig M., Fogel R., Guerin T., Banerji D., Patalano F., Goyal P., Pfister P., Kostikas K., Wedzicha J.A.* (2018) Long-term triple therapy de-escalation to indacaterol/glycopyrronium in patients with chronic obstructive pulmonary disease (SUNSET): a randomized, double-blind, triple-dummy clinical trial. Am. J. Respir. Crit. Care Med., **198**(3), 329–339. DOI: 10.1164/rccm.201803-0405OC
31. *Jordan A., Sivapalan P., Rømer V., Jensen J.-U.* (2023) Time-updated phenotypic guidance of corticosteroids and antibiotics in COPD: rationale, perspective and a proposed method. Biomedicines, **11**(5), 1395. DOI: 10.3390/biomedicines11051395
32. *Ellingsen J., Janson C., Bröms K., Lisspers K., Ställberg B., Högman M., Malinovschi A.* (2021) Neutrophil-to-lymphocyte ratio, blood eosinophils and COPD exacerbations: a cohort study. ERJ Open Res., **7**(4), 00471-2021. DOI: 10.1183/23120541.00471-2021
33. *Fahy J.V.* (2015) Type 2 inflammation in asthma — present in most, absent in many. Nat. Rev. Immunol., **15**(1), 57–65. DOI: 10.1038/nri3786
34. *Anaev E.Kh.* (2023) Eosinophilic chronic obstructive pulmonary disease: a review. Terapevticheskii Arkhiv, **95**(8), 696–700. DOI: 10.26442/00403660.2023.08.202316
35. *Biswas M., Suvarna R., Krishnan S.V., Devasia T., Shenoy Belle V., Prabhu K.* (2022) The mechanistic role of neutrophil lymphocyte ratio perturbations in the leading non communicable lifestyle diseases. F1000Research, **11**, 960. DOI: 10.12688/f1000research.123245.1

36. *Semenzato U., Biondini D., Bazzan E., Tiné M., Balestro E., Buldini B., Carizzo S.J., Cubero P., Marin-Oto M., Casara A., Baraldo S., Turato G., Gregori D., Marin J.M., Cosio M.G., Saetta M.* (2021) Low-blood lymphocyte number and lymphocyte decline as key factors in copd outcomes: a longitudinal cohort study. Respiration, **100**(7), 618–630. DOI: 10.1159/000515180
37. *Moon S.W., Leem A.Y., Kim Y.S., Lee J.-H., Kim T.-H., Oh Y.-M., Shin H., Chang J., Jung J.Y., KOLD Study Group* (2020) Low serum lymphocyte level is associated with poor exercise capacity and quality of life in chronic obstructive pulmonary disease. Sci. Rep., **10**, 11700. DOI: 10.1038/s41598-020-68670-3
38. *Huang Y., Jiang B., Miao X., Ma J., Wang J., Ding K., Chen X., Hu Q., Fu F., Zeng T., Hu J., Hu B., Yang D., Zhang X.* (2020) the relationship of lymphocyte to high-density lipoprotein ratio with pulmonary function in COPD. Int. J. Chron. Obstruct. Pulmon. Dis., **15**, 3159–3169. DOI: 10.2147/COPD.S276372
39. *Williams M., Todd I., Fairclough L.C.* (2021) The role of CD8+ T lymphocytes in chronic obstructive pulmonary disease: a systematic review. Inflamm. Res., **70**(1), 11–18. DOI: 10.1007/s00011-020-01408-z
40. *Ono Y., Fujino N., Saito T., Matsumoto S., Konno S., Endo T., Suzuki M., Yamada M., Okada Y., Sugiura H.* (2024) Characterization of IL-6R-expressing monocytes in the lung of patients with chronic obstructive pulmonary disease. Respir. Investig., **62**(5), 856–866. DOI: 10.1016/j.resinv.2024.07.013
41. *Lin C.-H., Li Y.-R., Lin P.R., Wang B.-Y., Lin S.-H., Huang K.-Y., Kor C.-T.* (2022) Blood monocyte levels predict the risk of acute exacerbations of chronic obstructive pulmonary disease: a retrospective case-control study. Sci. Rep., **12**, 21057. DOI: 10.1038/s41598-022-25520-8
42. *Zahorec R.* (2021) Neutrophil-to-lymphocyte ratio, past, present and future perspectives. Bratislava Medical Journal, **122**(7), 474–488. DOI: 10.4149/BLL_2021_078
43. *Ali A., Abdelhafiz A.S., Saleh M.M., Salem H., Rakha M.A., Ezzat S.* (2023) Monocyte to eosinophil ratio as a diagnostic biomarker for overlap syndrome and predictor of disease exacerbation. Int. J. Immunopathol. Pharmacol., **37**, 3946320231216321. DOI: 10.1177/03946320231216321
44. *Gutta L., Ahmed T.* (2022) NLR and PLR ratios — accessible and affordable predictors of disease severity in COPD. J. Assoc. Physicians India, **70**(4), 11–12.
45. *Liao Q.Q., Mo Y.-J., Zhu K.-W., Gao F., Huang B., Chen P., Jing F.-T., Jiang X., Xu H.-Z., Tang Y.-F., Chu L.-W., Huang H.-L., Wang W.-L., Wei F.-N., Huang D.-D., Zhao B.-J., Chen J., Zhang H.* (2024) Platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and eosinophil-to-lymphocyte ratio (ELR) as biomarkers in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Int. J. Chron. Obstruct. Pulmon. Dis., **19**, 501–518. DOI: 10.2147/COPD.S447519
46. *Ling M., Huiyin L., Shanglin C., Haiming L., Zhanyi D., Shuchun W., Meng B., Murong L.* (2023) Relationship between human serum albumin and in-hospital mortality in critical care patients with chronic obstructive pulmonary disease. Front. Med., **10**, 1109910. DOI: 10.3389/fmed.2023.1109910
47. *Zinellu E., Fois A., Sotgiu E., Mellino S., Mangoni A.* (2021) Serum albumin concentrations in stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. J. Clin. Med., **10**(2), 269. DOI: 10.3390/jcm10020269
48. *Mendy A., Forno E., Niyonsenga T., Gasana J.* (2018) Blood biomarkers as predictors of long-term mortality in COPD. Clin. Respir. J., **12**(5), 1891–1899. DOI: 10.1111/crj.12752
49. *Hassan A., Jabbar N.* (2022) C-reactive protein as a predictor of severity in chronic obstructive pulmonary disease: an experience from a tertiary care hospital. Cureus, **14**(8), e28229. DOI: 10.7759/cureus.28229
50. *Oshagbemi O., Franssen F., Wouters E., Maitland-van der Zee A., Driessen J., de Boer A., de Vries F.* (2020) Creactive protein as a biomarker of response to inhaled corticosteroids among patients with COPD. Pulm. Pharmacol. Ther., **60**, 101870. DOI: 10.1016/j.pupt.2019.101870
51. *Ben Saad A., Migaou A., Cheikh Mhamed S., Fahem N., Rouatbi N., Joobeur S.* (2020) Relationship between CRP levels and the severity of COPD acute exacerbations among group D COPD patients. Eur. Respir. J., **56**(Suppl 64), 2443. DOI: 10.1183/13993003.congress-2020.2443
52. *Banerjee S., Khubchandani J., Onukogu C., Okpom C., Johnson M.* (2024) Elevated C-reactive protein and mortality risk among COPD patients. Egypt. J. Bronchol., **18**, 38. DOI: 10.1186/s43168-024-00291-0
53. *Fattouh M., Alkady O.* (2014) Inflammatory biomarkers in chronic obstructive pulmonary disease. Egypt. J. Chest Dis. Tuberc., **63**(4), 799–804. DOI: 10.1016/j.ejcdt.2014.06.011
54. *Chen K., Pleasants K.A., Pleasants R.A., Beiko T., Washburn R.G., Yu Z., Zhai S., Drummond M.B.* (2020) Procalcitonin for antibiotic prescription in chronic obstructive pulmonary disease exacerbations: systematic review, meta-analysis, and clinical perspective. Pulm. Ther., **6**(2), 201–214. DOI: 10.1007/s41030-020-00123-8
55. *Özgür Cırık M., Baldemir R., Doğanay G.E., Ünver M., Avcı S.* (2020) The 30-day mortality predictor role of C-reactive protein/albumin ratio in critically ill COPD patients. Crit. Care Innov., **3**(4), 1–12. DOI: 10.32114/CCI.2020.3.4.1.12
56. *Atalay E., Erdoğdu H.İ., Tur B.K., Deniz Balyen L.S., Karabağ Y., Ardiç S.* (2019) The relationship between C reactive protein / albumin ratio and 1-year mortality in hospitalized elderly COPD patients with acute exacerbation. Turkish J. Geriatrics, **22**(1), 9–17. DOI: 10.31086/tjgeri.2019150567
57. *Li H., Ma Y., Xue J., He C., Zhan Z., Liu X., Chen P., Cai S., Zeng Y., Wu Q., Chen Y.* (2021) C-reactive protein to serum albumin ratio as a novel biomarker to predict prognosis in patients with chronic obstructive pulmonary disease. Clin. Lab., **67**(3), DOI: 10.7754/clin.lab.2020.200630
58. *Shen S., Xiao Y.* (2023) Association between C-reactive protein and albumin ratios and risk of mortality in patients with chronic obstructive pulmonary disease. Int. J. Chron. Obstruct. Pulmon. Dis., **18**, 2289–2303. DOI: 10.2147/COPD.S413912
59. *Tahanovich A., Kauhanka M., Chotko E., Gotko O., Prokhorova V.* (2024) Assessment of the effectiveness of treatment for squamous cell lung cancer based on determination of intra- and extracellular metabolism indicators in the blood. Eurasian Oncology Journal, **12**(2), 134–150. DOI: 10.34883/PI.2024.12.2.017
60. *Gong C., Yang Y., Chen M., Xie Z.* (2020) Effect of procalcitonin on the prognosis of patients with COPD. Biomed. Rep., **12**(6), 313–318. DOI: 10.3892/br.2020.1298

61. *Restrepo M., Sibila O., Anzueto A.* (2018) Pneumonia in patients with chronic obstructive pulmonary disease. Tuberc. Respir. Dis. (Seoul), **81**(3), 187–197. DOI: 10.4046/trd.2018.0030
62. Using procalcitonin to guide therapy for acute COPD exacerbations. Retrieved April 9, 2025, from: https://www.jwatch.org/na48613/2019/03/07/using-procalcitonin-guide-therapy-acute-copd-exacerbations
63. *Saldías P.F., Díaz P.O., Dreyse D.J., Gaggero B.A., Sandoval A.C., Lisboa B.C.* (2011) Etiology and biomarkers of systemic inflammation in mild to moderate COPD exacerbations. Revista medica de Chile, **140**, 10–18.
64. *Waschki B., Kirsten A., Holz O., Müller K.-C., Meyer T., Watz H., Magnussen H.* (2011) Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. Chest, **140**(2), 331–342. DOI: 10.1378/chest.10-2521
65. *Koutsokera A., Kiropoulos T.S., Nikoulis D.J., Daniil Z.D., Tsolaki V., Tanou K., Papaioannou A.I., Germenis A., Gourgoulianis K.I., Kostikas K.* (2009) Clinical, functional and biochemical changes during recovery from COPD exacerbations. Respir. Med., **103**(6), 919–926. DOI: 10.1016/j.rmed.2008.12.006
66. *Teder P., Vandivier R.W., Jiang D., Liang J., Cohn L., Puré E., Henson P.M., Noble P.W.* (2002) Resolution of lung inflammation by CD44. Science, **296**(5565), 155–158. DOI: 10.1126/science.1069659
67. *de Grendele H.C., Kosfiszer M., Estess P., Siegelman M.H.* (1997) CD44 activation and associated primary adhesion is inducible via T cell receptor stimulation. J. Immunol., **159**(6), 2549–2553.
68. *Noguera A., Gomez C., Faner R., Cosio B., González-Périz A., Clària J., Carvajal A., Agustí A.* (2012) An investigation of the resolution of inflammation (catabasis) in COPD. Respir. Res., **13**(1), 101. DOI: 10.1186/1465-9921-13-101
69. *Dong Y., Arif A.A., Guo J., Ha Z., Lee-Sayer S.S.M., Poon G.F.T., Dosanjh M., Roskelley C.D., Huan T., Johnson P.* (2020) CD44 loss disrupts lung lipid surfactant homeostasis and exacerbates oxidized lipid-induced lung inflammation. Front. Immunol., **11**, 29. DOI: 10.3389/fimmu.2020.00029
70. *Heider K.-H., Kuthan H., Stehle G., Munzert G.* (2004) CD44v6: a target for antibody-based cancer. Cancer Immunol. Immunother., **53**(7), 567–579. DOI: 10.1007/s00262-003-0494-4
71. *Camacho F.I., Muñoz C., Sánchez-Verde L., Sáez A.I., Alcántara M., Rodríguez R.* (1999) CD44v6 expression in inflammatory bowel disease is associated with activity detected by endoscopy and pathological features. Histopathology, **35**(2), 144–149. DOI: 10.1046/j.1365-2559.1999.00712.x
72. *Romero-Palacios P.J., Alcázar-Navarrete B., Díaz Mochón J.J., de Miguel-Pérez D., López Hidalgo J.L., Garrido-Navas M.D.C., Quero Valenzuela F., Lorente J.A., Serrano M.J.* (2019) Circulating pulmonary cells as biomarkers of COPD aggressivity. Crit. Rev. Oncol. Hematol., **136**, 31–36. DOI: 10.1016/j.critrevonc.2019.02.003
73. *Fu X., Zhang F.* (2018) Role of the HIF-1 signaling pathway in chronic obstructive pulmonary disease. Exp. Ther. Med., **16**(6), 4553–4561. DOI: 10.3892/etm.2018.6785
74. *Chiş A.F., Soritau O., Catana A., Pop M.* (2018) VEGF serum levels in COPD patients without pulmonary hypertension — a case control study. Eur. Respir. J., **52**(Suppl 62), PA4071. DOI: 10.1183/13993003.congress-2018.PA4071
75. *Rong B., Liu Y., Li M., Fu T., Gao W., Liu H.* (2018) Correlation of serum levels of HIF-1α and IL-19 with the disease progression of COPD: a retrospective study. Int. J. Chron. Obstruct. Pulmon. Dis., **13**, 3791–3803. DOI: 10.2147/COPD.S177034
76. *Valipour A., Schreder M., Wolzt M., Saliba S., Kapiotis S., Eickhoff P., Burghuber O.C.* (2008) Circulating vascular endothelial growth factor and systemic inflammatory markers in patients with stable and exacerbated chronic obstructive pulmonary disease. Clin. Sci. (London), **115**(7), 225–232. DOI: 10.1042/CS20070382
77. *Hughes C.E, Nibbs R.J.B.* (2018) A guide to chemokines and their receptors. FEBS J., **285**(16), 2944–2971. DOI: 10.1111/febs.14466
78. *Henrot P., Prevel R., Berger P., Dupin I.* (2019) Chemokines in COPD: from implication to therapeutic use. Int. J. Mol. Sci., **20**(11), 2785. DOI: 10.3390/ijms20112785
79. *Tangedal S., Aanerud M., Persson L.J.P., Bakke P.S., Eagan T.M.L.* (2015) MIG and IP-10 levels in induced sputum of stable and exacerbated COPD patients. Eur. Respir. J., **46**(Suppl 59), PA3885. DOI: 1183/13993003.congress-2015.PA3885
80. *Quint J.K., Donaldson G.C., Goldring J.J.P., Baghai-Ravary R., Hurst J.R., Wedzicha J.A.* (2010) Serum IP-10 as a biomarker of human rhinovirus infection at exacerbation of COPD. Chest, **137**(4), 812–822. DOI: 10.1378/chest.09-1541
81. *Xue H., Chen Q., Lan X., Xu H., Yang H., Lin C., Xue Q., Xie B.* (2024) Preventing CXCL12 elevation helps to reduce acute exacerbation of COPD in individuals co-existing type-2 diabetes: a bioinformatics and clinical pharmacology study. Int. Immunopharmacol., **132**, 111894. DOI: 10.1016/j.intimp.2024.111894
82. *Stuart M.J., Baune B.T.* (2014) Chemokines and chemokine receptors in mood disorders, schizophrenia, and cognitive impairment: a systematic review of biomarker studies. Neurosci. Biobehav. Rev., **42**, 93–115. DOI: 10.1016/j.neubiorev.2014.02.001
83. *Mukaida N.* (2003) Pathophysiological roles of interleukin-8/CXCL8 in pulmonary diseases. Am. J. Physiol. Lung Cell. Mol. Physiol., **284**(4), 566–577. DOI: 10.1152/ajplung.00233.2002
84. *Kim V., Cornwell W.D., Oros M., Durra H., Criner G.J., Rogers T.J.* (2015) Plasma chemokine signature correlates with lung goblet cell hyperplasia in smokers with and without chronic obstructive pulmonary disease. BMC Pulm. Med., **15**, 111. DOI: 10.1186/s12890-015-0103-2
85. *Zarcone M.C., Duistermaat E., Alblas M.J., van Schadewijk A., Ninaber D.K., Clarijs V., Moerman M.M., Vaessen D., Hiemstra P.S., Kooter I.M.* (2018) Effect of diesel exhaust generated by a city bus engine on stress responses and innate immunity in primary bronchial epithelial cell cultures. Toxicol. In Vitro, **48**, 221–231. DOI: 10.1016/j.tiv.2018.01.024
86. *Reutershan J., Morris M.A., Burcin T.L., Smith D.F., Chang D., Saprito M.S., Ley K.* (2006) Critical role of endothelial CXCR2 in LPS-induced neutrophil migration into the lung. J. Clin. Invest., **116**(3), 695–702. DOI: 10.1172/JCI27009
87. *Zhang J., Bai C.* (2018) The significance of serum interleukin-8 in acute exacerbations of chronic obstructive pulmonary disease. Tanaffos, **17**(1), 13–21.
88. *Kuźnar-Kamińska B., Mikuła-Pietrasik J., Witucka A., Romaniuk A., Konieczna N., Rubiś B., Książek K., Tykarski A., Batura-Gabryel H.* (2018) Serum from patients

with chronic obstructive pulmonary disease induces senescence-related phenotype in bronchial epithelial cells. Sci. Rep., **8**, 12940. DOI: 10.1038/s41598-018-31037-w
89. *Pignatti P., Moscato G., Casarini S., Delmastro M., Poppa M., Brunetti G., Pisati P., Balbi B.* (2005) Downmodulation of CXCL8/IL-8 receptors on neutrophils after recruitment in the airways. J. Allergy Clin. Immunol., **115**(1), 88–94. DOI: 10.1016/j.jaci.2004.08.048
90. *Aaron S.D., Angel J.B., Lunau M., Wright K., Fex C., le Saux N., Dales R.E.* (2001) Granulocyte inflammatory markers and airway infection during acute exacerbation of chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med., **163**(2), 349–355. DOI: 10.1164/ajrccm.163.2.2003122
91. *Han M.K., Quibrera P.M., Carretta E.E., Barr R.G., Bleecker E.R., Bowler R.P., Cooper C.B., Comellas A., Couper D.J., Curtis J.L., Criner G., Dransfield M.T., Hansel N.N., Hoffman E.A., Kanner R.E., Krishnan J.A., Martinez C.H., Pirozzi C.B., O'Neal W.K., Rennard S., Tashkin D.P., Wedzicha J.A., Woodruff P., Paine R. 3rd, Martinez F.J.* (2017) Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. Lancet Respir. Med., **5**(8), 619–626. DOI: 10.1016/S2213-2600(17)30207-2
92. *Wuyts A., d'Haese A., Cremers V., Menten P., Lenaerts J.P., de Loof A., Heremans H., Proost P., van Damme J.* (1999) $NH_2$- and COOH-terminal truncations of murine granulocyte chemotactic protein-2 augment the *in vitro* and *in vivo* neutrophil chemotactic potency. J. Immunol., **163**(11), 6155–6163.
93. *Tanino M., Betsuyaku T., Takeyabu K., Tanino Y., Yamaguchi E., Miyamoto K., Nishimura M.* (2002) Increased levels of interleukin-8 in BAL fluid from smokers susceptible to pulmonary emphysema. Thorax, **57**(5), 405–411. DOI: 10.1136/thorax.57.5.405
94. *Qiu Y., Zhu J., Bandi V., Atmar R.L., Hattotuwa K., Guntupalli K.K., Jeffery P.K.* (2003) Biopsy neutrophilia, neutrophil chemokine and receptor gene expression in severe exacerbations of chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med., **168**(8), 968–975. DOI: 10.1164/rccm.200208-794OC
95. *Chen J., Dai L., Wang T., He J., Wang Y., Wen F.* (2019) The elevated CXCL5 levels in circulation are associated with lung function decline in COPD patients and cigarette smoking-induced mouse model of COPD. Ann. Med., **51**(5–6), 314–329. DOI: 10.1080/07853890.2019.1639809
96. *Nie L., Liu Z.-J., Zhou W.-X., Xiang R.-L., Xiao Y., Lu B., Pang B.-S., Gao J.-M.* (2010) Chemokine receptor CXCR3 is important for lung tissue damage and airway remodeling induced by short-term exposure to cigarette smoking in mice. Acta Pharmacol. Sin., **31**(4), 436–442. DOI: 10.1038/aps.2009.192
97. *Tahanovich A., Kadushkin A.* (2017) Chemokine receptor CXCR3 expression on naive and memory B-lymphocytes of patients with COPD. Eur. Respir. J., **50**(Suppl 61), PA2025. DOI: 10.1183/1393003.congress-2017.PA2025
98. *Xue M.-Q., Liu J., Sang J.-F., Su L., Yao Y.-Z.* (2017) Expression characteristic of CXCR1 in different breast tissues and the relevance between its expression and efficacy of neo-adjuvant chemotherapy in breast cancer. Oncotarget, **8**(30), 48930–48937. DOI: 10.18632/oncotarget.16893
99. *Dupin I., Henrot P., Maurat E., Abohalaka R., Chaigne S., El Hamrani D., Eyraud E., Prevel R., Esteves P., Campagnac M., Dubreuil M., Cardouat G., Bouchet C., Ousova O., Dupuy J.-W., Trian T., Thumerel M., Begueret H., Girodet P.-O., Marthan R., Zysman M., Freund-Michel V., Berger P.* (2025) CXCR4 blockade alleviates pulmonary and cardiac outcomes in early COPD. Am. J. Respir. Cell Mol. Biol., DOI: 10.1165/rcmb.2024-0303OC. Epub ahead of print.
100. *Duplin I., Dubreuil M., Freund-Michel V., Maurat E., Campagnac M., Ousova O., Trian T., Girodet P.-O., Berger P.* (2019) Targeting CXCR4 as a therapeutic strategy to improve outcomes in a mouse model of early chronic obstructive pulmonary disease (COPD). ERJ Open Res., **5**(Suppl 2), PP225. DOI: 10.1183/23120541.lungscienceconference-2019.PP225
101. *Nasser M.W., Raghuwanshi S.K., Grant D.J., Jala V.R., Rajarathnam K., Richardson R.M.* (2009) Differential activation and regulation of CXCR1 and CXCR2 by CXCL8 monomer and dimer. J. Immunol., **183**(5), 3425–3432. DOI: 10.4049/jimmunol.0900305
102. *Schulz C., Stoelcker B., Ruhland B., Jentsch N., Steege A.* (2012) Bronchoepithelial expression of CXCR1 and CXCR2 does not facilitate transepithelial migration of neutrophils. Respiration, **84**(2), 108–116. DOI: 10.1159/000332826
103. *Fahimi F., Alam M.J., Ang C., Adhyatma G.P., Xie L., Mackay C.R., Robert R.* (2023) Human CXCR1 knock-in mice infer functional expression of a murine ortholog. J. Leukoc. Biol., **114**(4), 373–380. DOI: 10.1093/jleuko/qiad085
104. *Kureshi C.T., Dougan S.K.* (2024) Cytokines in cancer. Cancer Cell, **43**(1), 15–35. DOI: 10.1016/j.ccell.2024.11.011
105. *Yamagata T., Sugiura H., Yokoyama T., Yanagisawa S., Ichikawa T., Ueshima K., Akamatsu K., Hirano T., Nakanishi M., Yamagata Y., Matsunaga K., Minakata Y., Ichinose M.* (2007) Overexpression of CD-11b and CXCR1 on circulating neutrophils: its possible role in COPD. Chest, **132**(3), 890–899. DOI: 10.1378/chest.07-0569
106. *Stockley J., Peat L., Walton G., Lord J., Sapey E.* (2014) The role of chemokine receptors in the aberrant migration of COPD neutrophils. Eur. Respir. J., **44**(Suppl 58), P3859. DOI: 10.1183/13993003/erj.44.Suppl_58.P3859
107. *Yang M., Xu D., Liu Y., Guo X., Li W., Guo C., Zhang H., Gao Y., Mao Y., Zhao J.* (2022) Combined serum biomarkers in non-invasive diagnosis of non-alcoholic steatohepatitis. PLOS One, **10**(6), e0131664. DOI: 10.1371/journal.pone.0131664

Received: 24.04.2025.
Revised: 13.06.2025.
Accepted: 17.06.2025.

# ПРОГНОЗИРОВАНИЕ ТЕЧЕНИЯ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНИ ЛЁГКИХ С ИСПОЛЬЗОВАНИЕМ БИОМАРКЕРОВ В КРОВИ

***Д.И. Мурашко[1]*, А.Д. Таганович[1], Н.Н. Ковганко[1], И.А. Никитина[1], А.В. Колб[1], Л.С. Богуш[2], Е.И. Давидовская[2], О.А. Будник[2]***

[1]Белорусский государственный медицинский университет,
220116, Беларусь, Минск, пр. Дзержинского, 83; *эл. почта: dashamurashka@mail.ru
[2]Республиканский научно-практический центр пульмонологии и фтизиатрии,
220080, Беларусь, Минск, Долгиновский тракт, 157

Хроническая обструктивная болезнь лёгких (ХОБЛ) является одной из самых распространённых патологий дыхательной системы, которая характеризуется нарастающим ограничением воздушного потока. Течение ХОБЛ нестабильно и нередко сопровождается периодами обострения, когда респираторные симптомы заболевания существенно усиливаются. Частота обострений ХОБЛ является важным предиктором её течения, позволяющим прогнозировать снижение функции лёгочной ткани и исход заболевания. В настоящее время оценка риска будущих обострений ХОБЛ у пациента осуществляется на основании истории предыдущих обострений, а об улучшении его состояния судят на основании ослабления симптомов ХОБЛ. Отсутствие объективных критериев не позволяет однозначно судить о вероятности развития острых состояний и эффективности лечения пациентов с ХОБЛ. На основании анализа литературных данных сделан вывод о потенциальной информативности определения с этой целью уровня хемокинов (CXCL5, CXCL8, CXCR1/2, CD44v6), HIF-1α, прокальцитонина, альбумина и С-реактивного белка, клеток лейкоцитарного ряда, а также их возможной комбинации в периферической крови пациентов с ХОБЛ.

*Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).*

**Ключевые слова:** ХОБЛ; биомаркеры; CXCL5; CXCL8; CXCR1/2; CD44v6; HIF-1α; белки острой фазы воспаления; клетки крови

**Финансирование.** Работа выполнена в рамках ГПНИ 4 “Трансляционная медицина” (подпрограмма 4.2 “Фундаментальные аспекты медицинской науки”) на 2021–2025 годы, задания 4.2.44 “Определить динамику изменений содержания в крови провоспалительных белков, цитокинов, их рецепторов и клеток у пациентов с хронической обструктивной болезнью лёгких”.

Поступила в редакцию: 24.04.2025; после доработки: 13.06.2025; принята к печати: 17.06.2025.