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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

CLINICAL SIGNIFICANCE OF SYSTEM, PULMONARY BIOMARKERS İN SEVERE EXACERBATİONS OF CHRONİC OBSTRUCTİVE PULMONARY DİSEASE AND OPTİMİZİNG THE TREATMENT OF THE DISEASE

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GENERAL DESCRIPTION OF THE RESEARCH

Relevance of the topic: Chronic obstructive pulmonary disease (COPD) is irreversible, progressive disease, characterized by limited airflow rate and inflammatory reaction of the lung tissue to pathogens and gases, resulting in systemic changes. Over the last 15-20 years, the incidence of respiratory diseases has increased in worldwide, and chronic obstructive pulmonary disease is one of them. The figures published in the European White Book in 2013 year prove it once again.

According to World Health Organization data, 3 million people die from COPD each year, and it is estimated that in the years 1990-2030, it will move from the 6th to the 2nd place among the diseases that cause death, and from the 12th to the 5th place in terms of morbidity [1] . It is assumed that the death from COPD will increase twice in 2030 year due to the increase in smoking[2]. Necessary population studies on the epidemiology of COPD cannot be conducted because they are too expensive. Therefore, there is no information on the exact number of patients with COPD worldwide: various experts note that this number fluctuates between 44 and 600 million [3].

COPD patients present an acute clinical condition, that called severe exacerbation of COPD[4]. The main reason for patients to go to the hospital is severe exacerbations, which sometimes do not result in the full effectiveness of treatment. According to Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations:

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[1] WHO| Top 10 causes of death [Internet]. WHO. [cited 2018 May 29]. Available from: http: //www.who.int/gho/ mortality_burden_disease/causes death/top 10/en/

[2] Статистика ХОБЛ // Официальный сайт «Российское респираторное общество» -2004 – URL: http: //www. sotiety. pulmonology.ru /http^www.hobl. Info/

[3] European Lung White Book. Chronic Obstructive Pulmonary Disease // European Foundation . – 2003, - P. 34-43

[4] Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2018 Report. Available at https: // goldcopd. Org/. Accessed 30 July. 2018

"COPD exacerbation is an acute condition characterized by worsening of respiratory symptoms, which deviates from normal daily changes and leads to correction of the used therapy" [5]. A severe exacerbation of COPD is one of the main reasons why patients go to the hospital for emergency care [6]. It should be noted that COPD exacerbations consist of an increase in the frequency and severity of cough, as well as changes in the volume and character of sputum [7]. It should be noted that severe exacerbations are one of the main causes of death of COPD patients. The development of exacerbations already reveals the individual character of COPD [8]. Repeated exacerbations lead to impaired gas exchange in COPD patients, long-term deterioration of external respiratory function, and higher costs of treatment [9]. According to modern recommendation, COPD is "a completely irreversible disease, characterized by limited airflow in the lungs: airflow velocity restriction is associated with a progressive inflammatory response of the lungs to harmful particles and gases"[10]. Although the main target of COPD is the respiratory system, the disease is systemic, as noted by the American Thoracic and European Respiratory Society[11].

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[5] Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the Diagnosis, management, and prevention of chronic obstructive pulmonary disease. GOLD 2015 report. 117 p. www. goldcopd.com

[6] Авдеев, С.Н. Значение обострений для пациентов с ХОБЛ / С.Н. Авдеев // Эффективная фармакотерапия. - 29/2014, - с. 36-41

[7] Spagnolo, P. Long-term macrolide treatment for chronic respiratory disease / P. Spagnolo, L.M. Fabbri, A. Bush // Eur Respir J. - 2013; 42: - P. 239-251

[8] Hurst, J. R. Susceptibility to exacerbation in chronic obstructive pulmonary disease / J. R. Hurst, J.Vestbo, A. Anzueto [et al.] // N. Enge. J. Med. - 2010. Vol. 363. №12. - P. 1128-1138

[9] Mackay, A. J. COPD exacerbations. Causes, prevention and treatment / A. J. Mackay, J. R. Hurst // Med. Clin. N. Amer. - 2012; 96: - P. 789-808

[10] Global initiative for chronic obstructive lung disease – (GOLD)). Глобальная стратегия диагностики, лечения и профилактики хронической обструктивной болезни легких. Пересмотр 2011 г., с. 1-81

[11] Гноевых, В.В. Табакокурение и эпидемиология хронической обструктивной болезни легких / В.В. Гноевых, Е.А. Шалашова, А.А. Куприянов [и др.] // Биомедицинский журнал. – 2011, - том 12, - с. 825-838

According to GOLD's latest recommendations, a comprehensive assessment of COPD should be based on the diagnosis of symptoms, lung function, risk of exacerbation, and co-morbidities [12]. However, the symptoms of COPD: weight loss, intolerance to physical load, exacerbations, re-admission, etc. does not fully reflect the severity of the disease. Therefore, it is important to study new approaches and strategies to identify the characteristics of the disease, the assessment of individual risk for each patient.

The study of biological markers allows to determine the pathogenesis, severity, prognosis and effectiveness of treatment of COPD. However, the study of biomarkers in multiple COPD patients concluded that the data of biomarkers and "oxidative stress" studied by invasive and non-invasive examinations, did not adequately reflect the relationship between disease severity and these indicators.

Thus, the relationship between systemic and pulmonary biological markers in severe exacerbations of COPD and the severity of the disease and frequent exacerbations have not yet been fully elucidated.

In view of the above, the study of the diagnostic value of systemic and pulmonary biomarkers remains an urgent problem in severe exacerbations of COPD, which is the purpose and task of our study.

Object and subject of research:

The study included 149 patients with severe exacerbations of COPD, including eosinophil group n = 61, and non-eosinophil group n = 88 patients, with 134 men and 15 women.

The aim of the study:

Optimizing disease treatment by studying the importance and interrelationships of systemic and pulmonary biomarkers in severe exacerbations of COPD.

[12] Global Initiative for Chronic Obstructive Lung disease. Global Strategy for Diagnosis, Management, and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease; updated 2012. Available from: http://www.goldcopd.org

Research objectives:

1. To study the characteristics of the concentration of systemic biomarkers (neutrophils, C-reactive protein, leukocyte count) in the blood in severe exacerbations of COPD.
2. To study the characteristics of the concentration of some pulmonary biomarkers (eosinophils and neutrophils in induced sputum) in severe exacerbations of COPD.
3. To study the interaction between systemic and pulmonary biomarkers in severe exacerbations of COPD.
4. Development of principles of effective pathogenetic treatment scheme based on changes in systemic and pulmonary biological markers during severe exacerbations of COPD.

Research methods:

1. Laboratory tests: examination of blood and sputum
2. Determination of arterial blood gases
3. Spirometry
4. Chest computed tomography
5. Pulsoximetry
6. 6 - Minute Walking Test (MWT)
7. Prospective clinical observation (monitoring of the patient's condition and exacerbations, hospitalization due to exacerbations and admission to the intensive care unit)

The main theses for the defense:

- Systemic and pulmonary biomarker parameters during COPD exacerbations are important conditions for assessing the severity of the disease.
- Abnormalities of the system and pulmonary biomarkers studied in severe exacerbations of COPD indicate the development of complications in the course of the disease.
- An increase in the level of eosinophils in blood and sputum can be evaluated as a prognostic marker during severe exacerbations of COPD.
- In severe exacerbations of COPD, the effect of the number of eosinophils in the blood on the frequency of exacerbations can be observed.

Scientific novelty:

1. In case of severe exacerbations of COPD, a joint clinical assessment of some systemic and pulmonary biomarkers have been performed.

2. The effect of COPD exacerbations of systemic and pulmonary biomarkers on severity, hospitalization, admission to the intensive care unit and lethality have been studied.

3. During disease exacerbations, monitoring of exacerbation outcomes have been performed by assessing systemic and pulmonary biomarkers.

4. Taking into account systemic and pulmonary biomarkers, new principles of pathogenetic treatment of exacerbations have been developed.

Theoretical and practical significance:

Research of biomarkers in the diagnosis of COPD exacerbations, optimization of treatment with the development of a rational treatment scheme, increasing the stable period in patients with COPD exacerbation, reducing the length of hospital stay of patients, the use of these results in pulmonology departaments.

Approbation

The main point of the dissertation was reported and discussed at: a scientific congress dedicated to the 120th anniversary of the professor Surkhay Haydar Akhundov (Baku 2017).

The main aspects of the research are set out at an expanded meeting of the Department of "Therapeutic and pediatric propaedeutics" with the participation of employees of others internal medicine departments of the Azerbaijan Medical University (14.03.2022, protocol №1), discussed at the scientific seminar of the Dissertation Council ED 2.27 operating at Azerbaijan Medical University (17.05.2022, protocol №7).

Implementation of research results

The results of this study have found practical application in the department of "Therapeutic and pediatric propaedeutics" of the Azerbaijan Medical University and the department of "Pulmonology and Allergology" of the Education Therapeutical Clinic of the Azerbaijan Medical University.

The name of the organization where the dissertation has been accomplished

The dissertation work was carried out at the "Therapeutic and pediatric propaedeutics" department of the Azerbaijan Medical University and the "Pulmonology and Allergology" department of the Education Therapeutical Clinic of the Azerbaijan Medical University.

Published works. Based on the results of the dissertation, 14 scientific works were published: 9 of which are articles and 5 are theses, including 2 articles and 1 thesis in foreign publishing houses.

Dissertation structure and volume. The dissertation is written on 151 (170504 symbols) pages of computer text. It is organized in the following order: "Title page" (477), "Contents"(3378), "Introduction" (8190), "Literature review"(69067), "Materials and methods" (10655), "Results of research" (40652), "Optimization of treatment in severe exacerbations of chronic obstructive pulmonary disease" (10255), "Discussion of acquired" results" (24870), "Results" (1840), "Practical recommendations" (1120), "References", "Abbreviations". The research work is illustrated with 25 pictures and 24 tables. The bibliographic index consists of 274 sources, of which 2 works were submitted in Azerbaijani, 49 works in Russian and 223 works in other languages.

MATERIALS AND RESEARCH METHODS

The examination was conducted in the Department of Pulmonology and Allergology of the Education Therapeutical Clinic of the Azerbaijan Medical University in 2016-2019 years.

Patients were informed and volunteers were involved in the examination. Patients were diagnosed based on the criteria of the latest version of the GOLD 2019 strategy. Inclusion criteria for the examination:

1. Patients aged 50-80 years;
2. Criteria for exacerbation of COPD (increased shortness of breath, increased sputum volume and increased sputum purulence)[13];

[13] Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the Diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2019 report, 155 p. www. goldcopd.com

3. 30% <FEV_1 <50 from the required level and FEV_1 / FVC <70%;

4. Chronic respiratory failure in all patients;

Exclusion criteria for the examination:

1. Pulmonary thromboembolism
2. Patients with cerebrovascular disorders;
3. Bronchiectasis;
4. Pulmonary tuberculosis;
5. Patients with malignant tumors;
6. Patients who do not want to follow the doctor's appointment.

After obtaining voluntary consent from patients, 149 patients with severe exacerbations of COPD in II, III, IV stages were included to examination. Patients fully met the inclusion criteria and received examination and treatment at the Department of Pulmonology and Allergology of the Education Therapeutical Clinic of the Azerbaijan Medical University. Selection of patients was based on the results of anamnestic data, objective and laboratory-instrumental examinations. During the collection of anamnesis, information was provided on the assessment of the duration of the disease, the determination of the smoking index, and whether the patient was in an environment of industrial pollution.

Physical examination of patients included the collection of anamnesis: assessment of the duration of the disease, assessment of the smoking index, objective examination of patients.

In addition to physical examination of all patients, spirometry-pulmonary function test (PFT), electrocardiography, X-ray examination of the lungs, computed tomography (CT), laboratory examination of blood and induced sputum, blood gas examination, pulse oximetry and 6-minute walking test (6 MWT).

In addition to assessing the clinical picture, severity of shortness of breath, cough, and sputum, the characteristics of each symptom were assessed using a specific scoring system. Cough was assessed on a 5-point scale. In particular, CAT (COPD assessment test) was used to assess COPD and mMRC (Modified British Medical Research

Council) questionnaires were used to assess shortness of breath. Wheezing was rated on a 4-point scale [0-3]:

0 - no dry wheezing;

1 - dry wheezing is heard only during forced breathing;

2 - dry wheezing is heard during quiet breathing;

3 - Dry wheezing is heard against the background of weakened or "dumb lungs".

6 MWT - performed according to a special standard protocol. First of all, patients were informed about the purpose of the examination and consent was obtained. Give them 6 minutes at their own pace along the corridor and were offered to cover the maximum distance during the test.

However, they were allowed to stop and rest when needed during the test. Phrases were used to encourage them during the test. For example: "Everything is fine", "Continue in the same way", etc. Shortness of breath, pulse, and saturation were assessed on the mMRC scale at the beginning and end of the test. Patients stopped the test if developed severe shortness of breath, chest pain, or dizziness.

Smoking index [SI] in patients (box / year) was calculated by the following formula: SI = number of cigarettes smoked per day x year of smoking / 20. If the SI is> 10 boxes / year, this is considered a significant risk for the development of COPD.

In the diagnosis of COPD, the determination of pulmonary function test plays an important role in assessing its severity. Spirometry is one of the most important tests for studying the functional parameters of the bronchopulmonary tree, which provides information about changes in air velocity in the distal parts of the respiratory system.

The spirometry was performed using the Bionet (Korea) device. The following indicators were examined during the examination:

- Forced vital capacity (FVC);
- Forced expiratory volume in 1 second (FEV_1);
- Vital Lung capasity on inspiration (VLC)

FEV_1, FVC and their ratio FEV_1/ FVC are key indicators in the diagnosis of COPD to determine the nature of external respiratory dysfunction.

The indicators of post-bronchodilation test for FEV_1 provides information on both the stage and severity of the disease. Bronchodilation test:

- to deny bronchial asthma;
- to reason about the prognosis of the disease;
- necessary to assess the effectiveness of treatment. Inhaled sympathomimetic short-acting β_2 agonists (Ventolin, GlaxoSmithKline, 4 doses) were used for the postbronchodilation test. After 15 minutes the results were evaluated by repeated spirometry. β_2 - agonists should be used 6 hours before the test, and long-acting β_2 - agonists should be used 12 hours before the test results are obtained. A 12% increase in FEV_1 after a bronchodilation test is considered a positive bronchodilation response: bronchial obstruction is considered reversible.

Induced sputum obtained by inhalation with a hypertonic solution of Na Cl was taken for bacteriological and cytological examination of sputum. Leukocytes, neutrophils, eosinophils and epithelial cells were counted under a microscope in gram-stained sputum. Such a sputum sample containing less than 10 epithelial cells and more than 25 leukocytes in the visual field (x100) was taken for culture. Planting was carried out using Vitek 2 (France) and Oxoid (England) agar.

Induced sputum was obtained by inhalation of 3-5% hypertonic solution using an ultrasonic nebulizer. After inhalation of 3-5% hypertonic solution during 5-30 minutes, the patient coughs and sputum is expelled. Before inhalation with a nebulizer, the patient inhales with salbutamol (200 mcg, 2 breaths), which prevents bronchospasm that may occur during nebulizer inhalation. Spirometry was performed before and after this procedure to monitor pulmonary functional indicators.

Inhalation was carried out in 7-minute sessions, the concentration of the solution was increased by 1% every 7 minutes and 3%, 4%, 5% solution was used. If FEV_1 is reduced by 20% during spirometry, inhalation is stopped. After each session, the patient coughed up sputum into special containers. Induced sputum was sent for examination within 1 hour after collection. In addition of infectious agents, induced sputum allows to study the cellular and non-cellular factors of inflammation, as well as to reflect on the intensity of the inflammatory

process, its activity and severity. This examination was well performed by the patients and no complications were observed.

In the laboratory examination of blood, leukocyte count, neutrophil count, eosinophils, C-reactive protein (CRP) were determined. Leukocytes, neutrophils, eosinophils, macrophages, CRP were detected in serum. In the morning, on an empty stomach, a sample of venous blood was taken and examined. A general blood test was performed using a Sysmex x T-4000 i (Kobe, Japan). The concentration of CRP was tested using Dimension x pand plus (Siemens, Germany). Blood pH, pCO_2, pO_2, levels were studied using Medica EasyStat analyzer (USA). Concentrations of these systemic biomarkers were determined before and after treatment. All these examinations were conducted in the laboratory of the Azerbaijan Medical University.

Computed tomography is a more accurate method of X-ray examination, which studies the internal structure of the body in a stratified manner. Computed tomography plays an important role in the diagnosis of various forms of emphysema in patients with COPD. Thus, in patients with COPD, CT allows to detect the anatomical characteristics of bronchial damage and the presence of this damage in the proximal or distal parts of the bronchi. CT scans show pathological area and even their accurate localization. CT of Toshiba Agulion (Japan) was used to examine our patients.

Methods of mathematical and statistical analysis. The results of the study were statistically analyzed by biostatistics (variation, discriminant, dispersion, correlation). The ANOVA (F-Fisher) and Mann-Whitney tests were used to compare the quantitative values of the study groups. Hypothesis “0” was rejected when the statistical results of both tests were $p < 0.050$. The study used the $\chi 2$-Pearson (Chi-square Pearson) criterion to compare quality indicators. In order to reveal the relationship between quantitative and qualitative indicators, the ρ-Spearman correlation coefficient was calculated and the coefficient was statistically estimated. Calculations were performed in the EXCEL-2013 and SPSS-21 package programs

RESEARCH RESULTS AND THEIR DISCUSSION

Clinical characteristics of COPD patients with severe exacerbations. Evaluation of high and low levels of eosinophils in the blood in patients with COPD showed a sharp decrease in the number of exacerbations in patients with high eosinophil levels against the background of inhaled corticosteroid therapy (ICS). In addition, an increase in the number of eosinophils in the blood is associated with an increase in the number of exacerbations of the disease, which once again indicates that the number of eosinophils in the blood should be presented as a potential prognostic marker. In the study, the amount of eosinophils in the peripheral blood at the time of exacerbation of COPD was very different between patients in the eosinophilic and non-eosinophilic groups 0.408 ± 0.023 and 0.065 ± 0.017; ($p < 0.001$). Elevated eosinophil counts in peripheral blood were associated with an increase in the annual incidence of severe exacerbations in COPD patients. However, due to the good response to systemic corticosteroids in severe exacerbations in these patients, their transfer to the intensive care unit was significantly lower than in the group of non-eosinophilic patients ($p = 0.001$).

Hospitalization for COPD exacerbations during the 1-year follow-up was different in both groups of patients. A higher incidence of COPD exacerbations was reported in the eosinophilic group of patients 39 (63.9%) and 40 (45.5%); ($p = 0.026$). Despite the higher frequency of COPD exacerbations in eosinophilic patients, the need for oxygen support at home, the number of patients in the non-eosinophilic group was 9 (14.8%) and 26 (29.5%); ($p = 0.036$). The use of inhaled drugs was more common in patients with eosinophilic group 58 (95.1%) and 66 (75.0%); ($p = 0.001$). Higher rates of using inhaled corticosteroids were still observed in the eosinophilic group of patients 49 (80.3%) and 47 (53.4%); ($p = 0.001$). The highest frequency of wheezing at the time of hospitalization was observed in the eosinophilic group 38 (62.3%) and 33 (37.5%); ($p = 0.003$). The use of ICS in the post-hospital period was almost identical in both groups 51 (83.6%) and 73 (83.0%); ($p = 0.917$). This fact proves that in clinical practice, the determination of ICS in patients with COPD is

carried out without the assessment of biomarkers. Also, hospitalization in the intensive care unit (ICU) was observed more in the non-eosinophilic group 50 (56.8%) and 2 (3.3%); (p = 0.005), (table 1).

Table 1

Demographic characteristics of the patients

Parameters	Total (n=149)	Eosinophilic group (n=61)	Non-eosinophilic group (n=88)	"P" value
Men Women	134 (89,9%) 15 (10,1%)	57 (93,4%) 4 (6,6%)	77 (87,5%) 11 (12,5%)	χ^2 =1,405 p =0,236
Smoke Does not smoke (ex)	80 (53,7%) 69 (46,3%)	41 (67,2%) 20 (32,8%)	39 (44,3%) 49 (55,7%)	χ2 =7,595 p =0,006
GOLD II degree III degree IV degree	 60 (40,3%) 52 (34,9%) 37 (24,8%)	 25 (41,0%) 20 (32,8%) 16 (26,2%)	 35 (39,8%) 32 (36,4%) 21 (23,9%)	χ2 =0,226 p =0,893
Hospitalization for COPD last year	79 (53,0%)	39(63,9%)	40 (45,5%)	χ2 =4,939 p =0,026
Use oxygen at home	35 (23,5%)	9(14,8%)	26 (29,5%)	χ2 =4,386 p =0,036
Any inhalation drug	124 (83,2%)	58(95,1%)	66 (75,0%)	χ2 =10,405 p =0,001
Corticosteroid inhalation	96 (64,4%)	49(80,3%)	47(53,4%)	χ2 =11,391 p =0,001
Wheezing	71 (47,7%)	38(62,3%)	33 (37,5%)	χ2 =8,879 p =0,003
Use of ICS in the post-hospital period	124 (83,2%)	51(83,6%)	73 (83,0%)	χ2 =0,011 p =0,917
Hospitalization to ICU	52 (34,9%)	2(3,3%)	50 (56,8%)	χ2 =7,978 p =0,005
Non-invasive ventilation	64 (43,0%)	16 (26,2%)	48 (54,5%)	χ2 =11,789 p =0,001
Mechanical ventilation	19 (12,8%)	2 (3,3%)	17 (19,3%)	χ2 =8,331 p =0,004
Inhospital treatment with corticosteroids	142 (95,3%)	59 (96,7%)	83 (94,3%)	χ2 =0,465 p =0,495
Antimicrobial treatment	91 (61,1%)	36 (59,0%)	55 (62,5%)	χ2 =0,184 p =0,668

Note: p - statistical significance of the difference between the indicators of the groups (according to χ2-Pearson)

Re-admission for COPD exacerbations has been different in both groups of patients. A higher frequency of COPD exacerbations was reported in patients in the eosinophilic group of 39 (63.9%) and 40 (45.5%); ($p = 0.026$).

The highest rate of exacerbations in severe exacerbations of COPD was observed in the presence of higher eosinophil counts (when eosinophil counts were 0.43-2.2x10 g / ml or 4.6-12.4%) and compared to other concentrations of eosinophils significantly differentiated. Another interesting point is that higher eosinophil counts (≥0.35x10g / ml) are associated with lower lung function (FEV_1) during severe exacerbations of COPD, and a higher incidence of wheezing has been reported in this group of patients. However, it should be noted that high concentrations of eosinophils in the blood were accompanied by greater variability of lung function in these patients, and a significant increase in lung function was observed after using of short-term systemic corticosteroids ($p = 0.05$).

Higher levels of eosinophils are associated with lower FEV_1 levels during exacerbations of COPD. When the highest eosinophil counts were noted, the FEV_1 index was 33.2 ± 0.4% ($p <0.001$). Comparison of eosinophilic and non-eosinophilic group patients in COPD exacerbations was characterized by lower FEV_1 values in eosinophilic group patients 33.2 ± 0.4% and 39.4 ± 0.8%; ($p <0.001$). There were also differences in airflow velocity limitation (FEV_1 /FVC) in both groups of patients, 45.0 ± 0.8% and 53.6 ± 0.6%; ($p <0.001$). In eosinophilic patients, the degree of pulmonary dysfunction during severe exacerbations of COPD was positively correlated with the intensity of wheezing. Higher levels of eosinophils were also characterized by increased wheezing and the use of systemic corticosteroids in this group of patients showed significant improvement in both clinical symptoms (wheezing) and lung function (FEV_1) in a short time ($p = 0.05$), (figure 1).

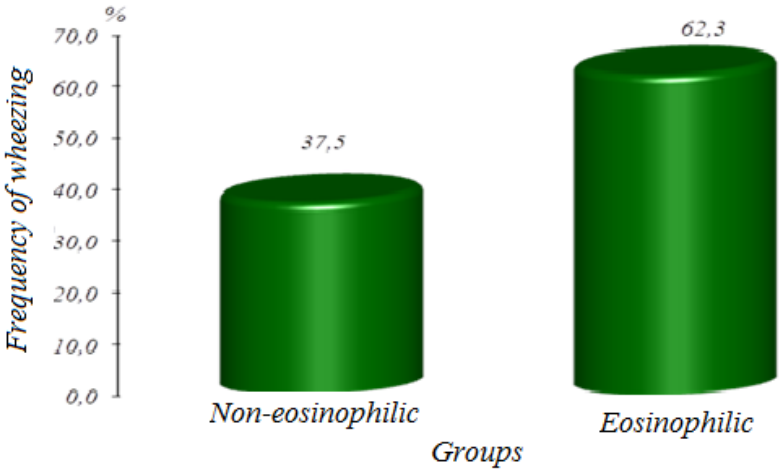

Figure 1. Comparison of frequency of “wheezing” in both groups at the time of hospitalization

The main clinical indicators of the patients included in the study were characterized (table 2).

A comparison of patients showed that there was a significant difference between the average exacerbations in the eosinophilic group last year. Thus, more exacerbations were observed in the eosinophilic group: of 3.05 ± 0.19 and 1.43 ± 0.10; ($p < 0.001$) exacerbations. Between groups CAT scores were 19.4 ± 0.5 and 18.9 ± 0.4; ($p = 0.459$), mMRC scores were 1.97 ± 0.13 and 2.06 ± 0.13; ($p = 0.646$), the 6-minute walking test were 360.8 ± 13.6 and 371.9 ± 7.3 m; ($p = 0.438$) and no significant differences were observed. Comparison of the number of samples of potential pathogenic microorganism (PPM) in sputum between two groups showed different results. PPM positive was detected $2.82 \pm 0.25 \times 10^4$ in non-eosinophilic group patients, but this indicator was recorded in eosinophil group patients: $0.77 \pm 0.24 \times 10^4$; ($p < 0.001$). This proves once again that bacterial infection is more important in the exacerbation of the disease in non-eosinophilic patients.

Table 2

Characteristics of the main clinical indicators of the patients included in the study

Parameters	Eosinophilic group (n = 61)	Non-eosinophilic group (n = 88)	P_F	P_U
Frequency of exacerbations (before study)	3,05 ± 0,19 (1,0 - 6,0)	1,43 ± 0,10 (0,0 - 3,0)	<0,001	<0,001
mMRC scores	1,97 ± 0,13 (1,0 - 4,0)	2,06 ± 0,13 (0,0 - 4,0)	0,646	0,484
CAT scores	19,4 ± 0,5 (14,0 - 26,0)	18,9 ± 0,4 (12,0 - 25,0)	0,459	0,593
6 DYT, m	360,8 ± 13,6 (188,0 - 539,0)	371,9 ± 7,3 (260,0 - 482,0)	0,438	0,663
Post FEV_1 (L)	1,20 ± 0,05 (0,6 - 1,8)	1,43 ± 0,02 (1,1 - 1,7)	<0,001	<0,003
Post FEV_1,%	46,6±1,0 (32,7 - 58,8)	52,4 ± 0,7 (42,0 - 62,0)	<0,001	<0,001
Post FVC (L)	2,78 ± 0,06 (2,0 - 3,6)	2,85 ± 0,04 (2,3 - 3,5)	0,274	0,367
Post FEV_1 / FVC,%	0,440 ± 0,020 (0,194 - 0,810)	0,507 ± 0,008 (0,324 - 0,680)	P = 0,001	P = 0,001
Return %	8,41 ± 0,51 (2,0 - 20,0)	6,90 ± 0,43 (0,0 - 13,0)	0,025	0,051
Total cell count in sputum $x10^6$ / g	3,96 ± 0,29 (0,1 - 7,7)	4,18 ± 0,25 (0,1 - 8,2)	0,570	0,604
Neutrophils in sputum%	27,5 ± 1,9 (1,5 - 53,3)	74,9 ± 5,1 (0,0 - 158,0)	<0,001	<0,001
Eosinophils in sputum%	4,70 ± 0,28 (1,2 - 9,1)	0,43 ± 0,02 (0,0 - 0,8)	<0,001	<0,001
The amount of eosinophils in sputum $x10^6$ / g	0,105 ± 0,006 (0,03 - 0,18)	0,022 ± 0,001 (0,00 - 0,04)	<0,001	<0,001
The amount of neutrophils in sputum $x10^6$ / g	1,00 ± 0,06 (0,21-1,73)	3,85 ± 0,22 (0,10-6,90)	<0,001	<0,001
PPM positive ($\geq 1x10^4$ copy / ml),%	0,77 ± 0,24 (0,0 - 6,0)	2,82 ± 0,25 (0,0 - 8,0)	<0,001	<0,001

Note: Statistical significance of the difference between the indicators of the groups:

1. P_F - According to Fisher's criterion

2. P_U - according to the Wilcoxon (Manna-Whitney) criterion.

In addition, patients with ≥3% sputum eosinophil counts had less bacterial load than sputum eosinophil counts <3% (<0.001). It should be noted that in the non-eosinophilic group of patients more sputum neutrophils 78.4 ± 1.4 and 28.5 ± 1.7%, respectively; (p <0.001) and less eosinophils 0.44 ± 0.02 and 4.72 ± 0.32%, respectively; (p <0.001) was found.

At the same time, it should be noted that a significant positive correlation was observed between bacterial load and neutrophil concentration in sputum in the examined patients (p = 0.001).

Comparative characteristics of blood and sputum between PPM positive and negative groups in stable and exacerbated periods of the disease

Regardless of the positivity of PPM, a significant increase in white blood cells was observed in the blood during the period of exacerbation compared to the stable period of the disease 7.51 ± 0.22 and 9.20 ± 0.27 $x10^9$ / l; (p <0.001); for PPM positive patients, 6.90 ± 0.25 and 9.95 ± 0.37$x10^9$ / l; (p <0.001); for PPM negative patients. A more pronounced increase in neutrophils in the blood was recorded in the group of PPM-positive patients 4.24 ± 0.14 and 6.45 ± 0.48$x10^9$ / l; (p <0.001). This difference was also observed in the group of patients with PPM-negative. However, this difference was significantly lower in the group of patients with PPM-negative 4.22 ± 0.10 and 5.41 ± 0.20$x10^9$ / l; (p <0.001). A sharp decrease in the amount of eosinophils in the blood during the period of exacerbation compared with the stable period was observed in the group of patients with PPM positive 0.372 ± 0.097 and 0.158 ± 0.117$x10^9$ / l; (p <0.001). This proves once again that bacterial load in patients with COPD changes the profile of the inflammatory process in the respiratory tract and lungs, transforming eosinophilic inflammation into neutrophilic inflammation. In contrast, in the group of patients with PPM-negative, a marked increase in eosinophils was observed during exacerbations of 0.182 ± 0.014 and 0.242 ± 0.011$x10^9$ / l; (p <0.001) (figure 2).

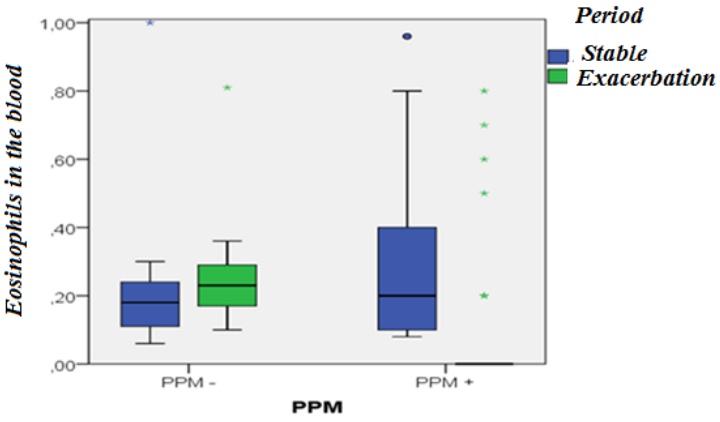

Figure 2. The amount of eosinophils in the blood during stable and severe exacerbation in PPM-positive and PPM-negative patients (PPM value $1x10^4$). PPM-potential pathogenic microorganisms

It should be noted that, depending on the PPM positivity in sputum, a significant difference was observed between the total cell concentration in patients who experienced both a stable and an exacerbation period. Thus, in the group of patients with PPM-positive in sputum, the total number of cells during the stable and exacerbation of the disease was 5.80 ± 0.44 and 9.45 ± 0.68 $x10^6$ / l; ($p < 0.001$), on the other hand, in the group of patients with PPM negative, high density of inflammatory cells in the sputum during exacerbation was recorded 3.14 ± 0.19 and 6.72 ± 0.63 $x10^6$ / l; ($p < 0.001$).

İf there is a difference in neutrophil counts when comparing stable and exacerbation periods in patients with PPM-positive in sputum 6.11 ± 0.68 and 9.29 ± 0.82 $x10^6$ / l; ($p = 0.001$); a significant decrease in the amount of neutrophils in the sputum of PPM-negative patients in the stable period was noted 0.78 ± 0.06 and 6.42 ± 0.79 $x10^6$ / l; ($p < 0.001$).

Changes in the amount of eosinophils in sputum were directly related to PPM positivity. Thus, in those with PPM-positive in

sputum, a sharp decrease in the amount of eosinophils in the sputum during exacerbation was noted 0.093 ± 0.009 and 0.012 ± 0.003 $x10^6$ / l; ($p < 0.001$). However, no differences in eosinophil counts were found in patients with PPM-negative sputum, regardless of the stage of the disease, 0.025 ± 0.007 and 0.034 ± 0.014 $x10^6$ / l; ($p = 0.994$).

It should be noted that a decrease in the number of lymphocytes in the sputum of COPD patients during exacerbation of the disease was found only in the group of PPM-positive patients 0.092 ± 0.013 and 0.015 ± 0.004 $x10^6$ / l; ($p < 0.001$). This fact once again proves that infectious exacerbations of the disease occur in the context of a sharp decrease in bronchopulmonary resistance. Thus, the results of the comparisons show that the changes in cell profiles in the sputum and blood of patients are directly due to the positivity of PPM in the blood and sputum, which differs in the stages of the disease. Elevation of neutrophil concentrations in the blood during exacerbation is more pronounced in PPM-positive patients ($p = 0.001$) and a sharp decrease in eosinophil counts in patients with PPM-positive exacerbation ($p < 0.001$), in contrast to eosinophil concentration $p < 0.001$).

Clinical characteristics of patients and the association between some comorbid conditions and mortality. Association of some clinical indicators with mortality was studied in the patients involved in the study (table 3).

One of the key points in table- 3 is the very low incidence of death in the eosinophilic group of patients in the assessment of mortality 2 (10%) and 18 (90%); ($p = 0.002$).This proves once again that the response to corticosteroid therapy during COPD exacerbations in eosinophilic patients is very high, and systemic corticosteroids lead to better results in the management of exacerbations of the disease in eosinophilic patients. One of the important results is that low body mass index (BMI) is associated with an increased risk of mortality. As is well known, cachexia and loss of muscle mass are systemic manifestations of COPD. In this case, dystrophy of muscle mass occurs as a result of the entry of inflammatory products from the lungs into the systemic circulation.

According to the results of the study, when comparing the died and the survived, a significant difference between the BMI was found 19.8 ± 0.6 and 23.8 ± 0.5 kg / m^2; (p = 0.002). At the same time, these factors have a significant impact on the final outcome of the disease after exacerbations of COPD in comorbid patients.

In terms of age, patients over the age of 70 were more in the group of died, than group of survived: 13 (65.0%) and 58 (45%); (p = 0.130). In terms of smoking status, were currently predominant in the died group 17 (85.0%) and 52 (40.3%); (p <0.001).

Table 3

Association between clinical characteristics and mortality of patients involved in the study

Factor	Died n=20	Survived n=129	χ2; p
Non-eosinophilic	18 (90%)	70 (54,3%)	χ2 =9,146
Eosinophilic	2 (10%)	59 (45,7%)	p =0,002
Age groups			χ2 =5,649
<50 years	0 (0,0%)	5 (3,9%)	p =0,130
50-59 years	0 (0,0%)	22 (17,1%)	
60-69 years	7 (35,0%)	44 (34,1%)	
≥70 years	13 (65,0%)	58 (45,0%)	
Gender			χ2 =0,655
Man	19 (95,0%)	115 (89,1%)	p =0,418
Women	1 (5,0%)	14 (10,9%)	
GOLD			χ2 =4,179
I degree	0 (0,0%)	0 (0,0%)	p =0,124
II degree	6 (30,0%)	54 (41,9%)	
III degree	11 (55,0%)	41 (31,8%)	
IV degree	3 (15,0%)	34 (26,4%)	
BMI	19,8±0,6 (15,78-24,09)	23,8±0,5 (15,94-33,97)	P_F =9,918 P =0,002
Smoking			χ2 =13,909
Ex-smokers	3 (15,0%)	77 (59,7%)	<0,001
Smokers	17 (85,0%)	52 (40,3%)	

Note: p - statistical significance of the difference between the indicators of the groups (according to χ2-Pearson)

The study found an association between comorbid conditions, heart failure and plasma troponin levels and mortality. Thus, heart failure was predominant in the death group with high rates: 20 (15.5%) and 8 (40.0%); (p = 0.009). Elevated plasma troponin levels were also highly associated with mortality rates: 7

(35%) and 16 (12.4%); (p = 0.009). As is well known, cardiac events accelerate after COPD exacerbations. According to the study, concomitant heart disease increases the tendency to serious consequences after severe exacerbations of COPD. There are a number of potential pathophysiological mechanisms that explain the interaction between COPD and cardiovascular disease. Thus, pulmonary inflammation directly leads to the formation of atheromatous plaque and arterial remodulation. Smoking is a risk factor for the development of COPD and cardiovascular pathology, reduces hyperinflation of the lungs, intrathoracic blood volume and left ventricular function. Future treatments that may be the target of cardiac manifestations may be useful in improving patient outcomes after severe exacerbations of COPD.

The results of the study show that specific severity factors of the disease are associated with mortality (GOLD group D patients and long-term oxygen therapy). This association is logical because there is a very serious association between exacerbations and mortality in COPD patients with the highest frequency of exacerbations and symptoms in GOLD D group patients. On the other hand, GOLD group D patients receive long-term oxygen therapy, and the fact that both risk factors are associated increases the risk of mortality in patients. Thus, recipients of long-term O_2 therapy predominated in the group of the died: 17 (85.5%) and 41 (31.8%); (p <0.001). In our observation, GOLD group D patients were found in the died group: 19 (95.0%) and 40 (31.0%) patients; (p <0.001). The increase in mortality in this group of patients was characterized by a sharp decrease in eosinophils and more acute indicators of systemic inflammation.

Association between clinical characteristics and mortality of patients hospitalized in the intensive care unit

Some risk factors associated with the mortality of patients admitted to the ICU have been identified. Thus, more deaths were observed in the non-eosinophilic group: 2 (10%) and 18 (90%); (p = 0.068). The most important factor associated with an increased risk of mortality among hospitalized patients with ICU is the age of over 75 years. Thus, patients over the age of 75 had a relative

predominance in the died group -13 (65.0%) and 17 (53.1%); (p = 0.423), this can be assessed as an unmodified independent risk factor.

The important role of some comorbid conditions in the study of risk factors associated with increased mortality among patients admitted to the ICU during severe exacerbations of COPD has been noted. Thus, in addition to the mortality rate of patients admitted to the ICU, the effect of heart failure was found. Thus, among those who died and those who survived heart failure were 8 (40.0%) and 6 (18.8%), respectively; (p = 0.034). On the other hand, in terms of the impact on mortality, long-term oxygen therapy was associated with 17 (85.0%) and 18 (56.2%); (p = 0.032). The effect of long-term steroid use associated with comorbidities on the mortality of patients admitted to the ICU was not found in 6 (30.0%) and 10 (31.2%); (p = 0.924). However, in most comorbid conditions, Cor -pulmonale predominated in patients who died: 15 (75.0%) and 12 (37.5%); (p = 0.008).

The presence of respiratory acidosis in the assessment of risk factors associated with increased mortality among patients admitted to the ICU also led to an increase in this indicator 18 (90.0%) and 21 (65.6%); (p = 0.048). The majority of deaths were GOLD group D patients: 19 (95.0%) and 30 (93.8%); (p = 0.851).

During the assessment of non-specific severity symptoms, the functional parameters of the lungs of the dead and the survivors differed significantly between patients who were placed in the ICU. Thus, in the group of died the FEV_1 index was lower at 37.2 ± 1.7 and 44.6 ± 1.1; (p <0.001). One of the notable changes in the interpretation of gas analysis of arterial blood was the increase in partial pressure (pCO_2) of carbon-2 oxide in the blood, which is associated with increased mortality 59.7 ± 1.5 and 41.3 ± 1.3; (p <0.001) and association with more severe respiratory acidosis. Comparison of the group of patients who died and those who were admitted to the ICU with the partial pressure of oxygen in the blood (pO_2) also showed different results: 41.8 ± 2.5 and 58.2 ± 1.2; (p <0.001). The effect of C-reactive protein in

the blood on patient mortality was not detected (p = 0.910) (table 4).

Table 4

Association between blood gases and mortality of patients involved in the study

Factor	Died n = 13	Survived n=20	P_F P_U
pH	7,336 ± 0,003 (7,3 - 7,4)	7,336 ± 0,004 (7,3 - 7,4)	P_F =0,926 P_U =0,813
pO_2, mmHg	41,8 ±2,5 (32,0 - 54,2)	58,2 ± 1,2 (48,8 - 67,0)	P_F =0,000 P_U =0,000
pCO_2, mmHg	59,7 ± 1,5 (48,5-68,0)	41,3 ± 1,3 (32,0 - 52,3)	P_F =0,000 P_U =0,000
FEV_1,%	37,2 ± 1,7 (26,0 - 45,0)	44,6 ± 1,1 (28,0 - 57,0)	P_F =0,001 P_U =0,000
C-reactive protein, mg/l	14,1 ± 2,6 (2,30 - 40,10)	15,4 ± 2,5 (1,70 - 51,60)	P_F =0,116 P_U =0,910

Note: Statistical significance of the difference between the indicators of the groups:

1. P_F - According to Fisher's criterion

2. P_U - according to the Wilcoxon (Manna-Whitney) criterion

One of the factors proven in the study was the highest mortality rate in the first 30 days of the year in all groups of patients within a year after hospitalization for COPD. However, the highest peak was recorded in patients who underwent invasive mechanical ventilation and was higher during the first 30 days than in patients who did not require ventilation. During the next 60 days of observation, it decreased, but remained relatively high (table 5).

As a rule, short-term administration of systemic corticosteroids is recommended in all patients with severe exacerbations of COPD, based on the guidelines of GOLD 2020. In our study, the clinical response to systemic corticosteroids was not the same (table 6).

Table 5

Assess the risk of mortality in patients during the first year after hospitalization according to COPD

Death				
	Do not need ventilation support	Non-invasive ventilation	Invasive ventilation	χ2; p
0-30 day No. Yes	 64 (97,0%) 2 (3,0%)	 59 (92,2%) 5 (7,8%)	 16 (84,2%) 3 (15,8%)	χ2 =4,053 p =0,132
31-60 day No. Yes	 63 (98,4%) 1 (1,6%)	 56 (94,9%) 3 (5,1%)	 14 (87,5%) 2 (12,5%)	χ2 =3,854 p =0,146
61-90 day No. Yes	 62 (98,4%) 1 (1,6%)	 55 (98,2%) 1 (1,8%)	 14 (100,0%) 0 (0,0%)	χ2 =0,247 p =0,884
91-180 day No. Yes	 62 (100,0%) 0 (0,0%)	 54 (98,2%) 1 (1,8%)	 13 (92,9%) 1 (7,1%)	χ2 =3,929 p =0,140
181-365 day No Yes	 62 (100,0) 0 (0,0%)	 54 (100,0%) 0 (0,0%)	 13 (100,0%) 0 (0,0%)	

Note: p - statistical significance of the difference between the indicators of the groups (according to χ2-Pearson)

Treatment failure was more common among non-eosinophilic patients receiving this therapy (18 (40.9%) and 1 (4.5%); (p = 0.005). Despite this therapy, persistent respiratory failure symptoms were more common among non-eosinophilic patients 22 (50.0%) and 2 (9.1%); (p = 0.003). Cases of ineffectiveness of treatment in patients and transfer to the intensive care unit due to the need to develop various complications were registered in the group of non-eosinophilic patients 21 (47.7%) and 1 (4.5%); (p = 0.001). The need for mechanical ventilation due to respiratory failure was more common in these groups of patients 20 (45.5%) and 2 (9.1%); (p = 0.007). Due to the need for more severe respiratory failure, invasive ventilation was also observed in more non-eosinophilic patients 16 (36.4%) and 1 (4.5%); (p = 0.013).

Table 6

Evaluation of the effect of systemic corticosteroids in severe exacerbations of COPD depending on the amount of eosinophils in the blood

Factors		Systemic corticosteroids (n=66)		p
		Eosinophilic group (n=22)	Non-eosinophilic group (n=44)	
Failure in treatment, n	No. Yes	21 (95,5%) 1 (4,5%)	26 (59,1%) 18 (40,9%)	$\chi 2 = 7{,}770$ P_P=0,005
Respiratory failure, n	No. Yes	20 (90,9%) 2 (9,1%)	22 (50,0%) 22 (50,0%)	$\chi 2 = 8{,}913$ P_P =0,003
Transfer to intensive care unit, n	No. Yes	21 (95,5%) 1 (4,5%)	23 (52,3%) 21 (47,7%)	$\chi 2 = 10{,}440$ P_P =0,001
The need for mechanical ventilation, n	No. Yes	20 (90,9%) 2 (9,1%)	24 (54,5%) 20 (45,5%)	$\chi 2 = 7{,}168$ P_P =0,007
Invasive ventilation, n	No. Yes	21 (95,5%) 1 (4,5%)	28 (63,6%) 16 (36,4%)	$\chi 2 = 6{,}190$ P_P =0,013
Eosinophils in the blood %	Before treatment	4,955±0,408 (2-8)	0,014±0,005 (0-0,1)	P_U< 0,001
	After treatment	3,273±0,355 (1-6)	0,005±0,003 (0-0,1)	P_U < 0,001
Stay in the hospital, days		3,14±0,40 (1-9)	4,84±0,35 (1-12)	P_U =0,002

Note: p - statistical significance of the difference between the indicators of groups:

P_P - According to Pearson's criterion

P_U - According to the Wilcoxon (Mann-Whitney) criterion

The results of the study showed that although eosinophilic patients had a higher risk of re- admission, their hospital stays were shorter than those of non-eosinophilic patients, and the use of systemic corticosteroids significantly reduced hospital stays: 3.14 ± 0.40 and 4.84 ± 0.35 days; (p = 0.002). The use of systemic corticosteroids in this group of patients minimizes treatment failures and significantly reduces the length of hospital stay.

Thus, the use of systemic corticosteroids in severe exacerbations of COPD has led to a reduction in the incidence of respiratory failure, transfer of patients to the intensive care unit and a significant reduction in the need for mechanical ventilation, invasive

ventilation. Systemic corticosteroids in patients with high concentrations of eosinophils in the blood significantly reduced the length of hospital stay.

As noted, despite the use of intensive therapy (systemic corticosteroids, bronchodilators and oxygen therapy) in a group of patients it was not possible to correct respiratory failure during severe exacerbations of COPD, and in this group of patients to regulate hypercapnic and decompensated respiratory failure (respiratory acidosis) non-invasive ventilation (NIV) has been applied. The use of non-invasive ventilation in patients led to a significant reduction in hospital stay (8.2 ± 4.1 and 11.8 ± 5.3; $p = 0.001$). In addition, the use of NIV led to a sharp decrease in patients' need for intubation 3 (18.8 ± 9.8) and 12 (92.3 ± 1.4); $p = 0.001$. As the most important indicator in the assessment of patient outcomes, nosocomial mortality was significantly lower in the group of patients undergoing NIV regimen 1 (6.3 ± 6.1) and 5 (38.5 ± 13.5); $p = 0.095$.

One of the main points of these observations is that after the first day of NIV administration, the gas content of the blood changes significantly towards positive dynamics. Thus, the use of two-lewels of NIV in patients after 24 hours led to a significant decrease in pCO_2 ($p = 0.003$), an increase in pO_2 ($p = 0.004$) and the return to normal after 4 days. At the same time, respiratory acidosis ($pH < 7.35$), an indicator of decompensation of respiratory failure, decreased during 24 hours and although not statistically accurate, but changed to normal ($p = 0.125$).

Thus, the use of two-levels NIV in the basic intensive therapy of patients with severe COPD exacerbations with acute hypercapnic respiratory failure leads to a reduction in their hospital stay, a reduction in the need for intubation, hospital deaths and, in all cases, respiratory acidosis is disappeared. Therefore, in this group of patients with severe COPD exacerbations, the use of two- levels of non-invasive ventilation is recommended for this therapy due to the low effectiveness of basic intensive therapy.

CONCLUSIONS

1. The presence of ≥2% of eosinophils in the blood in COPD is accompanied by exacerbation of the disease. At the same time, very high levels of eosinophils (> 0.35x109 / l) lead to an increase in the frequency of wheezing in 62.3% of patients in the eosinophilic group and 37.5% of patients in the non-eosinophilic group ($\chi 2 = 8.879$; $p = 0.003$) [8, 12].

2. In patients with non-eosinophilic COPD, despite a statistically significant increase in the amount of C-reactive protein in the blood (3.8 times; 22.9 ± 1.7 mg / l and 6.1 ± 0.7 mg / l; $p < 0.001$) does not affect mortality in such patients admitted to the İCU (14.1 ± 2.6 and 15.4 ± 2.5 mg / l; $p = 0.910$) [3, 7, 13].

3. Changes in cell profiles in the sputum and blood of COPD patients were different during periods of stable and exacerbation of the disease. The amount of eosinophils in the blood was 2.4 times less in the period of exacerbation ($p < 0.001$) in the case of PPM positive than in the stable period, and 1.3 times more ($p < 0.001$) in the period of exacerbation compared to the stable period in the case of PPM negative [12].

4. Although eosinophilic patients had a higher risk of re-admission to the hospital, their hospital stay was shorter than of non-eosinophilic patients 4.84 ± 0.35 and 3.14 ± 0.40 days; $p = 0.002$; and the use of corticosteroids in these patients significantly reduced cases of respiratory failure 2 (9.1%) and 22 (50.0%); $p = 0.003$; cases of transfer of patients to the intensive care unit 1 (4.5%) and 21 (47.7%); $p = 0.001$; and cases of the need for invasive ventilation 1 (4.5) and 16 (36.4%); $p = 0.013$ [10,11].

5. Among the patients of COPD admitted to the intensive care unit, the death rate was 90.0% in the non-eosinophilic group and 10% in the eosinophilic group (p=0,068). The use of two-levels NIV in basic intensive therapy in patients with severe COPD with acute hypercapnic respiratory failure has been shown to reduce their hospital stay (8.2 ± 4.1 and 11.8 ± 5.3 days, $p < 0.001$) and the need for intubation (18, 8 ± 9.8 and 92.3 ± 1.4, $p < 0.001$), a decrease in

nosocomial mortality (38.5 ± 13.5% and 6.3 ± 6.1%, p = 0.095) and, in all cases, respiratory acidosis is disappeared [13].

PRACTICAL RECOMMENDATIONS

1. An increase in the number of eosinophils in the blood in patients with COPD is associated with an increase in the number of exacerbations of the disease. Therefore, the number of eosinophils in the blood can be assessed as a potential prognostic marker.

2. Although eosinophilic patients have a higher risk of re-admission, the use of systemic corticosteroids significantly reduces the length of hospital stay in these patients.

3. A sharper reduction in the number of exacerbations in the background of ICS therapy in patients with high eosinophil levels during the assessment of high and low levels of eosinophils in the blood in patients with COPD can be used for direct application of systemic corticosteroid therapy.

4. Assessment of comorbid conditions may be helpful in improving patient outcomes after severe exacerbations of COPD.

5. The use of two-levels NIV in additional to basic intensive therapy of patients with severe COPD exacerbations with acute hypercapnic respiratory failure leads to a reduction in their hospital stay, a reduction in the need for intubation, nosocomial mortality and, in all cases, respiratory acidosis is disappeared.

List of scientific references, published on the topic of the dissertation

1. Məmmədov C.T., Bağırzadə A.Ə., Babayeva F.R., Yusifov V.Q., Quliyev R.Ə., Abbasəliyeva K.T. / Ağciyərlərin xroniki obstruktiv xəstəliyinin müxtəlif fenotipləri- klinikası, diaqnostikası və müalicə prinsipləri // "Sağlamlıq", - 2015, №3, - səh. 187-190.
2. Məmmədov C.T., Abbasəliyeva K.T., İsmayılzadə C.S., Bağırzadə A.Ə., Babayeva F.R., Quliyev R.Ə., Yusifov V.Q. / Komorbid kardio-vaskulyar xəstəlikləri və ağciyərlərin xroniki obstruktiv xəstəliyi olan şəxslərdə qaz mübadiləsinin bəzi xüsusiyyətləri //"Sağlamlıq",- 2016, №3, - səh. 197-200.
3. Abbasəliyeva K.T., Məmmədov C.T., Bağırzadə A.Ə., Babayeva F.R., Quliyev R.Ə. / Xronik obstruktiv ağciyər xəstəliyinin kəskinləşməsinin diaqnostikasında sistem və pulmonar biomarkerlərin əhəmiyyəti // "Azərbaycan Tibb Jurnalı", - 2016, №3, - səh. 136-142.
4. Abbasəliyeva K.T., Məmmədov C.T., Bağırzadə A.Ə., Babayeva F.R., Yusifov V.Q./Ağciyərin xronik obstruktiv xəstəliyinin ağır kəskinləşmələri və müalicəsinə müasir yanaşma // "Azərbaycan təbabətinin müasir nailiyyətləri", - 2016, №3, - səh. 22-27.
5. Abbasəliyeva K.T., Məmmədov C.T., Bağırzadə A.Ə. / Ağciyərin xronik obstruktiv xəstəliyində C-reaktiv zülal sistem iltihabın biomarkeri kimi // "Allerqologiya, immunologiya və immunoreabilitasiya üzrə V Azərbaycan milli konqresi materialları", - 2016, - səh. 16-19.
6. Sadıqov Ə.S., Abbasəliyeva K.T. / Xronik obstruktiv ağciyər xəstəliyinin müalicəsinə müasir yanaşmalar // "Allerqologiya, immunologiya və immunoreabilitasiya üzrə V Azərbaycan milli konqresi materialları", - 2016, - səh. 118-121.
7. Abbasəliyeva K.T., Məmmədov C.T. / Ağciyərin xronik obstruktiv xəstəliyində kəskinləşmələrin ağırlıq dərəcəsinin qiymətləndirilməsində bəzi klinik göstəricilərin əhəmiyyəti // "Surxay Heydər oğlu Axundovun anadan olmasının 120 illiyinə həsr edilmiş elmi-praktik konfransın materialları", - 2017, - səh. 78-79.
8. Abbasəliyeva K.T., Məmmədov C.T., Sadıqov Ə.S., Yusifov V.Q. / Ağciyərin xronik obstruktiv xəstəliyinin

kəskinləşmələri zamanı eozinofillər və xəstələrin rehospitalizasiya riski // “Sağlamlıq”, - 2018, №3, - səh. 115-119.

9. Sadıqov Ə.S., Abbasəliyeva K.T., Bağırzadə A.Ə., Hüseynova Ş.R., Sadıqova G.B. / Ağciyərin xronik obstruktiv xəstəliyinin kəskinləşmələri zamanı personal terapiyanın seçimi // ”Əməkdar elm xadimi, professor Abbas Əhməd oğlu Axunbəylinin anadan olmasının 80 illik yubileyinə həsr olunmuş elmi konfransın materialları”, - 2018, - səh. 162-163.

10. Abbasəliyeva K.T./ Ağciyərlərin xronik obstruktiv xəstəliyinin ağır kəskinləşmələrinin müalicəsinin optimallaşdırılması// “Azərbaycan təbabətinin müasir nailiyyətləri”, - 2020, №1, - səh. 95-97.

11. Abbasəliyeva K.T. / Ağciyərin xronik obstruktiv xəstəliyinin ağır kəskinləşmələrində bir il ərzində xəstələrin yenidən hospitala qayıtma halları və ölüm riskinin qiymətləndirilməsi // “Sağlamlıq”, - 2020, №3, - səh. 76-80.

12. Абасалиева К.Т., Садыгова Г.Б., Бабаева Ф.Р. / Взаимосвязь между эозинофилами и бактериальной перегрузкой при стабилном течении и обострении ХОБЛ // «Медицинские новости», - 2020, №2, - стр. 71-73.

13. Абасалиева К.Т., Мамедов Дж.Т., Исмаилзаде Д.М., Садыгова Г.Б. / Связь между сопутствующими состояниями и смертностью пациентов, поступающих в отделение интенсивной терапии при тяжелых обострениях хронической обструктивной болезни легких // «Восточноевропейский журнал внутренней и семейной медицины», - 2020, №2, - стр. 97-102.

14. Абасалиева К.Т., Мамедов Дж.Т. / Факторы риска и коморбидность, влияющие на уровень смертности в отделениях интенсивной терапии при тяжелых обострениях хронической обструктивной болезни легких // «Сборник статей по материалам XXXIX международной научно-практической конференции. Современная медицина: новые подходы и актуальные исследования», - 2020, №8 (35), - стр. 6-9.

LIST OF ABBREVIATIONS

BMI	–	body mass index
CAT	–	COPD Assessment Test
COPD	–	chronic obstructive pulmonary disease
CRP	–	C- reactive protein
FEV_1	–	forced expiratory volume in 1 second
FVC	–	forced vital capacity
GOLD	–	Global Initiative for Chronic Obstructive Lung Disease
ICS	–	inhaled corticosteroid
ICU	–	intensive care unit
mMRC	–	Modified Medical Research Council Dyspnea Scale
6 MWT	–	6 minute walking test
NIV	–	non-invasive ventilation
PFT	–	pulmonary function test
PPM	–	potential pathogenic microorganisms
SI	–	smoking index

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