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CLINICAL AND IMMUNOLOGICAL FEATURES OF DIFFERENTIAL DIAGNOSIS OF CROSS BRONCHIAL ASTHMA SYNDROME AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

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The monograph presents modern data on etiopathogenetic risk factors for the development of coronary heart disease, in particular hyperuricemia and anxiety-depressive syndrome. Modern literary sources from both CIS countries and foreign countries are presented. The studied literature data allowed the authors to consider some molecular genetic factors of predisposition to the development of coronary artery disease. The main etiopathogenetic factors are anxiety-depressive syndrome, asymptomatic hyperuricemia and its connection with genetic markers (genotypes of pro-inflammatory and anti-inflammatory cytokines), as well as pro- and anti-inflammatory cytokines. Based on our own clinical and laboratory studies, the molecular genetic features of the course of unstable variants of angina are described depending on etiopathogenetic risk factors.

ABBREVIATIONS

BA - bronchial asthma
MBA - mild bronchial asthma
MSBA - moderate-severe bronchial asthma
SBA - severe bronchial asthma
BHR - bronchial hyperreactivity
WHO - World Health Organization
GC - glucocorticosteroids
RT - respiratory tract.
VCL - vital capacity of the lungs
SI - smoker index
EAC - exhaled air condensate
HDL - high density lipoprotein
FEV - forced expiratory volume
PEF - peak expiratory flow
SOBACOPD - syndrome of overlap of bronchial asthma and chronic obstructive pulmonary disease
FER - function of external respiration
FVC - forced vital capacity
COPD - chronic obstructive pulmonary disease
ECG - electrocardiography
OS - overlap syndrome
ACT - Asthma control test
CAT - COPD assessment test
GINA- The Global Initiative for Asthma
GOLD- Global Initiative for chronic Obstructive Lung Disease
IgE - immunoglobulin E
IL-4 - interleukin 4
IL-8 - interleukin 8
NO2/NO3 - nitric oxide
SGRQ - hospital Saint St. George's Respiratory questionnaire
TNF -α - tumor necrosis factor α

PREFACE

Today, during a pandemic, respiratory diseases represent not only a medical, but also a socio-economic problem, which is the most common, according to the World Health Organization, “the number of people suffering from bronchial asthma (BA) is 300 million, and chronic obstructive asthma lung disease (COPD) is the fourth leading cause of death.” In clinical practice, patients often encounter characteristic symptoms of both nosological forms, which leads to certain difficulties in diagnosis and treatment. Despite the similarity of symptoms, these diseases differ from a histological point of view, are characterized by different physiological abnormalities and differ in clinical manifestations. Currently, the main task of specialists is to slow down the progression of asthma and COPD and their combinations, taking into account the peculiarities of the pathogenetic pathways of disease development, improving the quality of life of patients and preventing the development of complications.

Despite the study of the mechanisms of development of bronchial asthma and COPD in the world, a number of scientific studies are being conducted to analyze the pathogenetic mechanisms in the principles of prevention and treatment, measures to prevent the disease and create a fundamental basis for early diagnosis. The diseases are progressive in nature, with clear systemic manifestations, especially in severe and extremely severe forms, despite differences in etiology, pathophysiology and clinical manifestations, which is explained by the presence of symptoms of COPD and bronchial asthma in 10-20% of cases. In asthma and COPD, assessment of the endothelial state, immunological status, functional state of the respiratory system and functional reserve of the lungs is of particular importance.

Our country has set a number of tasks to develop the medical industry, adapt medicine to the requirements of world standards, develop diagnostics, prevention and treatment of various somatic diseases. “Increasing the efficiency, quality and

accessibility of medical care, as well as the introduction of high-tech methods, supporting a healthy lifestyle and preventing diseases...". These objectives serve to reduce the level of disability in the population as a result of forecasting by assessing the age and recovery of patients with asthma and COPD, assessing the immunological status, functional state of the respiratory system and functional reserves of the lungs.

CHAPTER 1.
References

Modern views on the mechanisms of development of the overlap syndrome between BA and COPD

In recent years, bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD) have become major medical problems. According to the World Health Organization (WHO), by 2030, asthma and COPD will be one of the main characteristics of mortality [61; 102]. Today, about 230,000,000 people in the world suffer from COPD, of which 11.8% are men and 8.5% are women over 40 years of age [61;102].

COPD regularly kills more than 300 people in Europe and almost 3 million people in the world [23]. According to the "Study of Global Damage from Pathologies", this pathology will move to 3rd place by 2020, and in 2030. –will become one of the four main causes of mortality [2, 10, 18; 61; 102; 123]. According to world literature, the number of fatal cases of asthma is 250 thousand

people per year. According to research results, with rapid urbanization, the pathology will increase in 100-150 million people by 2025 [43].

COPD and asthma are independent chronic diseases of the respiratory system, especially common in the world. There are certain differences in the principles of manifestation of BA and COPD in the clinical picture of the disease and in prevention and therapy, while some of them have a common principle [41] . Certain issues are little studied in therapeutic practice; this creates additional difficulties in the work of even an informed specialist [41].

Bronchial asthma is a chronic inflammatory disease of the respiratory tract. The main cause of the disease is chronic allergic inflammation of the bronchial wall, as well as hyperreactivity of the bronchi to various irritants. The main symptoms are partial or reversible bronchial obstruction, accompanied by paroxysmal cough, wheezing, chest tightness, shortness of breath with various specific allergic and nonspecific irritants.

According to the international guideline, the occurrence of bronchial asthma is caused by long-term inflammation of the respiratory system. Inflammation in asthma is a combination of immunological and non-immunological mechanisms of its occurrence. This pathology must be associated with diseases that have a threshold effect, an additional polygenic type. Multifactorial diseases are characterized by the presence of clinical polymorphism of symptoms. However, in the population there is a certain number of clinically healthy individuals who have a lower threshold level of violation of the concept of “biological defects” as the first stage of the formation and development of BA.

Important role V etiology diseases play external factors :• pollution air ,• professional aggressive effects ,• increased contact With allergens (" life allergen "),• viral infections , urine (in volume number passive) and etc.

Immune reactions of types I, III and IV are involved in the formation of bronchial obstruction in BA. Compared to others, the leading role is played by (anaphylactic) types of hypersensitivity mechanisms involving IgE and G4.

The main factors in the pathogenesis of asthma are chronic allergic inflammation, which develops under the influence of a combination of various mediators released as a result of a reaction mediated by reagin. CD4 + T lymphocytes play an important role in the body's sensitivity. Activation and proliferation of Th2 subpopulations CD4 + T lymphocytes are influenced by allergenic pathogens.

Except In addition , CD4 + T lymphocytes secrete cytokines (IL - 4 , IL - 6 , IL - 10 , IL - 13) , and Also general And specific IgE . Each entry of an allergen into the body leads to the release of mediators by cells such as histamine, leukotrienes C_4, D_4, $E_{4,}$ and they lead to the development of allergic answer. The allergic response is manifested by asthma attacks and bronchial obstruction.

Chronic obstructive pulmonary disease (COPD) is a pathology manifested by a long-term decrease in breathing capacity, which becomes more severe and is a manifestation of long-term damage to the respiratory tract and lung parenchyma in response to the pathological effects of damaging gaseous substances. Long-term pathological conditions define the disease and bring a certain meaning to the clinical picture of the disease and prognosis.

COPD is a definite challenge for patients nowadays. The prevalence of COPD remains very high, but remains heterogeneous depending on the region of residence. The main reasons are differences in lifestyle. The prevalence of COPD among people over 45 years of age was more than 10%, while it was higher in men than in women [63; 102; 118;]

In a study conducted in the Russian Federation and including more than 7000 patients (average age 43 years), the main manifestation of COPD was more than 20% of all respiratory pathologies [46; 118].

COPD is characterized by an increase in the number of neutrophils, T-lymphocytes, and macrophages in various parts of the airways and lungs. In patients with COPD, proliferation of inflammatory cells occurs in the proximal and distal parts of the airway. Eosinophilia may be observed in some patients. In addition, many literature sources suggest that the initiation and progression of

chronic airway inflammation in COPD are mediators such as interleukin-8, 6 and tumor necrosis factor α [47]. The significance of COPD and asthma requires a thorough study of the combination of these diseases in one patient [57, 100]. The GINA and GOLD study noted a number of data on the syndrome of combined asthma and COPD [9,111]. According to the document of the GOLD and GINA working groups, the problem of diagnosis and refined diagnosis for bronchial asthma and chronic obstructive pulmonary disease is discussed [9]. Data on the prevalence of COPD and asthma in one patient are different and variable due to differences in the diagnosis of pathologies and deprivation of the “golden standard". The incidence of diseases ranges from 12 to 55% among patients with COPD and 13-61% in patients with asthma [74, 151]. The presence of both pathological conditions leads to various shortcomings in the diagnosis and treatment of these pathologies among all population groups. [74,151].

IN medical practice in patients often observed symptoms chronic obstructive illnesses lungs and other chronic diseases of the respiratory system , which often enters doctors V delusion And makes it difficult treatment. (Vanessa M. McDonald , PeterG ., Gibsonetal . 2014). Pathologies differ from the point of view of cytological examination, but there are a number of differences in the clinical typing of diseases [10].

In this regard, the purpose of our study was to study the combination of BA and COPD in world studies in recent years.

Values of the surface phenotype of lymphocytes at crossover syndrome between asthma and COPD

Patients with this pathology have a certain identity and a certain phenotype. The term "phenotype" was coined in 1909 by the Danish scientist W. Johansen , one of the authors of the modern trend of genetic testing. [37,42,93]. The phenotype determines significant characteristics of life and the structure of genetic typing. In modern science, phenotyping is considered a series of specific systematic definitions of pathology, treatment and prevention [37, 42, 93]. In COPD and

asthma, there are various forms of phenotypes that can vary depending on the duration of the pathologies.

Patients with asthma have a low level of pathological control, and the disease is characterized by reduced resistance to steroids and frequent use of potent drugs [36].

The COPD phenotype has a number of features, for which reason the pathology was often called long-term obstructive bronchitis or pulmonary emphysema based on the manifestation of certain indications. Currently, scientists define this condition as COPD [38]. In 2001, a key global program for the diagnosis, treatment and prevention of these diseases was shown [45]. This document was edited in subsequent years of the first and second decades of the 21st century [18,19]. In the current edition of GOLD, there are now 3 main manifestations of COPD: bronchitis, emphysema, mixed.

Currently, certain phenotypes of this disease are distinguished, differing depending on the severity and type of manifestation of existing comorbid conditions, response to therapy and variability in the manifestation of bronchial obstruction. Currently, a mixed phenotype of manifestations of BA and COPD is noted, and a number of similar points are also noted in the processes of manifestation of these diseases [6.23, 61].

In order to effectively distinguish between chronic obstructive pulmonary disease and asthma, it was necessary to use biomarker testing. Currently, the most widespread examination of surface markers of leukocytes, as well as antigens of the class CD3, CD4, CD16, CD 8, CD54, CD71, CD72, HLA-DR, CD95 as well as IgM and IgG for differential diagnostic measures in patients with chronic obstructive disease and atopic bronchial asthma [88]. In differential diagnostic procedures, significant differences are noted when studying lymphocyte phenotypes [88, 87].

It is noted that increased cytotoxic potential often leads to damage to the pulmonary parenchyma, which often initiates the development of pneumosclerosis

and emphysema in COPD [87, 88]. In patients with BA, the inhibition of lymphocyte function (CD95) occurs, and there is also data showing their readiness to receive antigen (HLA-DR).

Pronounced differences in the immune response in patients with asthma and COPD contribute to the understanding of the main differences in the moments of frequent exacerbation in these diseases [87,88]. It is noted that increased activity of lymphocytes and MK cells is often one of the main manifestations of genetic predisposition to the onset of COPD, while it is noted that the high concentration of various types of lymphocytes in patients with COPD is a consequence of a decrease in their apoptosis due to the expression of Basligand [87, 88].

Symptomatic criteria for the overlap syndrome between asthma and COPD

Combined forms of these pathologies are often the result of the simultaneous manifestation of a number of danger components, the leading of which are considered to be tobacco use, untreated asthma, as well as the recurrent course of respiratory infections. In this aspect, the formation of each individual component depends on the patient's genome [32].

The presence of a number of undesirable effects often complicates the diagnosis of the disease, in some heavy smokers and elderly patients, which violates the correct management of patients and the principles of rational pharmacotherapy.

A number of patients develop symptoms of simultaneous manifestations of asthma and COPD, which contributes to the severity of the disease and often worsens the underlying symptoms. The simultaneous presence of asthma and COPD is reflected by severe exacerbations, deterioration of general condition, degradation of FEV1, severe complications, decreased exercise tolerance, as well as a reduction in the level of leukocyte inflammation in the mucous membrane of the respiratory tract [61,43,82,102,127]. Rational corticosteroid therapy is

associated with an increased need for β2-agonists in comparison with various manifestations of COPD [61, 43, 82, 102, 127].

As a result of differences in the symptoms of BA and COPD and the lack of standards and guidelines for a differentiated diagnosis, differences in information about these pathologies are observed, as a result of which the frequency of combined manifestations of BA and COPD has increased significantly, almost 4 times [61, 151].

In order to optimize the diagnosis, as well as to highlight the manifest criteria for diagnosing the combination of COPD and bronchial asthma, a protocol for the management of this group of patients was created [39].

The GINA Committee and the later GOLD Committee, as a result of a bilateral agreement, published a document entitled “Definition of persistent diseases with concomitant asthma, COPD and SOBACOPD”. This document displays demonstrative signs of these respiratory diseases and provides evidence of the correct management strategy and management [61, 9, 31]. SOBACOPD, as a result of correct diagnosis, can distinguish this disease with impaired airway patency from asthma and COPD [6, 12, 104].

The leading principles for the management of SOBACOPD in patients are ranked according to the following principles [1, 5]:

- SPBA reflects the manifestations of both COPD and bronchial asthma;

- there are a number of difficulties in the aspect of diagnosis in elderly people, as well as in people with bad habits;

- A stepwise principle is required;

-Early detection of the disease and the principle of primacy of prevention and early rehabilitation in specialized institutions for all patients without exception are important;

- The specific aspect of the pathology influences the principles of early initiation of therapy, and the choice of drugs taking into account existing adverse reactions [61, 9, 24, 104].

A stepwise approach to diagnosing SOBACOPD is given below [9, 12]:

1) Early diagnosis of patients with chronic respiratory diseases;

2) Correct differentiation of BA from COPD and SOBACOPD;

3) Availability of an optimal institution for the treatment of this group of patients, depending on the severity;

4) Instrumental verification of airway obstruction;

5) Management of patients according to existing protocols [61, 24, 104].

The main thing in diagnosing the condition is the presence of similar signs of manifestation of 2 pathologies:

In the presence of several symptoms characteristic of bronchial asthma and COPD at the same time, the risk of having SOBACOPD increases [61, 9, 24, 58, 104].

Various studies aimed at identifying the pathogenetic similarity of these pathologies make it possible to more accurately carry out the optimal diagnostic procedure [88].

Similarities in the diagnosis of bronchial asthma and chronic lung disease are noted in approximately every 5-7 cases [9,122,139].

A number of researchers believe that the presence of certain criteria does not provide grounds for unambiguous differentiation of bronchial asthma from other chronic respiratory pathologies, especially in older people [9]. There is data that allows us to describe a number of phenotypes for the manifestation of SOBACOPD based on various clinical manifestations of the disease, as well as the results of genetic testing [9,113,141].

The formation of pathology is often based on the principles of leukocyte damage to the mucous membrane of the bronchial tree, which in turn leads to increased resistance to inhaled glucocorticoids. The use of beta2 agonists in inhaled form contributes to an increase in the consumption of corticosteroids, while the use of monotherapy can lead to an uncontrolled form of bronchial asthma, especially in individuals with comorbid pathologies [56].

In the literature, SOBACOPD is considered as a separate nosological form, while respiratory obstruction in patients with COPD often leads to an incorrect

diagnostic approach in patients with SOBACOPD [4]. Half of the patients with COPD in the clinical cases demonstrated an increased level of dependence on inhaled bronchodilators [4, 121].

Patients with COPD are at risk of severe impairment of bronchial obstruction over a certain period [4,42]. These principles imply the importance of the correct diagnostic method in SOBACOPD patients [4].

For this disease, studies possible plasma and sputum biomarkers [4]. Iwamoto and his co-authors [4, 107] studied 4 possible biomarkers of COPD (surfactant protein A, soluble form of end-stage glycation receptors, myeloperoxidase and neutrophil gelatinase). Professor F u [4, 113] showed the importance of analyzing the main cytokines in patients; the study noted an increase in the level of these immunoglobulins. Interleukin 6 levels were increased in patients with bronchial asthma, while there was a slight increase in interleukin 4 in patients with chronic obstructive pulmonary disease [4,113].

In a study of genes in patients with COPD, various genotypes of SOBACOPD were noted, which are worth noting as important risk factors for this condition [4, 96]. Christiansen [4, 94] conducted additional genetic testing in patients with asthma and COPD.

the **GLUCOLD** study group, patients with COPD showed a difference in Th 2, which was directly related to the elimination of major lymphocyte factors, an increase in the level of eosinophils in tissues, and a positive response to the use of bronchodilators. Gene expression has been reported as a result of increased airway patency in patients on inhaled corticosteroids compared to long-term pacifier use [4, 94]. To date, there are no standards for the treatment and management of patients with these pathologies, which often requires additional research [4].

Currently, the management of patients with SOBACOPD is based on the same principles that are used in the treatment of bronchial asthma. Main products for patients with asthma are inhaled GCs in combination with long- acting b2-agonists.

Therapeutic methods for the treatment of patients with crossover syndrome of BA and COPD

The use of a combination of bronchodilators and inhaled corticosteroids is considered the gold standard for COPD, and oral or systemic corticosteroids are often not required [60].

Inhaled bronchodilators long actions (b2-agonists) and anticholinergics long-term actions play a major role in the treatment of both diseases. There are two main pharmacological tactics bronchodilation: directly stimulating b2-adrenergic receptors and to some extent inhibiting the effect of acetylcholine [23]. Compliance with rational pharmacotherapy methods when using bronchodilators is most important in patients with SOBACOPD.

In cases of prescribing bronchodilator therapy, it is important to carry out diagnostic procedures that allow assessing the state of receptors for respiratory tract.

It is important that, despite the lack of innervation of muscarinic receptors in the respiratory tract, in this case the mechanism of beta-2 adrenergic receptors is activated. This discovery made it possible to explain the bronchodilator effect of bronchodilators when used by inhalation [56, 128].

It is noted that the sensitivity of adrenergic receptors decreases as a result of the irrational use of bronchodilator therapy, which in turn leads to an unreasonable increase in both the dosage and frequency of use of salbutamol, which leads to a decrease in sensitivity in patients of the older age group.

The parasympathetic division of the autonomic nervous system is the main trigger mechanism, the activation of which can lead to long-term airway compromise in patients with COPD [56].

The pharmacodynamic properties of most bronchodilators are based on the mechanism of their expanding action on beta2 adrenergic receptors in the bronchi, while the use of muscarinic receptor activators has a similar effect to this group of drugs, which may be especially important in patients with severe manifestations of bronchial asthma. [56,13].

The combined use of beta-2 agonists with drugs that inhibit the release of acetylcholine often has pronounced synergism, which is important in the treatment of COPD [56].

Long-acting drugs such as long-acting beta2 agonists have recently become widely used. [45, 52]. Most authors agree that the use of this group of drugs leads to uncontrolled aspects in half of the cases of severe manifestations of bronchial asthma [67, 126.]

Countless latest research discovered the main role of cholinergic devices in the pathogenesis of asthma. It has been confirmed that the effects of tobacco smoke, inflammation, and infections can increase the tone of the parasympathetic nervous system [56, 52]. In addition, it was noted that the use of beta 2 agonists often causes an addictive effect and a decrease in resistance [4, 37, 56].

Thus, a review of the main studies in recent years shows that the use of pathogenetic therapy in the treatment of asthma and COPD currently includes beta2 agonists, anticholinesterase drugs, as well as long-acting bronchodilators in combination with inhaled corticosteroids [56,10, 23, 57, 104] .

The most widespread use of pathogenetic therapy in combination with beta2 agonists and inhaled GCs in the treatment of COPD [56, 9].

The greatest importance in modern rational pharmacotherapy is given to the principles of monotherapy and prevention/prevention of disease attacks, while a separate aspect is put forward for improvement state of life, giving up bad habits, tobacco, alcohol, as well as carrying out regular preventive procedures [56, 24, 104].

CHAPTER 3.

3.1 Characteristics of patients examined by group

101 patients were examined, in the hospital at the Samarkand City Medical Association, from 2018 to 2021. Indications for hospitalization were the following criteria: exacerbation of asthma and COPD, remission of the disease if there is a need for planned anti-relapse treatment.

The study involved 19 male patients (54.3%) and 16 female patients (45.7%) (Fig. 3.1.1) with bronchial asthma of varying severity.

The age ranking of patients was as follows: 8 patients- under 40 years (22.8%), - 27 patients (77.1 %) from 40 to 70 years, patients over 70 years were not identified, while the middle age was 47.14 ± 9 ,4 years. The median disease duration was 9.2 years.

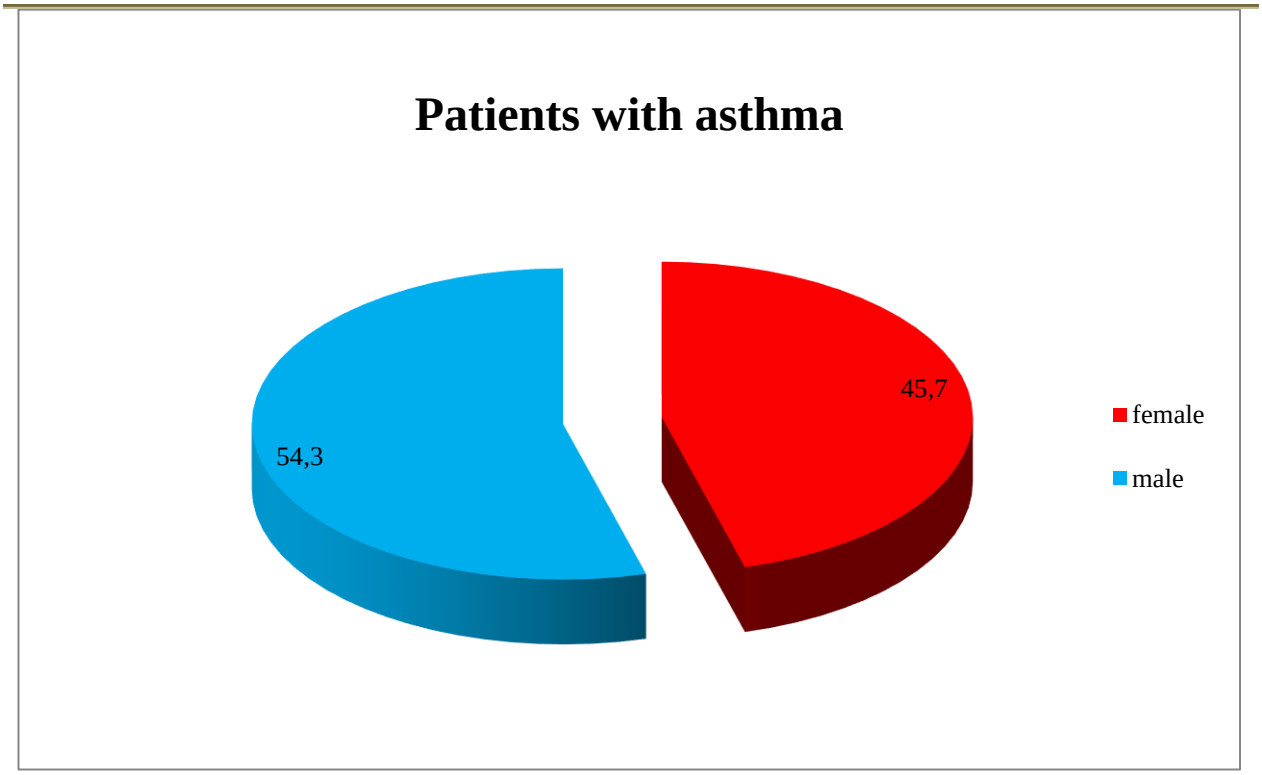


Figure 3.1.1. Distribution of patients by gender (%).

The severity of the disease was determined depending on FEV 1 and the characteristics of the attacks. The course of the disease is given below in Figure 3.1.2.

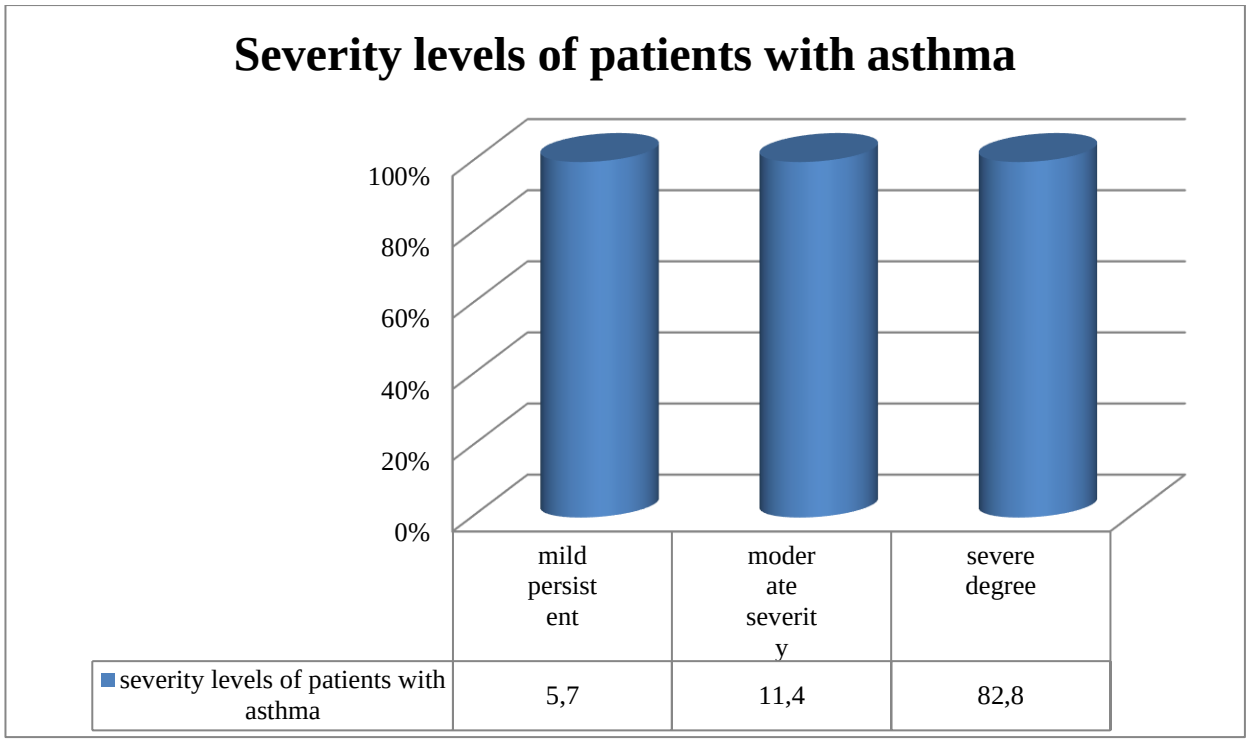


Figure 3.1.2. Distribution of patients (%) depending on the severity of asthma

All patients with BA underwent an ERF study, the results of which were very varied.

35 patients with COPD were examined. The distribution of patients according to severity was carried out in accordance with the classification given in the international GOLD program (version 2019):

In accordance with this classifications Stage 1 was diagnosed in 3 patients (8.5%), stage 2 - in 4 patients (11.4%), stage 3 - in 17 patients (48.6%), stage 4 - in 11 patients (31.4%).

All patients with COPD were in the acute stage. Among them, 20 (57.1%) were men and 15 (42.9%) women (Fig. 3.1.3).

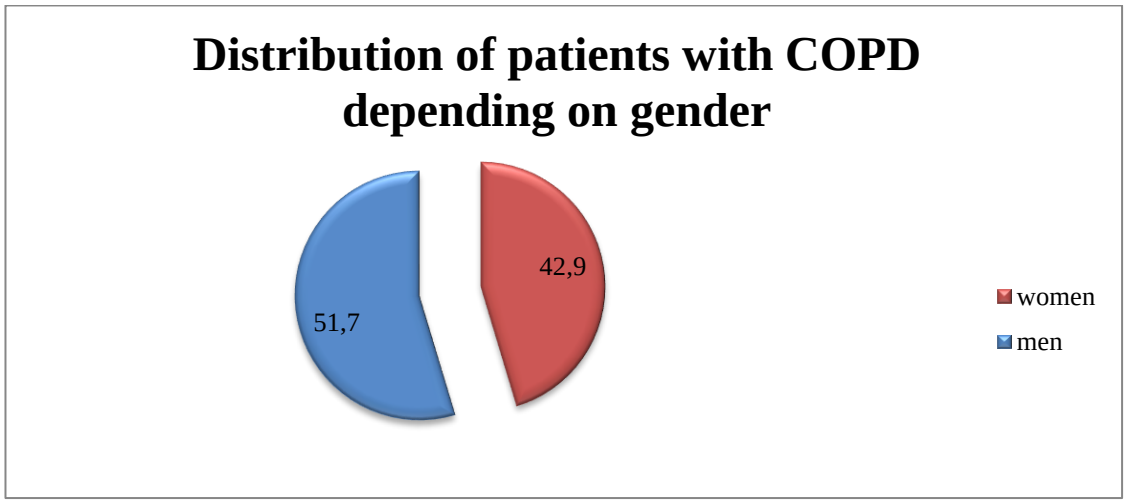


Figure 3.1.3. Distribution of patients (%) by gender.

Smoking factor was of great importance in patients belonging to the COPD group. At the first stage of the disease, 75% were smokers, which is 2 times more than in MBA. Smokers with moderate COPD were 78.0% and had a smoker's index (SI) of -15.3 packs/year. All patients with severe COPD smoked, SI 31.4 ± 10 packs/year. All patients with extremely severe COPD were heavy smokers and the SI was 33.4 ± 6.28 packs/year.

The group of patients with a combination of BA + COPD (n =31) was in 30.7% of cases (Fig. 3.1.4), where 54.7% were men (n =17), 45.3% (n =14). women. The average age of the patients was 64.9±3.2 years.

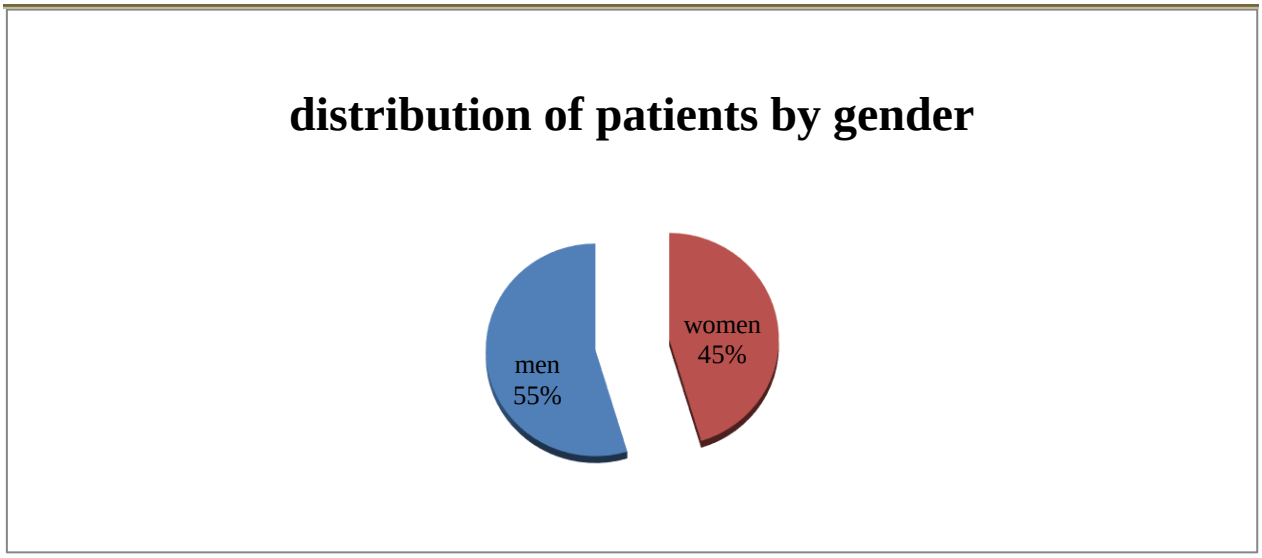


Figure 3.1.4. Distribution of patients with BA + COPD (%) depending on gender.

As a rule, there were serious violations of respiratory function, but with persistence of asthma attacks, partial reversible obstruction, and in some cases, positive results of allergy tests.

The total volume of laboratory and instrumental studies of patients with asthma and COPD that we used shows the approximate quantitative equivalence necessary for their subsequent comparison.

3.2 Characteristics of the quality of life of patients with syndrome of crossover of asthma and COPD

Numerous questionnaires have been developed to assess the quality of life of patients with obstructive changes, which in our study were the main pathogenetic causes of the syndromic manifestation of nosological forms of the disease: asthma, COPD and asthma + COPD.

When assessing the quality of life of patients with asthma, COPD and asthma + COPD according to the St. George's Hospital questionnaire (Table 3.2.1), it was noted that when summing up the scores, the “symptoms” parameters were rated 217.5 ± 9.1, which was significantly less in comparison with the indicators of groups II and III of patients (P <0.001). When assessing the “activity” parameter, the sum of points was 342.8±12.8, which was significantly less in comparison with

indicators of groups II and III of patients (P <0.001). A similar trend was noted when assessing the “ impact of the disease ” parameter, so in patients of group I the sum of points was 510.1 ± 18.9, which was significantly lower in comparison with the indicators of patients with COPD and BA + COPD.

Table 3.2.1

Indicators of the St. George's Hospital questionnaire in patients with asthma, COPD, asthma + COPD

Options	Group I BA	Group II COPD	Group III BA+COPD	P_1	P_2	P_3
symptoms	217.5±9.1	282.5±12.8	295.2 ± 14.5	<0.001	<0.001	>0.5
activity	342.8±12.8	422.1±17.2	482.1 ± 26.2	<0.001	<0.001	<0.05
influence of the disease	510.1±18.9	724.2±25.4	7 58.2 ± 28.4	<0.001	<0.001	>0.5

Note: P_1 - reliability of differences in indicators between groups of patients with BA and COPD, P_2 - groups of patients with BA and BA + COPD, and P_3 - groups of patients with COPD and BA + COPD.

In patients with COPD, when assessed by the St. George's Hospital questionnaire, it was noted that the sum of the scores for the “symptoms” parameter was 282.5 ± 12.8, which was significantly higher in comparison with the indicators of group I (P <0.001), while when compared with There was no statistically significant difference in the indicators of group III (P >0.5). When assessing the “activity” parameter, the sum of points was 422.1±17.2, which was significantly higher in comparison with the indicators of group I (P <0.001), while when compared with the indicators of group III there was no statistically significant difference (P >0 ,5). A similar trend was noted when assessing the parameter “influence of the disease”, so in patients of group II the total score was 724.2 ± 25.4, which was significantly higher in comparison with the indicators of group I (P <0.001), while when compared with the indicators Group III there was no statistically significant difference (P >0.5) .

The quality of life indicator was studied to determine the patient's adaptability to the disease. For this purpose, in patients with asthma, COPD and

asthma + COPD, an assessment test was used - the CAT test, the results of which are given below. (Table 3.2.2).

Table 3.2.2

CAT test indicators in patients with asthma, COPD, asthma+COPD

Options	Group I BA	Group II COPD	Group III BA+COPD	P_1	P_2	P_3
N minor	7.2±0.5	9.2±0.6	9.8±0.5	<0.01	<0.001	>0.5
Moderate	14.4±0.7	17.4±0.9	19.3±0.8	<0.01	<0.001	>0.1
Expressed	20.1±1.2	26.8±1.4	28.7±1.2	<0.001	<0.001	>0.2
Very serious	25.2±1.3	31.7±1.5	38.1±1.9	<0.001	<0.001	<0.01

Note: P_1 - reliability of differences in indicators between groups of patients with BA and COPD, P_2 - groups of patients with BA and BA + COPD, and P_3 - groups of patients with COPD and BA + COPD.

Of the 35 patients with bronchial asthma, the SAT test assessment showed that the disease had a minor impact on their daily life in 7 (20.0%) patients, moderate impact in 13 (37.1%) patients, pronounced impact in 12 (34.3%) patients, and very serious impact in 3 (8.6%) patients.

Of the 35 patients with COPD, the disease had a minor impact on their daily life in 6 (17.1%) patients, moderate impact in 11 (31.4%) patients, pronounced impact in 13 (37.1%) patients, and very serious impact in 5 (14.3%) patients.

Of the 31 patients with bronchial asthma + COPD, the disease had a minor impact on their daily life in 4 (12.9%) patients, moderate impact in 10 (32.3%) patients, pronounced impact in 12 (38.7%) patients, and very serious impact in 5 (16.1%) patients.

Analysis of the quality of life using the CAT test determined that all indicators of the impact of the disease on everyday life in patients with COPD were higher in comparison with patients suffering from BA + COPD. The difference between the groups examined in all sections, except for the “moderate ” component, was statistically significant.

In a comparative analysis of the CAT test in groups of patients with asthma, COPD and asthma + COPD, a very high total score of 21.27 ± 4.25 was found, indicating a clear impact of COPD on the quality of life, but when studying the total score of the CAT test among patients with combined pathology, this indicator was higher by 2.78 ± 0.6 points than in patients with isolated COPD and averaged 24.05 ± 4.81, this indicates that the combined pathology had a rather negative impact on the lives of patients .

As the severity of the disease increased, the total score reflecting the patient's subjective feelings increased (cough, chest tightness, shortness of breath when climbing stairs, sputum, limited physical activity at home) and showed a deterioration in the quality of life of patients.

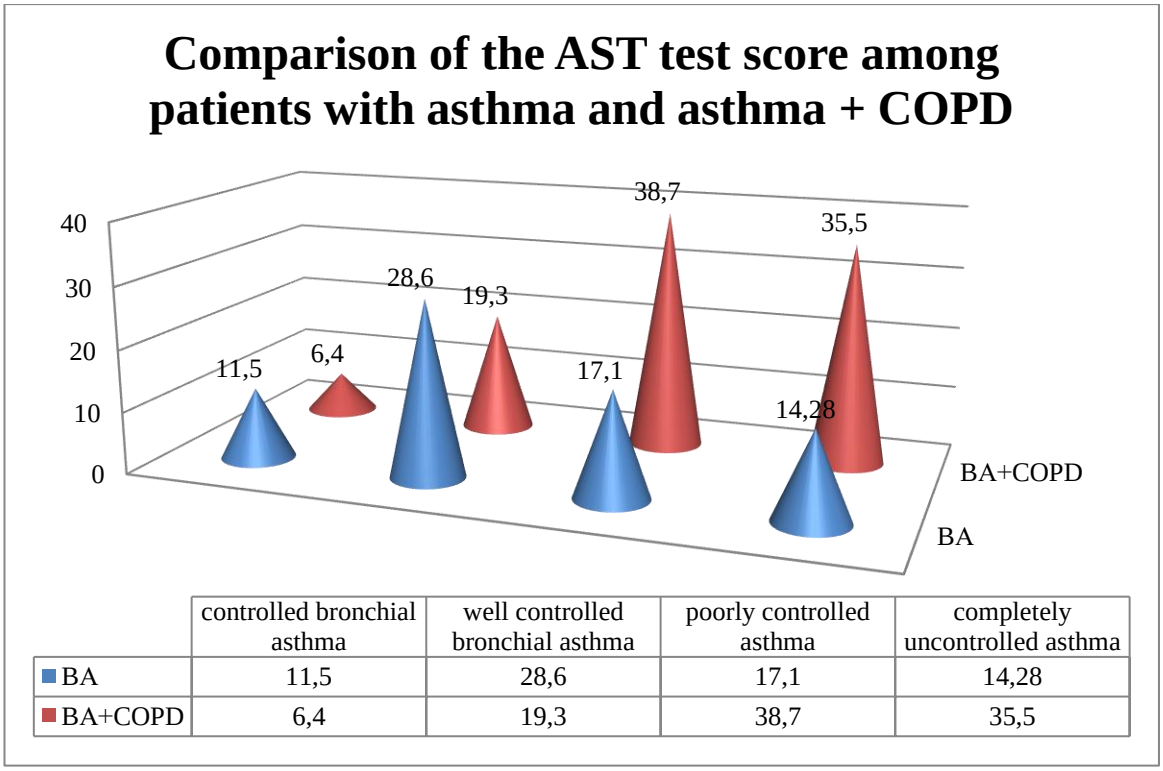
Thus , the total CAT test score in the group of patients with moderate COPD was 26.8 ± 5.36, while in the group of patients with severe COPD it was already 31.7 ± 6.3 ($p < 0.05$). When calculating the results of the CAT test among patients with comorbidity, a very strong impact of the disease on quality of life was found, and in patients with average body weight, their score was 28.7 ± 5.74, which was associated with isolated COPD.

All CAT test results in patients with asthma + COPD were significantly worse than in patients with asthma, COPD, and the difference was statistically significant in all cases. This suggests that the nosological form of the disease has a significant impact on the quality of life of patients, and therefore this category of patients requires reasonable correction of the disease.

We carried out AST - testing, in patients of groups I (BA) and III (BA + COPD), in which, out of 5 questions and 5 answer options, the patient gives answers, the results of which are summarized and a conclusion is given to determine the patient’s ability to self-monitor bronchial attacks asthma.

When conducting a survey on the AST test among patients with asthma, the following data were revealed: 4 (11.4%) patients controlled their condition, 10 (28.6%) patients with asthma well controlled their condition, 6 (17.1%) patients

had uncontrolled asthma and 5 (14.3%) patients had completely uncontrolled asthma.



	controlled bronchial asthma	well controlled bronchial asthma	poorly controlled asthma	completely uncontrolled asthma
BA	11,5	28,6	17,1	14,28
BA+COPD	6,4	19,3	38,7	35,5

Figure 3.2.1. AST test indicators among patients with asthma and asthma+COPD

When conducting a survey on the AST test among patients with asthma + COPD, the following data were revealed: 2 (6.5%) patients controlled their condition, 6 (19.4%) patients with asthma well controlled their condition, 12 (38.7%) patients had uncontrolled asthma and 11 (35.5%) patients had completely uncontrolled asthma, as can be seen from Figure 3.2.1 among patients with BA + COPD much more often, namely 21.6% uncontrolled and 21.22% completely uncontrolled asthma , which once again confirms the combined course of these two pathologies significantly reduces the quality of life of patients. When studying the average AST test scores among patients with asthma and asthma + COPD, statistically distinguishable indicators were also obtained among these groups of patients (Table 3.2.2).

Table 3.2.2.

Average AST test scores among patients with asthma and asthma+COPD

Groups	Patient's ability to control asthma attacks (in points)			
	full control	well controlled, but not completely	uncontrolled asthma	seriously out of control
Group I BA	25.8 ±1.2	2 3.4±1.7	17.4±0.9	13.8±0.7
Group III BA+COPD	25.4±1.1	21.8±1.5	15.9±0.7	11.7±0.6
P	>0.5	>0.5	<0.05	<0.05

Note: P – significance of differences between the compared groups.

Since the AST test has good reliability, repeatability and high sensitivity to changes in the disease, it is the method of choice and is recommended as the main tool for assessing quality in patients who experience attacks of bronchial asthma.

Thus, we studied the quality of life indicators of patients with COPD, asthma and asthma + COPD, where it was revealed that patients with a combined course had relatively reduced quality of life indicators, in contrast to patients with isolated pathology. Also, when studying the state of self-control of asthma attacks, an identical picture was revealed, i.e. patients with concomitant pathology (BA + COPD) had more cases with a lack of control of asthma attacks, which indicates that when introducing patients with concomitant pathology, it is necessary to more carefully diagnose and treat to improve the quality of life of patients.

3.3 Analysis of cytokines and immunoglobulin E in the blood and in the cerebrospinal fluid in patients with bronchial asthma, chronic obstructive pulmonary disease and their combination in the acute stage.

The state of the body's immune reactivity plays an important role in the pathogenesis of airway inflammation in chronic diseases. Inflammation of the respiratory tract is one of the main pathogenetic links of asthma, COPD, carried out with the help of cytokines and other immunocompetent cells [55]. In this regard, we studied the indicators of pro-inflammatory (TNFα, IL -8) and anti-inflammatory (IL -4) cytokines and immunoglobulin (IgE) in the blood and in the EAC of patients with BA, COPD and their combination in the stage of exacerbation of the disease (Table 3.3 .1).

When comparing the indicators of interleukin - 8 (IL -8) in the blood and in the EAC among 3 comparable groups in the acute stage, it was revealed that among patients with COPD, unlike patients with BA ($P < 0.05$), BA + COPD was statistically significant high rates ($P < 0.001$) (Table 3.3.1, Tab. 3.3.2). When comparing BA+COPD and BA, a high value of IL -8 was revealed among patients with BA; this indicator was also statistically significant in the blood ($P < 0.05$) and statistically insignificantly high when studying IL -8 in the CVB ($P < 0.05$).

Table 3.3.1

Indicators of cytokines and immunoglobulin E in the blood and in the cerebrospinal fluid in patients with asthma, COPD and COPD+BA in the acute stage

Indicators	BA (n= 35)	COPD (n= 35)	BA+COPD (n= 31)	P_1	R_2	R_3
IL -4 in blood (pg /ml)	69.1±4.1	31.5±1.8	42.1±2.4	<0.001	<0.001	<0.001
IL -4 in EAC pg /ml	4.0±0.2	2.5±0.1	3.5±0.2	<0.001	>0.1	<0.001
IL -8 in blood (pg /ml)	60.8±3.8	72.5±4.7	60.4 ± 2.8	<0.05	> 0.5	<0.001
IL -8 in EAC (pg /ml)	62.1±3.5	74.2±4.8	52.2±2.5	<0.05	<0.02	<0.001
TNF - α in blood (pg /ml)	19.2±1.1	10.4±0.7	31.2±1.7	<0.001	<0.001	<0.001
TNF - α in EAC (pg /ml)	2.6±0.1	2.5±0.1	3.1±0.2	>0.5	<0.02	<0.01
Total IgE in blood (IU/ml)	285.2±17.2	89.5±5.2	212.2±12.4	<0.001	<0.001	<0.001

Note: P_1 - reliability of differences in indicators between groups of patients with BA and COPD, P_2 - groups of patients with BA and FD + COPD, and P_3 - groups of patients with COPD and BA + COPD.

When studying interleukin -4 (IL -4), a slightly different picture was revealed. Patients with BA and BA+COPD had statistically significant high data, in contrast to patients with COPD, both in the blood and in the EAC (P <0.001) . When comparing patients with BA and BA + COPD, a high level of anti-inflammatory interleukin-4 was revealed among patients with comorbid pathology in the blood and in the EAC (P <0.001). Thus, patients with comorbid pathology in the acute stage, unlike patients with asthma and COPD, have statistically high rates.

When studying the level of cytokines in patients with asthma and COPD (Fig. 3.3.1), it was actually revealed one-sided nature of changes. The level of IL-4 production in patients with asthma was significantly higher both in the blood - 69.1±4.1 pg /ml, and in the exhaled air condensate - 4.0±0.2 pg /ml, compared with COPD in the blood was 31.5±1.8 pg /ml and exhaled air condensate 2.5±0.1 pg /ml, at which significant differences were detected (P>0.001).

In a comparative assessment of IL-4 in the blood serum in patients with BA + COPD, the level of cytokine production was higher (P <0.001) (42.1±2.4 pg /ml) than in patients with COPD (31.5±1.8 pg /ml).

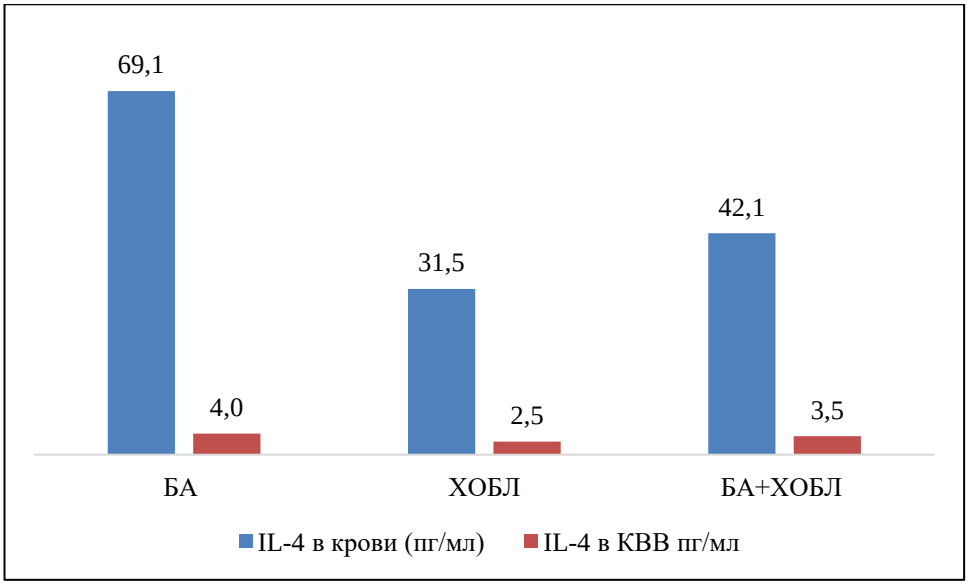


Figure 3.3.1. Level of IL-4 production in patients with asthma, COPD and asthma+COPD in the acute stage.

The slight change in the production of IL-4 cytokines in patients with COPD compared to patients with asthma is probably due to the fact that these types of cytokines do not play a leading role in the pathogenesis of COPD inflammation.

However, in a comparative analysis of the level of the cytokine IL-4 in patients with BA and BA + COPD in the acute stage, a multidirectional pattern was revealed, so if the content of IL-4 in the blood had a significant difference with the predominance in BA, then in the condensate of exhaled air the production of the cytokine in this group did not have such a significant difference (P >0.1).

IL-4 is a Th2 immune mediator that leads to the formation of allergic inflammation and a disease pathogenesis reaction specific to asthma, COPD and their combination.

However, the increase in the production of IL-4 in each group of patients can be explained by the activation of inflammatory processes by nonspecific factors and allows us to confirm that IL-4 is the main cytokine in the development of allergic inflammation and this is confirmed by research.

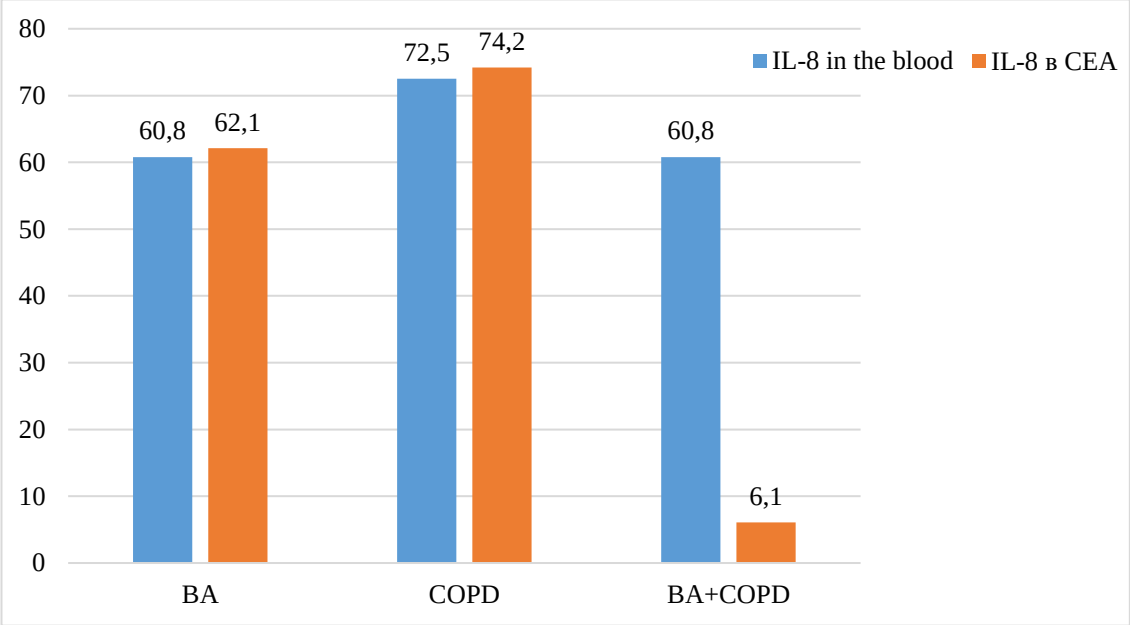


Figure 3.3.2. Level of IL-8 production in patients with asthma, COPD and asthma+COPD in the acute stage.

When studying the production of IL-8, a statistically significant difference was noted in patients with BA compared to the group of patients with COPD

(Figure 3.3.2). This activation of IL-8 is primarily a product that has been associated with granulocytes and neutrophils, as a response to toxic and bacterial pathogens[55]. IL-8 is known to be produced by neutrophils, and the predominance of its production in patients with COPD helps maintain neutrophilic inflammation in the airways. This conclusion was confirmed by the comparison of the level of IL-8 cytokine production in the blood and in exhaled air condensate in groups of patients with COPD (72.5±4.7 pg /ml and 74.2±4.8 pg /ml) and asthma +COPD (52.2±2.5 pg /ml and 31.2±1.7 pg /ml) for which significant significance of a high degree was determined ($P < 0.001$).

As a result, cytokines play a major role in the pathogenesis of inflammation of the respiratory tract in the combined course of diseases, with the leading type of inflammation being the neutrophilic type of inflammation, [55] leading to an increase in the production of IL-8 and a prolonged course of various types of respiratory tract damage. There was no significant difference in the levels of IL-8 in the blood of patients with asthma and COPD ($P > 0.5$). However, when comparing the results obtained in the exhaled air condensate of patients with asthma, the production of IL-8 was significantly higher than in patients with asthma + COPD ($P < 0.02$).

Differences in IL-8 were also found in groups of patients with COPD, in which the levels of cytokines in blood (72.5 ± 4.7 pg /ml) and in exhaled condensate (74.2 ± 4.8 pg /ml) were statistically significant, which is high compared to patients with BA+COPD (60.4 ± 2.8 pg/ml and 52.2 ± 2.5 pg /ml) ($P < 0.001$). IL-8 promotes the formation of fibrosis of the bronchial tree, which can lead to a more severe course of the disease , which is typical for the clinical course of COPD [55]. IL -8 is produced by neutrophils in response to an infectious agent. Elevated levels of these cytokines in COPD in these patients may be due to the presence of foci of chronic infection, activation of infectious agents that are common during the course of the disease and thus the persistence of neutrophilic inflammation.

According to the results analysis of the level of cytokines in patients with COPD, we can come to the conclusion that the inflammatory process of the airways is caused by immunological disorders [55]. Patients with COPD are characterized by increased production of IL-8, which is involved in the development of neutrophilic types of airway inflammation.

When studying the TNF -α level in the blood, significantly high levels were revealed among patients with BA 19.2±1.1 pg/ml, in contrast to COPD (P <0.001) (Fig. 3.3.3). When comparing COPD and BA+COPD, statistically significant high rates were revealed among patients with comorbidity both in the blood (P <0.001) and in the EAC (P <0.01) (Table 3.3.2). When comparing patients with BA and BA + COPD, TNF -α levels in the blood were higher among patients with comorbid pathology, respectively 19.2±1.1; 31.2±1.7 (P <0.001).

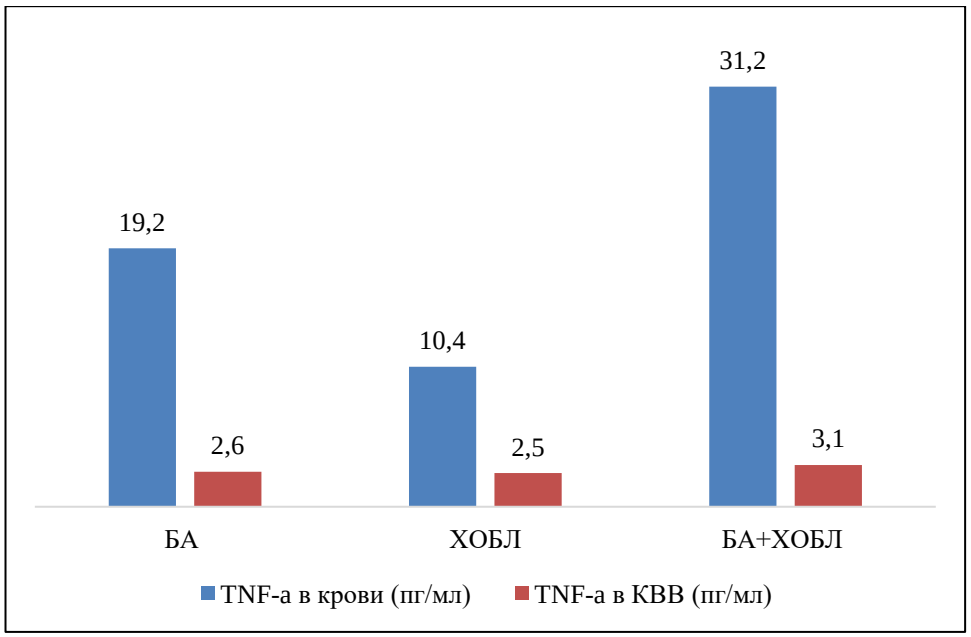


Figure 3.3.3. TNF-α level in patients with asthma, COPD and asthma+COPD in the acute stage.

When comparing immunoglobulin E levels among the above 3 groups in the acute stage (Figure 3.3. 4), it was revealed that patients with BA, unlike patients with COPD and BA+COPD, had significantly high levels in the blood, when comparing patients with COPD and BA+ COPD , high rates were found among

patients with concomitant pathology (P <0.001), which corresponds to the data of the literature sources we studied.

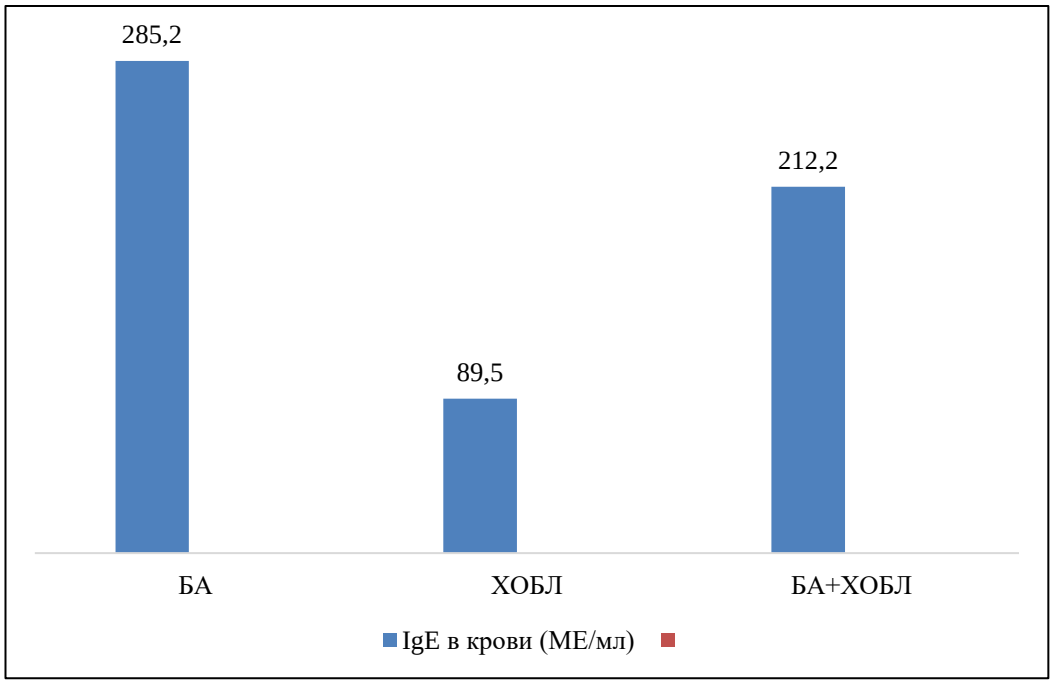


Figure 3.3.4. Level of immunoglobulin E in patients with asthma, COPD and asthma + COPD in the acute stage.

Thus, during the study of immunological parameters among the above groups (BA, COPD, BA + COPD), a significant increase in immunoglobulin E was revealed and in patients with combined pathology, the level of tumor necrosis factor TNF -α prevailed.

The results of the study show that the immunopathogenesis of the disease reflects the type of inflammation of the airways, while the development of asthma is characterized by a Th2 immune response, which manifests itself in an increase in the induced production of IL-4. Increased IL-8 production indicates a predominant non-Th2 immune response specific to COPD patients. The production of cytokines in asthma + COPD has properties similar to those in COPD, characterized by inflammation of the respiratory tract to a greater extent than in isolated COPD [55].

Thus, IL-4 and IL-8 play an important role in the immunopathogenesis of diseases and differ significantly in the distribution of cytokine production during the development of BA, COPD, and their combination. In asthma, IL-4 cytokines

predominate, which belong to the Th2 type of immunity, which is typical for the formation of allergic (eosinophilic) inflammation of the airways. In COPD, the level of IL-8 cytokines increases, the release of which occurs under the influence of activation of infectious agents (microbes, viruses) and toxins [55].

3.4 Analysis of cytokines and immunoglobulin E in the blood and in the EAC of patients with bronchial asthma, chronic obstructive pulmonary disease and their combination in remission.

The state of the body's immune reactivity plays an important role in the pathogenesis of airway inflammation in chronic diseases. Inflammation of the respiratory tract is one of the main pathogenetic links of asthma, COPD, carried out with the help of cytokines and other immunocompetent cells [55]. In this regard, we studied the indicators of pro-inflammatory (TNFα, IL -8) and anti-inflammatory (IL -4) cytokines and immunoglobulin (IgE) in the blood and in the EAC of patients with BA, COPD and their combination in the stage of remission of the disease (Table 3.4 .1).

When comparing the indicators of interleukin - 8 (IL -8) in the blood and in the EAC among 3 comparable groups in the acute stage, it was revealed that among patients with COPD, unlike patients with BA (P <0.05), BA + COPD was statistically significant high rates (P <0.001) (Table 3.3.1, Tab. 3.3.2). When comparing BA+COPD and BA, a high value of IL -8 was revealed among patients with BA; this indicator was also statistically significant in the blood (P <0.05) and statistically insignificantly high when studying IL -8 in the EAC (P <0.05). When studying interleukin -4 (IL -4), a slightly different picture was revealed. Patients with BA and BA+COPD had statistically significant high data, in contrast to patients with COPD, both in the blood and in the EAC (P <0.001). When comparing patients with BA and BA + COPD, a high level of anti-inflammatory interleukin-4 was revealed among patients with comorbid pathology in the blood and in the EAC (P <0.001). Thus, patients with comorbid pathology in the acute stage, unlike patients with asthma and COPD, have statistically high rates.

Table 3.4.1

Indicators of cytokines and immunoglobulin E in the blood and in the cerebrospinal fluid in patients with asthma, COPD and COPD+BA in remission

Indicators	BA (n= 35)	COPD (n= 35)	BA+COPD (n= 31)	P_1	R_2	R_3
IL -4 in blood (pg /ml)	66.5±3.7	13.2±0.6	20.7 ± 1.2	<0.001	<0.05	<0.001
IL -4 in EAC pg /ml	4.0±0.2	2.4±0.1	3.1±0.2	<0.001	<0.05	<0.001
IL -8 in blood (pg /ml)	33.5±1.8	69±3.7	54.4±3.1	<0.001	<0.001	<0.01
IL -8 in EAC (pg /ml)	5.9±0.3	6.5±0.3	6.2±0.3	>0.2	>0.5	>0.5
TNF - a in blood (pg /ml)	19.1±1.1	40.0±2.4	30.8±1.6	<0.001	<0.5	<0.001
TNF - a in EC (pg /ml)	2.5±0.1	4.0±0.2	3.2±0.2	<0.001	<0.001	<0.01
Total IgE in blood (IU/ml)	285±17.3	97.2±5.8	207.5±11.5	<0.001	<0.001	<0.001

Note: P_1 - reliability of differences in indicators between groups of patients with BA and COPD, P_2 - groups of patients with BA and BA + COPD, and P_3 - groups of patients with COPD and BA + COPD.

A study of the level of cytokines in patients with asthma and COPD (Fig. 3.4.1) revealed an almost one-sided nature of the changes. The level of interleukin-4 was higher in the blood of patients with BA - 66.5±3.7 pg /ml, and in the condensate of exhaled air - 4.0±0.2 pg /ml, in comparison with COPD in the blood it was 13.2± 0.6 pg /ml and in the exhaled air condensate 2.4±0.1 pg /ml, at which significant differences were revealed (P>0.001

In a comparative assessment of IL-4 in the blood serum of patients with BA + COPD, there was a significant increase (P <0.001) in the level of interleukin (20.7 ± 1.2 pg / ml) in comparison with COPD (13.2 ± pg / ml).

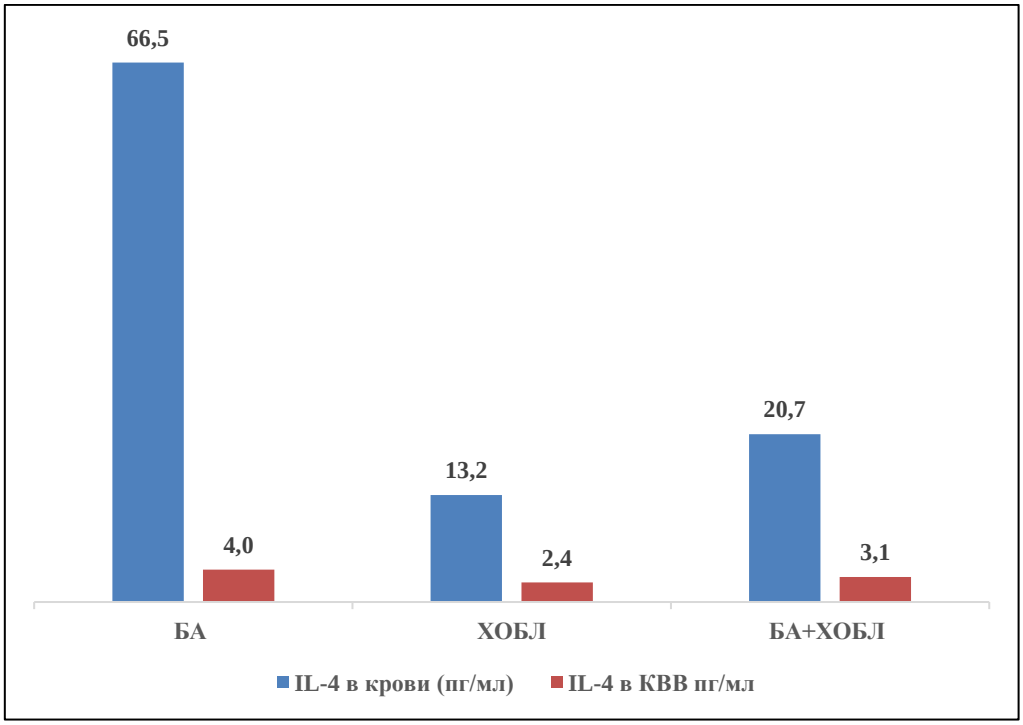


Figure 3.4.1. Level of IL-4 production in patients with asthma, COPD and asthma+COPD in remission

When comparing analyzes of the level of the cytokine IL-4 in patients with BA and BA + COPD, a multidirectional pattern was revealed, so if the content of IL-4 in the blood had a significant difference with the predominance in BA, then in the exhaled air condensate the production of the cytokine in this group did not have significant difference (P >0.1).

The Th2 type mediator, namely IL-4, plays an important role in the pathogenesis of asthma, COPD and their combination [55]. At the same time, the

increase in IL-4 production in patients of all groups can be associated with the activation of inflammatory processes through nonspecific factors and makes it possible to confirm that IL-4 is a key cytokine in the development of allergic inflammation, which is confirmed by research [55].

When studying IL-8 production, a statistically significant difference was also noted in patients with asthma compared with the group of COPD patients (Fig. 3.4.2).

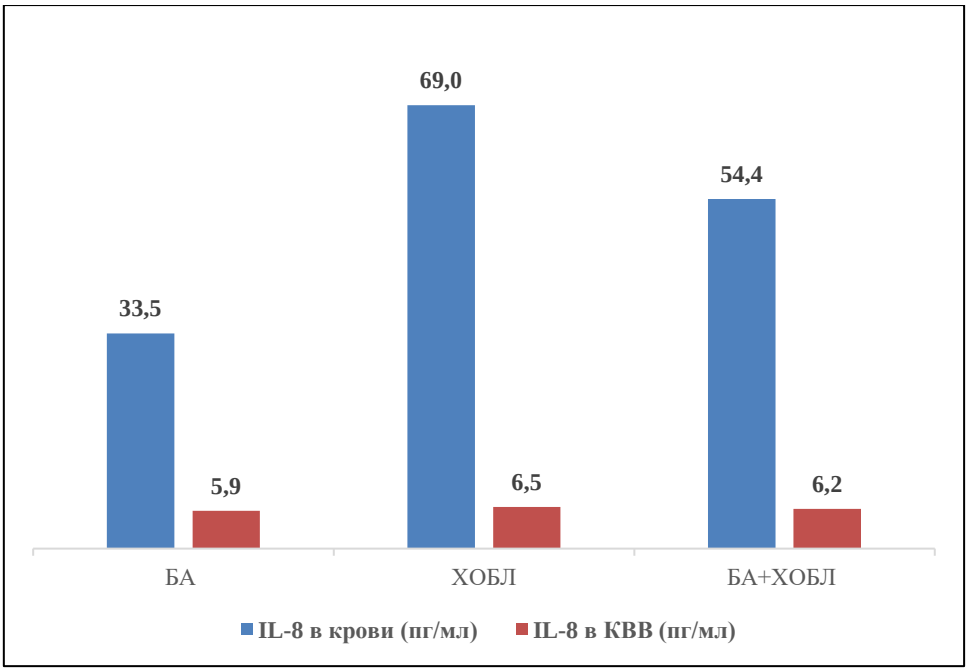


Figure 3.4.2. Level of IL-8 production in patients with asthma, COPD and asthma+COPD in remission

It is clear that IL-8 is produced by neutrophils and its dominance in COPD supports the neutrophilic type of inflammation in the airways [55]. This conclusion was confirmed by the comparison of the level of IL-8 cytokine production in the blood and in exhaled air condensate in groups of patients with COPD (69.0±3.7 pg /ml and 6.5±0.3 pg /ml) and asthma +COPD (54.4±3.1 pg /ml and 6.2±0.3 pg /ml) for which big significance of a high degree was determined ($P < 0.001$).

There were no significant differential values of IL-8 between the groups of BA patients and the BA+COPD group in the blood during the acute stage ($P > 0.5$). At the same time, when comparing acquired As a result, IL-8 production in the exhaled air condensate of patients with asthma was higher compared with patients with asthma + COPD, which was significant ($P < 0.02$).

In addition, in the acute stage, differences in the level of IL-8 were established in the groups of patients with COPD in the blood level of the cytokine was (72.5 ± 4.7 pg / ml) and in the condensate of exhaled air (74.2 ± 4.8 pg / ml) and was statistically higher compared to patients from the COPD+BA group (50.8±2.8 pg /ml and 52.2±2.5 pg /ml), respectively (P <0.001).

IL-8 promotes the formation of fibrosis of the bronchial tree, which can lead to a more severe course of the disease, which is typical for the clinical course of COPD[55].

IL-8 is a product of the immune system in response to an etiological factor. In COPD, an increase in the level of these cytokines, compared with patients from the BA group, may be justified by the presence of chronic foci of infection, activation of infectious agents, which often occur during the disease, and thus the persistence of neutrophilic inflammation [55].

Referring to the results of research work on the level of cytokines in patients with COPD, we can conclude that the inflammatory process of the respiratory tract is due to immunological disorders.

And the results of the study showed that the immunopathogenesis of diseases is based on the presence of inflammation of the respiratory tract, while the formation of asthma is characterized by a pronounced immune reaction. An increase in IL-8 production indicates a predominant Th2 immune response, which is typical for patients with COPD [55].

Therefore, IL-4, IL-8 play a necessary role significance in the immunopathogenesis of diseases and vary significantly from each other in terms of the predominance of cytokine production during the development of BA, COPD and their combination. In asthma, IL4 cytokines dominate, participating in the Th2 type of immune response, which took place in the formation of an allergic (eosinophilic) type of inflammation of the respiratory tract. In COPD, the levels of IL-8 cytokines, which are formed under the influence of infectious (bacteria, viruses) and toxins, increase [55] .

When studying the TNF -α level in the blood, significantly high levels were revealed among patients with BA 19.2±1.1 pg/ml, in contrast to COPD (P <0.001) (Fig. 3.4.3). When comparing COPD and BA+COPD, statistically significant high rates were revealed among patients with comorbidity both in the blood (P <0.001) and in the EAC (P <0.01) (Table 3.3.1). When comparing patients with BA and BA + COPD, TNF -α levels in the blood were higher among patients with comorbid pathology, respectively 19.2±1.1; 30.8±1.6 (P <0.001).

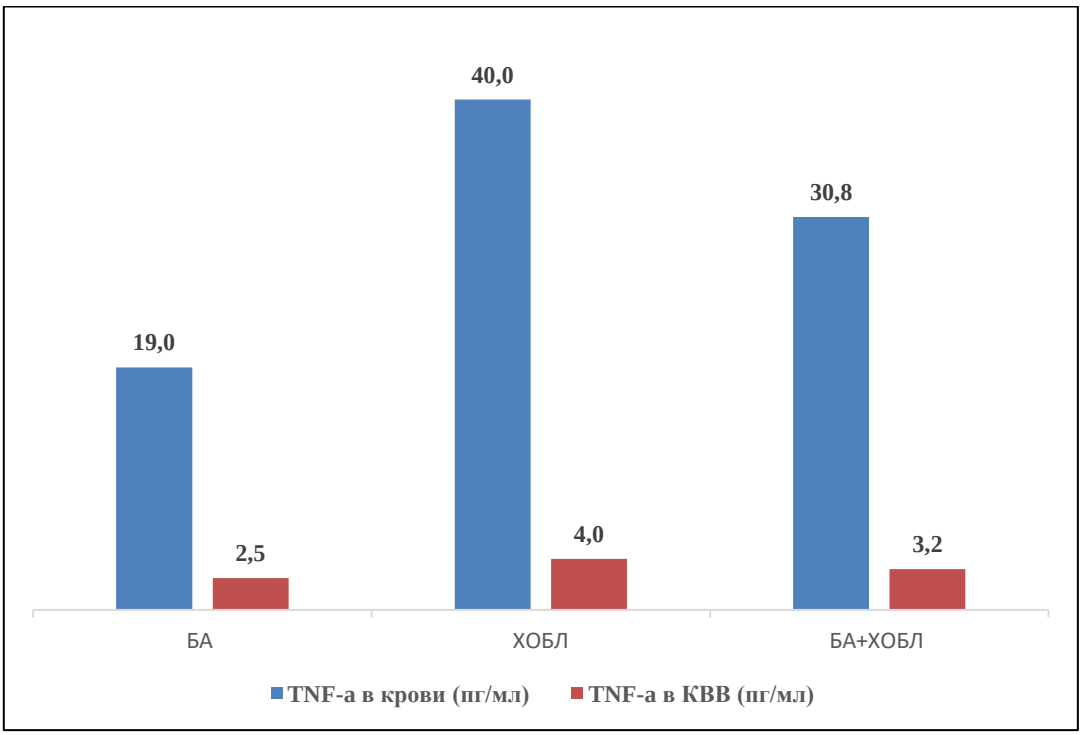


Figure 3.4.3. TNF-α level in patients with asthma, COPD and asthma+COPD in remission

When comparing immunoglobulin E indicators among the above 3 groups in the acute stage, it was revealed that patients with BA, unlike patients with COPD and BA + COPD , had significantly high levels in the blood; when comparing patients with COPD and BA + COPD, high indicators were revealed among patients with concomitant pathology (P <0.001) (Figure 3.4. 4), which corresponds to the data of the literature sources we studied.

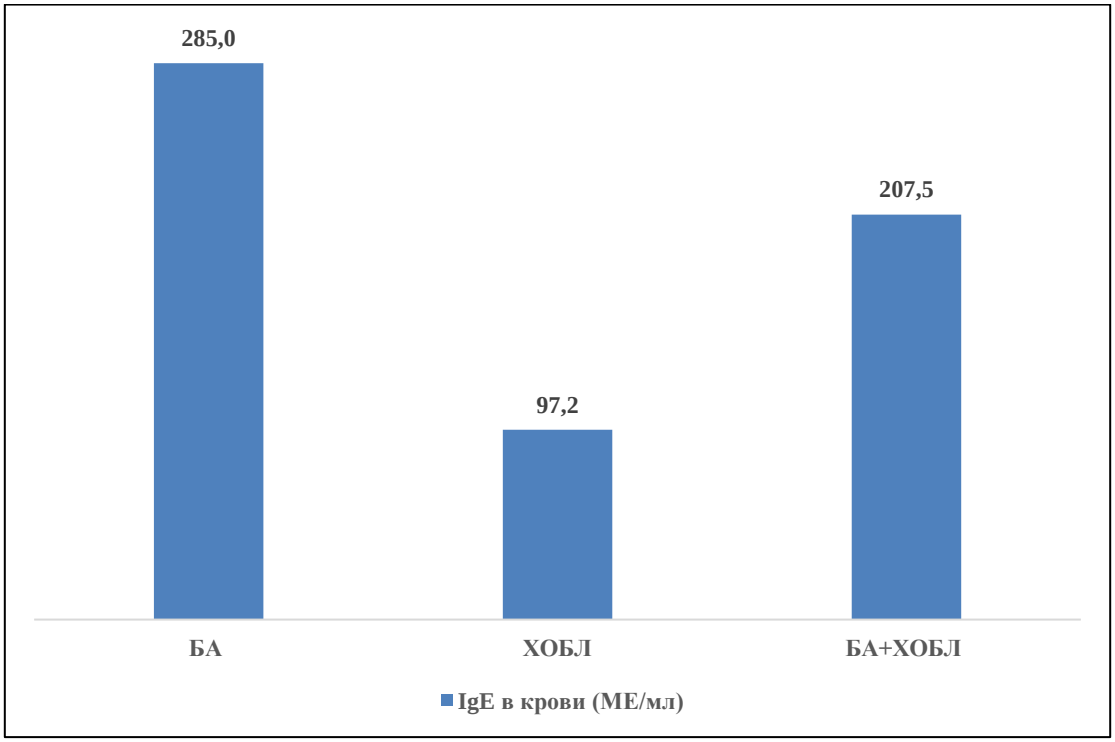


Figure 3.4.4. Level of immunoglobulin E in patients with asthma, COPD and asthma+COPD in remission

Thus, during the study of immunological parameters among the above groups (BA, COPD, BA + COPD), a significant increase in immunoglobulin E was revealed and in patients with combined pathology, the level of tumor necrosis factor TNF -α prevailed.

3.5 Indicators of endothelial function among patients with asthma, COPD and asthma+COPD

To identify endothelial dysfunction, we studied the ratio of NO_2 and NO_3 indicators both in the composition of EAC and in the blood. The results of these values, which were obtained from 20 people whom we defined as “practically healthy”, were accepted as the norm in our study: the NO_2/NO_3 ratio in the blood was –13.43-14.83 μmol /l and in the EBC 5 ,2-6.92 μmol /l. The control group consisted of 20 practically healthy people (12 men and 8 women) aged 49.13 ± 4.67 years. Volunteers from the control group had no chronic diseases, no bad habits, and did not take various types of medications.

Table 3.5.1

Assessment of endothelial function in patients with COPD and asthma in the acute stage

Indicators	COPD (n= 35)	BA (n= 35)	P
NO_2 and NO_3 in blood mmol /l	21.8±1.4	17.2±1.1	<0.01
NO_2 and NO_3 in EAC mmol /l	12.5±0.7	7.7±0.5	<0.001

Note: P – significance of differences between the indicators of the compared groups

NO_2 /NO_3 ratios in contrast to practically healthy individuals, but it should be emphasized that patients with COPD had statistically high levels in the blood in relation to patients with asthma (P <0.01) and also in the composition of EAC (P <0.001), this confirms that among patients with COPD endothelial dysfunction is more pronounced (Table 3.5.1). During the remission stage, we identified an identical picture (Table 3.5.2).

Table 3.5.2

Indicators of the NO2/NO3 ratio in patients with COPD and asthma in remission

Indicators	COPD (n= 35)	BA (n= 35)	P
NO 2 and NO 3 in blood mmol /l	21.8±1.2	16±0.9	<0.001
NO 2 and NO 3 in EAC mmol /l	12±0.7	7.5±0.4	<0.001

Note: P – significance of differences between the indicators of the compared groups

When comparing patients with COPD and BA+COPD in the stage of exacerbation and remission (Table 3.5.3), we also found high rates in both groups, but they were statistically significantly high in patients with COPD both in the blood (P <0.05) and in EAC (P <0.001) .

Table 3.5.3

Indicators of the NO2/NO3 ratio in patients with COPD and BA+COPD in the acute stage

Indicators	COPD (n= 35)	BA+COPD (n= 31)	P
NO 2 and NO 3 in blood mmol /l	21.8±1.4	18.3±1.0	<0.05
NO 2 and NO 3 in EAC mmol /l	12.5±0.7	9.5±0.6	<0.001

P – reliability of differences between the indicators of the compared groups

Table 3.5.4

Indicators of the NO2/NO3 ratio in patients with COPD and BA+COPD in remission

Indicators	COPD (n= 35)	BA+ COPD (n= 31)	P
NO 2 and NO 3 in blood mmol /l	6.4±0.3	9.2±0.6	<0.01
NO 2 and NO 3 in EAC mmol /l	3.0± 0.2	4.2± 0.3	<0.01

Note: P – significance of differences between the indicators of the compared groups

When comparing patients with BA and BA+COPD in the acute stage (Table 3.5.5), in contrast to potentially healthy patients, the $NO_2/NO_{3\ ratio}$ was statistically significantly high both in patients with BA and in patients with concomitant pathology, but it should be noted. When comparing patients with BA and BA+COPD in the acute stage, there was no statistically significant difference in determining parameters in the blood and in the EAC.

Table 3.5.5

Indicators of the NO2/NO3 ratio in patients with BA and BA+COPD in the acute stage

Indicators	BA (n= 35)	BA+COPD (n= 31)	P
NO 2 and NO 3 in blood mmol /l	17.2±1.1	18.3±1.0	>0.5
NO 2 and NO 3 in EAC mmol /l	7.7±0.5	9.5±0.6	<0.02

Note: P – significance of differences between the indicators of the compared groups

When studying these indicators between the same groups in remission, a statistically significant difference was noted, expressed in increased concentrations of NO_2 and NO_3 in the EAC of patients with BA + COPD in comparison with patients with BA (Table 3.5.6).

Table 3.5.6

Indicators of the NO2/NO3 ratio in patients with BA and BA+COPD in remission

Shown	BA (n= 35)	BA+COPD (n= 31)	P
NO 2 and NO 3 in blood mmol /l	16±0.9	18±1.1	>0.2
NO 2 and NO 3 in EAC mmol /l	7.5±0.4	9.2±0.5	<0.01

Note: P – significance of differences between the indicators of the compared groups

Thus, in the course of our study, it was proven that patients with COPD are more susceptible to the occurrence of endothelial dysfunction in contrast to patients with asthma and asthma + COPD, and endothelial dysfunction is an important pathogenetic link in the development of COPD, which requires an additional in-depth study of these indicators in patients with chronic bronchopulmonary pathologies, and

recommends the appointment of this category of patients with drugs with the function of restoring endothelial dysfunction.

3.6. Features of the relationship between immunological parameters and the NO 2/ NO 3 ratio in patients with COPD, asthma, asthma + COPD in the blood and in the EAC

To determine the significance of immunological parameters, the NO 2/ NO 3 ratio during COPD, BA, BA + COPD **a number of** correlation analyzes were carried out to identify the relationship between cytokine indicators (IL -4, IL -8, TFN - a), IgE and NO 2/ NO 3 both in the blood and in the EAC with the subsequent construction of a correlation graph, diagram equations and values approximation .

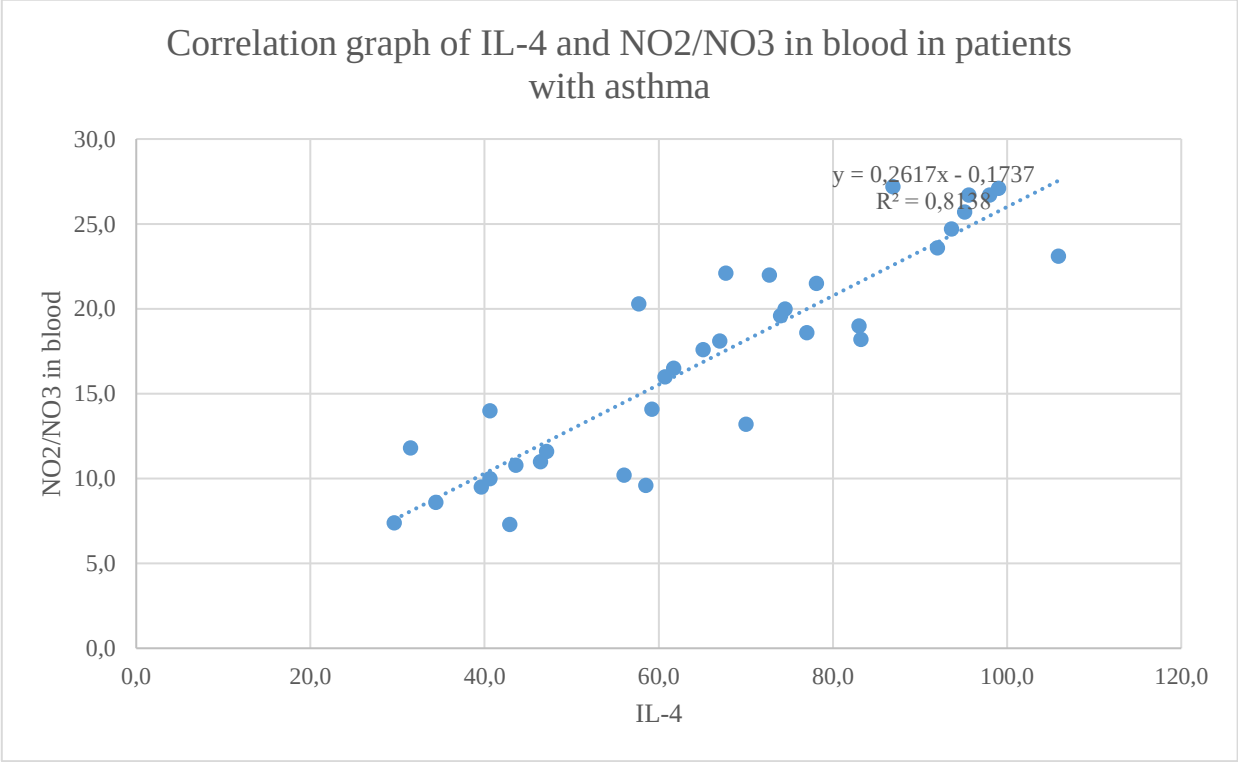


Figure 3.6.1. Correlation graph of IL-4 and NO2/NO3 in the blood of patients with asthma in the acute stage (P<0.001).

Data from patients with bronchial asthma shown in Figure 3.6.1 show a high uniform crowding of indicators in the form of an almost identical small deviation of points relative to the trend line. The data obtained indicate a very high direct correlation between the indicators IL -4 and NO 2/ NO 3 in the blood of patients with BA in the acute stage (r=0.90), which indicates the validity of using these

immunological parameters in the diagnosis and determination of the course of the disease.

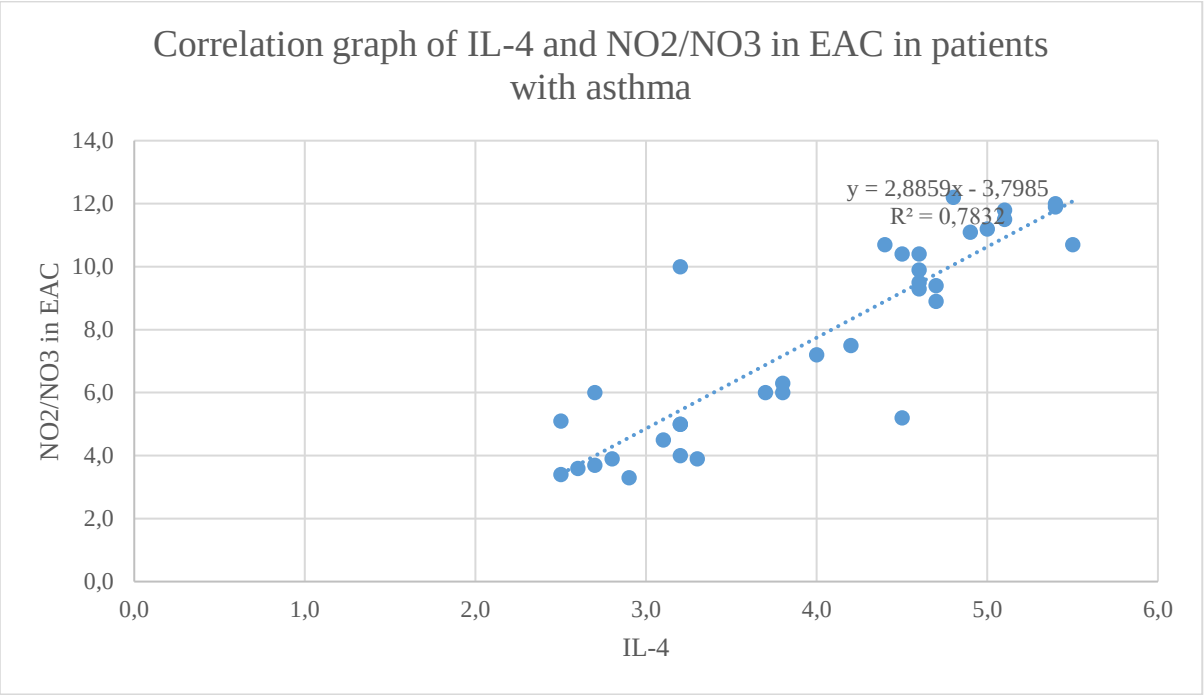


Figure 3.6.1. Correlation graph of IL-4 and NO2/NO3 in the EAC of BA patients in the acute stage (P<0.01).

A similar picture was noted when studying these indicators in the EAC, shown in Figure 3.6.2, even greater crowding of indicators is noted; only a small number of deviation points relative to the trend line are noted. The data obtained indicate a high direct correlation between the indicators IL -4 and NO 2/ NO 3 in the EAC of patients with BA in the acute stage (r = 0.88), which indicates the validity of using these immunological parameters in the diagnosis and determination of the course of the disease.

A study of the indicators of patients with bronchial asthma, shown in Figures 3.6.3 and 3.6.4, also shows a high uniform crowding of indicators with an insignificant amount of small deviation of the points above relative to the trend line, which indicates a very high direct correlation between the indicators IL -8 and NO 2/ NO 3 in the blood of patients with BA in the acute stage (r=0.91) and a high direct correlation between the indicators IL -8 and NO 2/ NO 3 in the EAC of patients with BA in the acute stage (r=0.88).

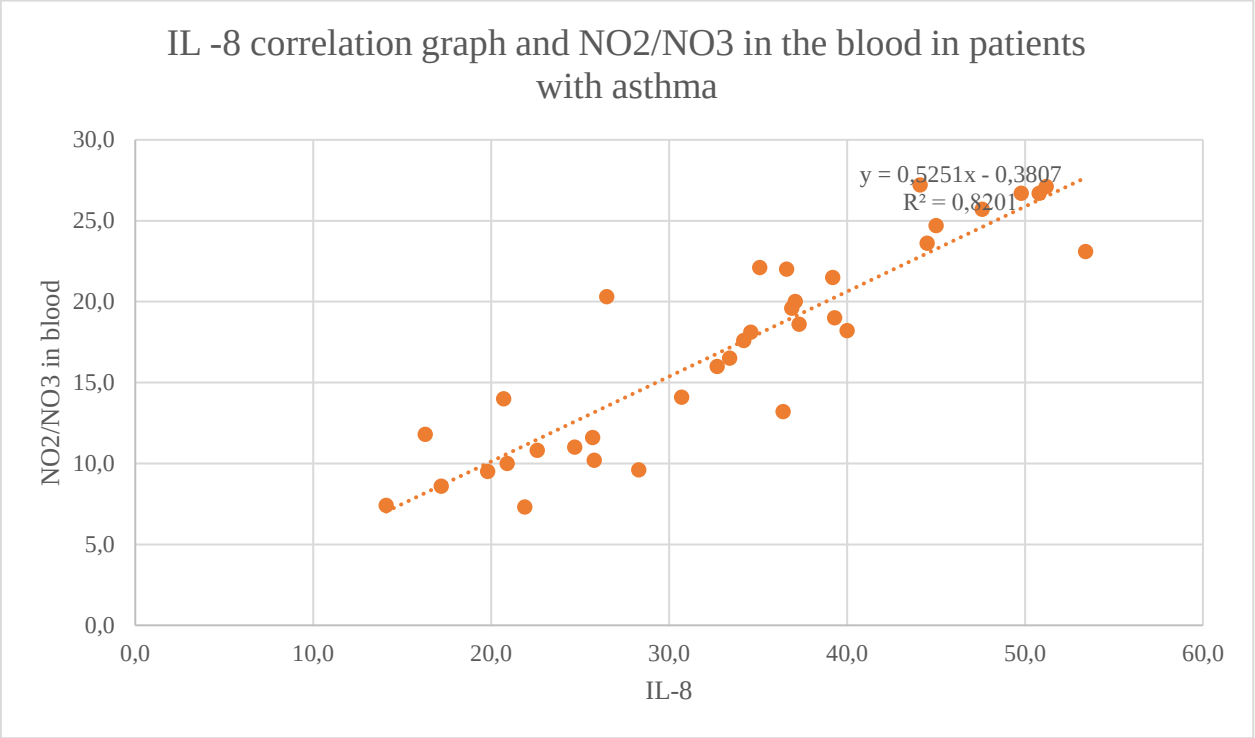


Figure 3.6.3. Correlation graph of IL-8 and NO2/NO3 in the blood of patients with asthma in the acute stage (P<0.01).

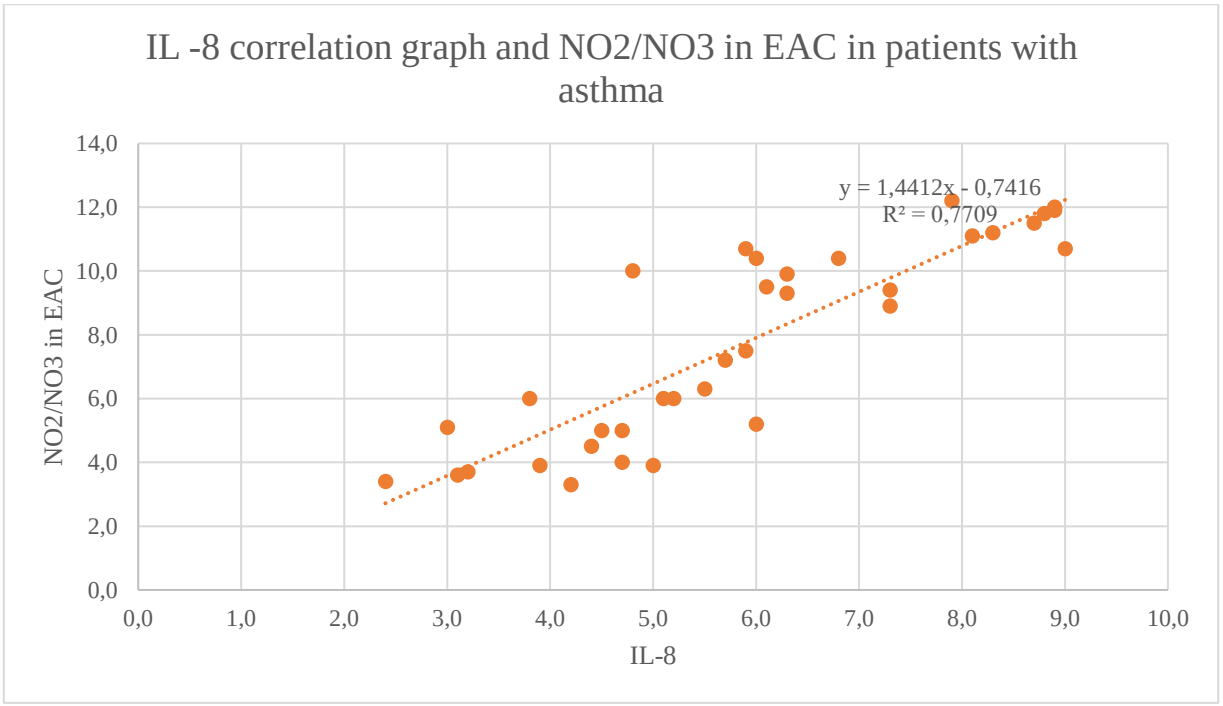


Figure 3.6.4. Correlation graph of IL-8 and NO2/NO3 in the EAC of BA patients in the acute stage (P<0.01).

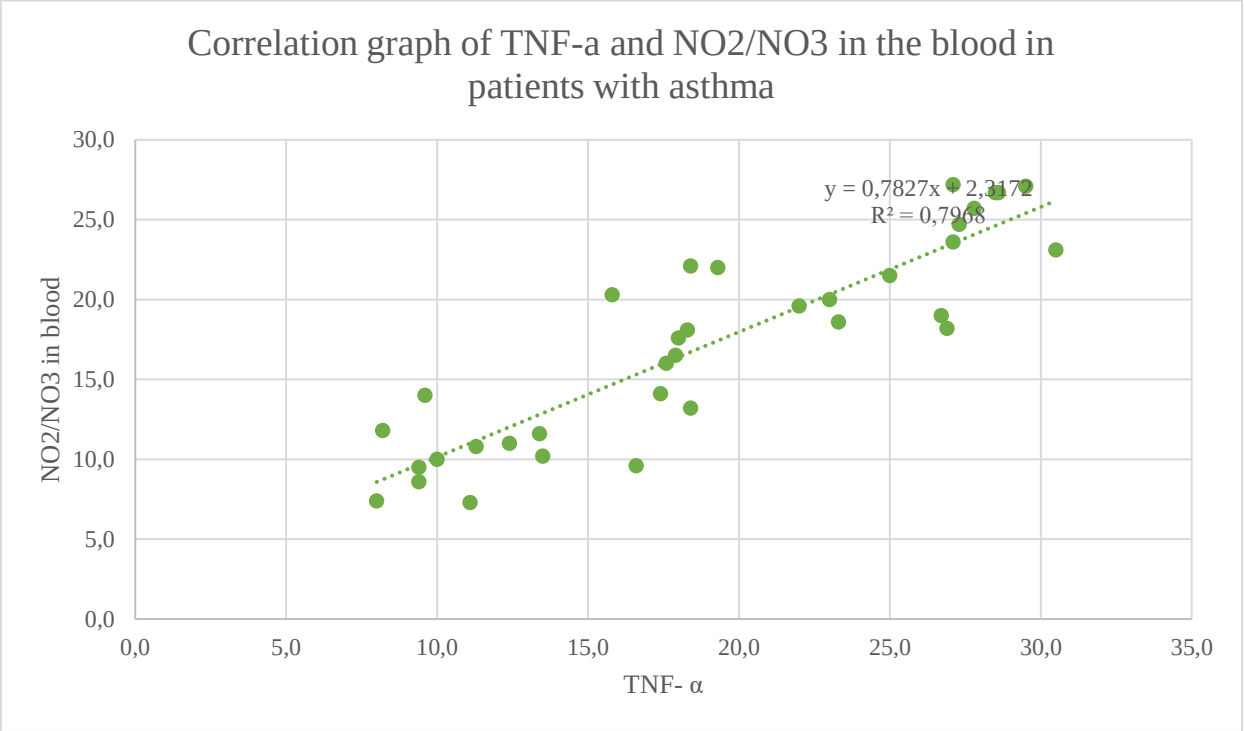


Figure 3.6.5. Correlation graph of TNF-α and NO2/NO3 in the blood of patients with asthma in the acute stage (P<0.01).

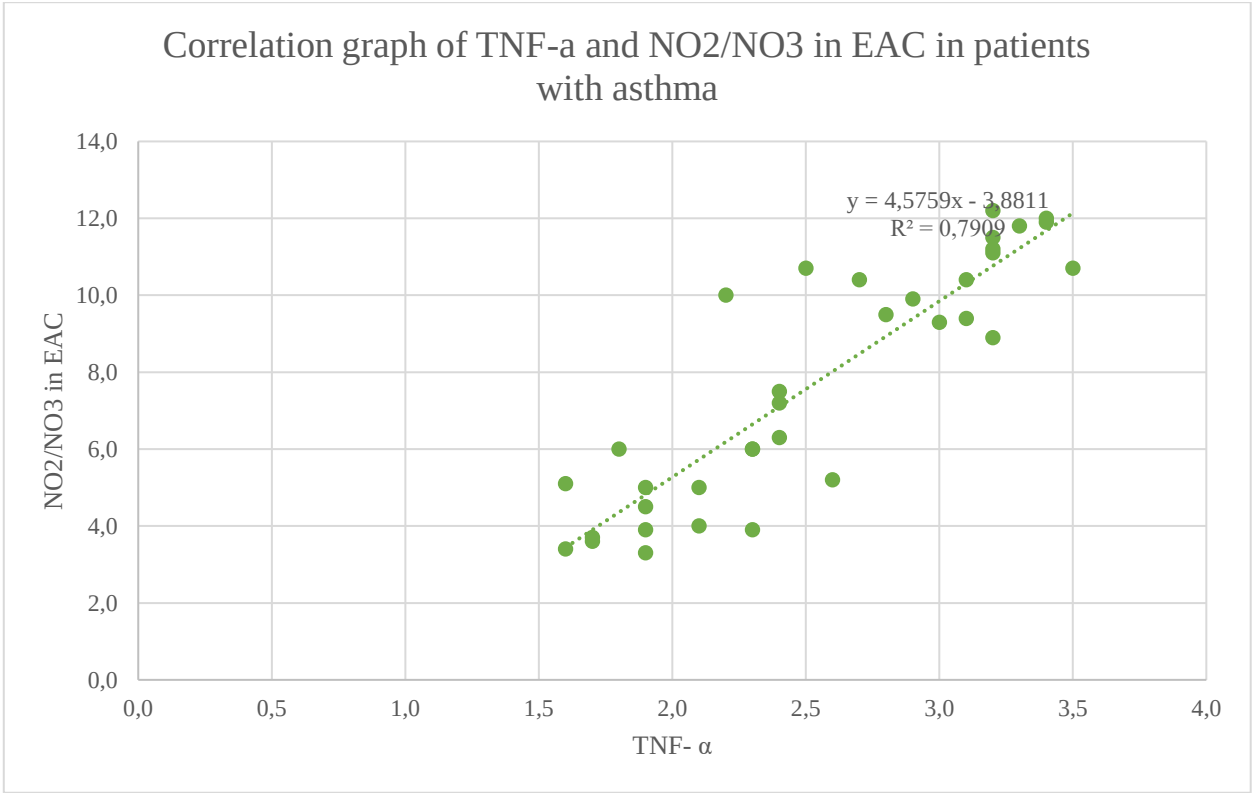


Figure 3.6.6. Correlation graph of TNF-α and NO2/NO3 in the EAC of BA patients in the acute stage (P<0.01).

Relatively similar graphs were noted when studying the correlation relationships between TNF - α and NO 2/ NO 3 in the blood and EAC of patients with bronchial asthma in the acute stage , shown in Figures 3.6.5 and 3.6.6, there is a crowding of indicators, with a more significant deviation relative to the line trend when studying indicators in the blood of patients and a less significant deviation relative to the trend line in the EAC of patients with bronchial asthma. The data obtained indicate a high direct correlation between the indicators TNF - α and NO 2 / NO 3 in the blood and ECV of patients with BA in the acute stage (r = 0.89; r = 0.89), which indicates the validity of using these immunological parameters in the diagnosis and determination of the course of the disease.

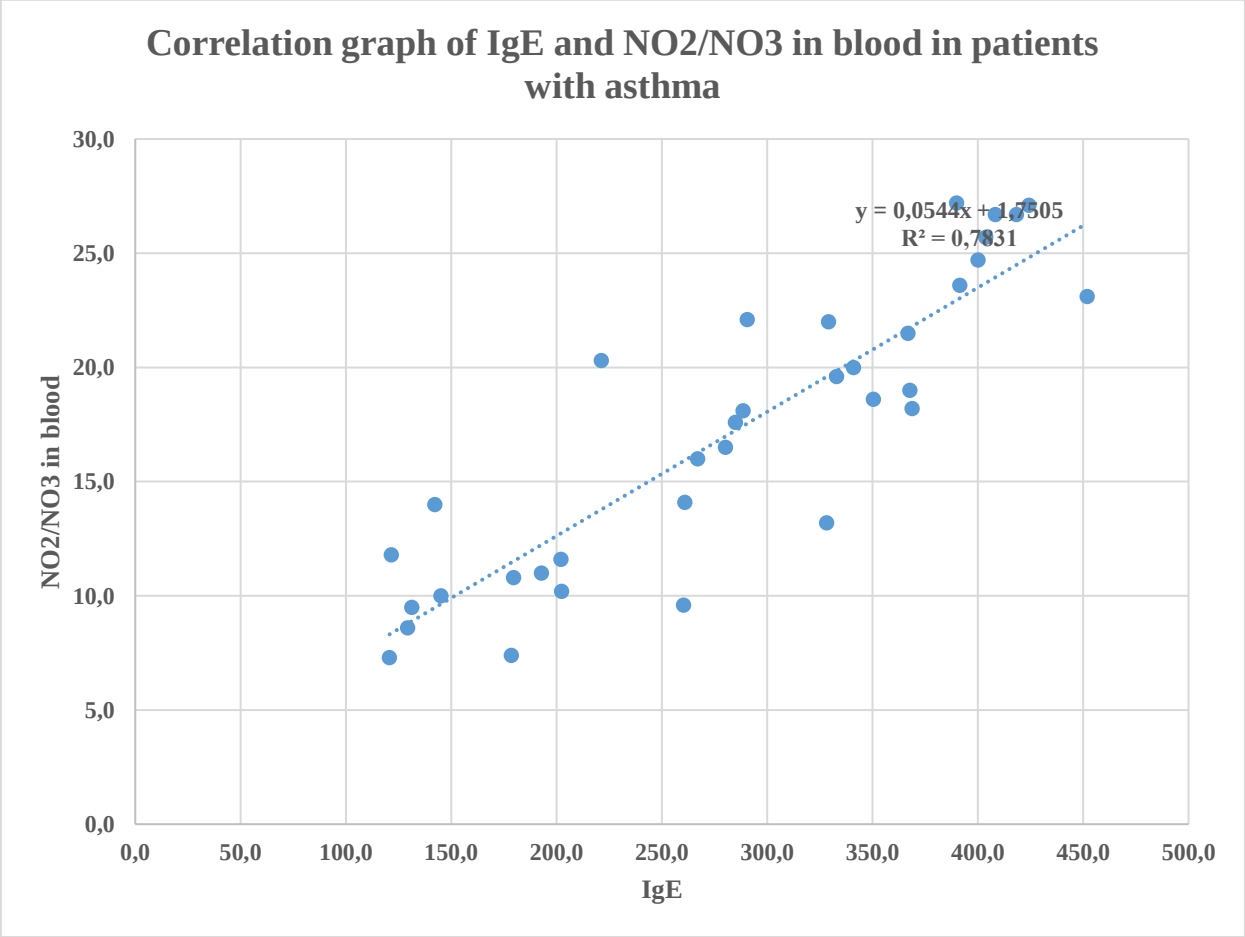


Figure 3.6.7. Correlation graph of IgE and NO2/NO3 in the blood of patients with asthma in the acute stage (P<0.01).

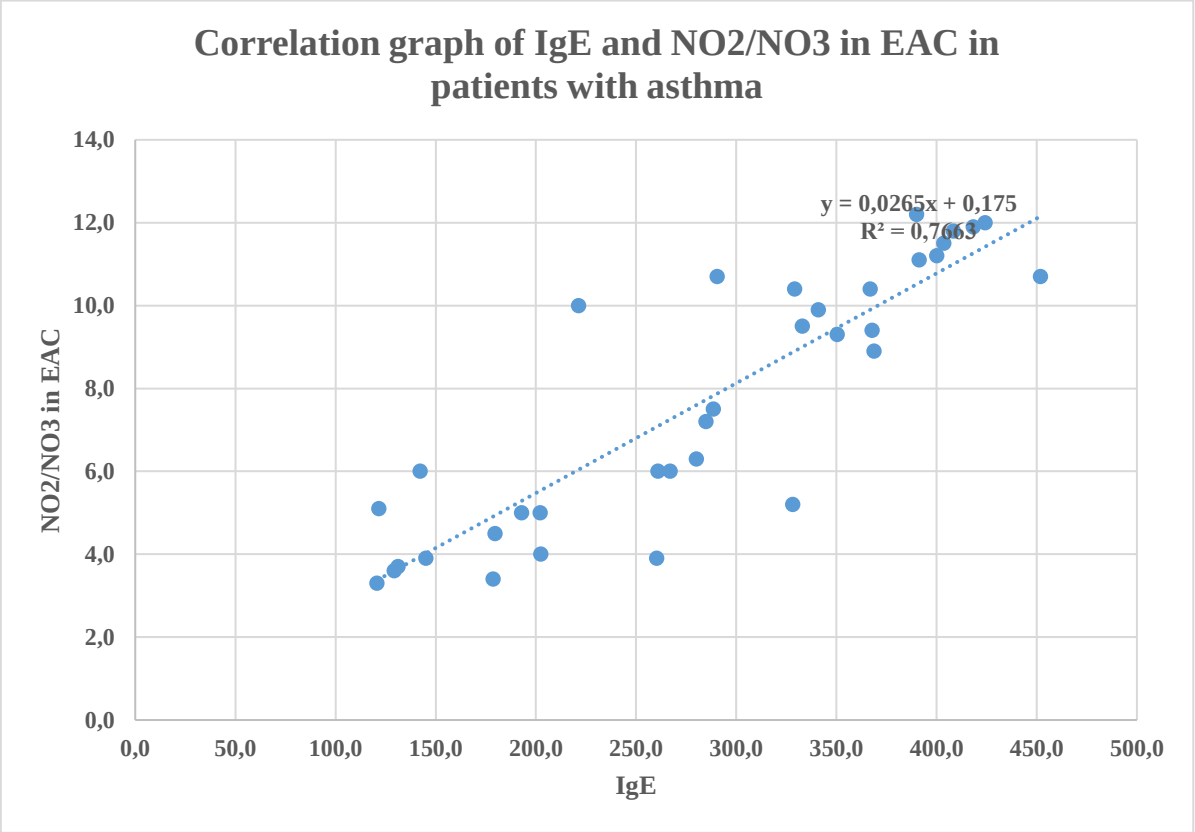


Figure 3.6.8. Correlation graph of IgE and NO2/NO3 in the EAC of patients with BA in the acute stage (P<0.05).

When studying the correlation relationships between IgE and NO 2/ NO 3 in the blood and EAC of patients with bronchial asthma in the acute stage , shown in Figures 3.6.7 and 3.6.8, crowding of indicators was noted, with a more significant deviation relative to the trend line when studying indicators in EAC of patients and a less significant deviation relative to the trend line in the blood of patients with bronchial asthma. The data obtained indicate a high direct correlation between the indicators IgE and NO 2/ NO 3 in the blood and EAC of patients with BA in the acute stage (r=0.88; r=0.88), which indicates the validity of using these immunological parameters in the diagnosis and determination of the course of the disease.

Thus, in the course of studying the relationship between immunological parameters and endothelial parameters in patients with BA in the acute stage, a high and very high strength of direct correlation was revealed, which confirms the dependence of the value of endothelial damage on the disturbance of immune

parameters. When comparing the above data in the remission stage, similar indicators were revealed.

Data from patients with COPD shown in Figures 3.6.9 and 3.6.10 show a high, uniform crowding of indicators in the form of an almost identical small deviation of points relative to the trend line. The data obtained indicate a very high direct correlation between the indicators IL -4 and NO 2/ NO 3 in the blood and EAC of patients with COPD in the acute stage (r=0.80; r=0.80), which indicates the validity of using these immunological parameters in the diagnosis and determination of the course of the disease.

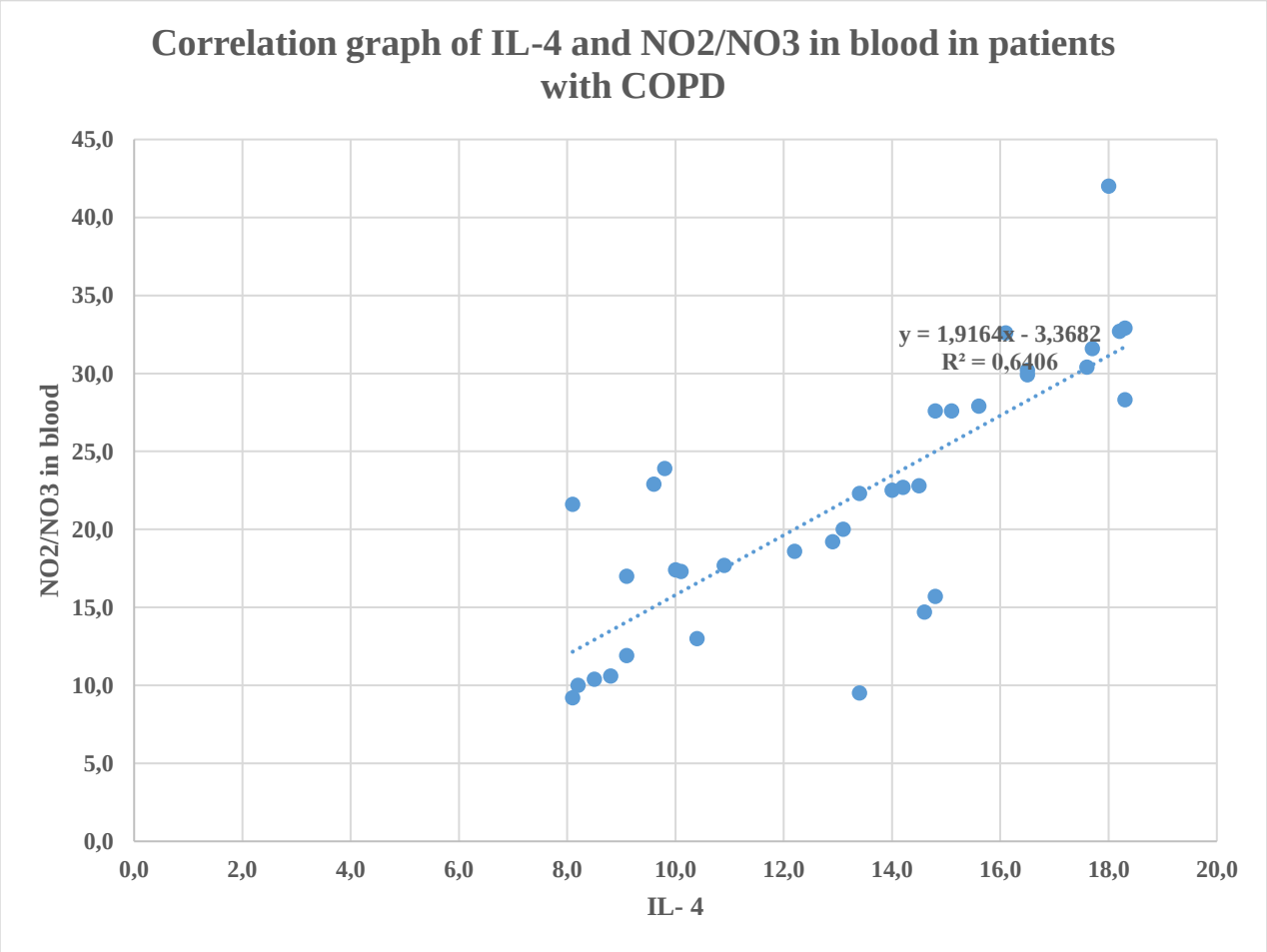


Figure 3.6.9. Correlation graph of IL-4 and NO2/NO3 in the blood of COPD patients in the acute stage (P<0.05).

(P- value <0.05).

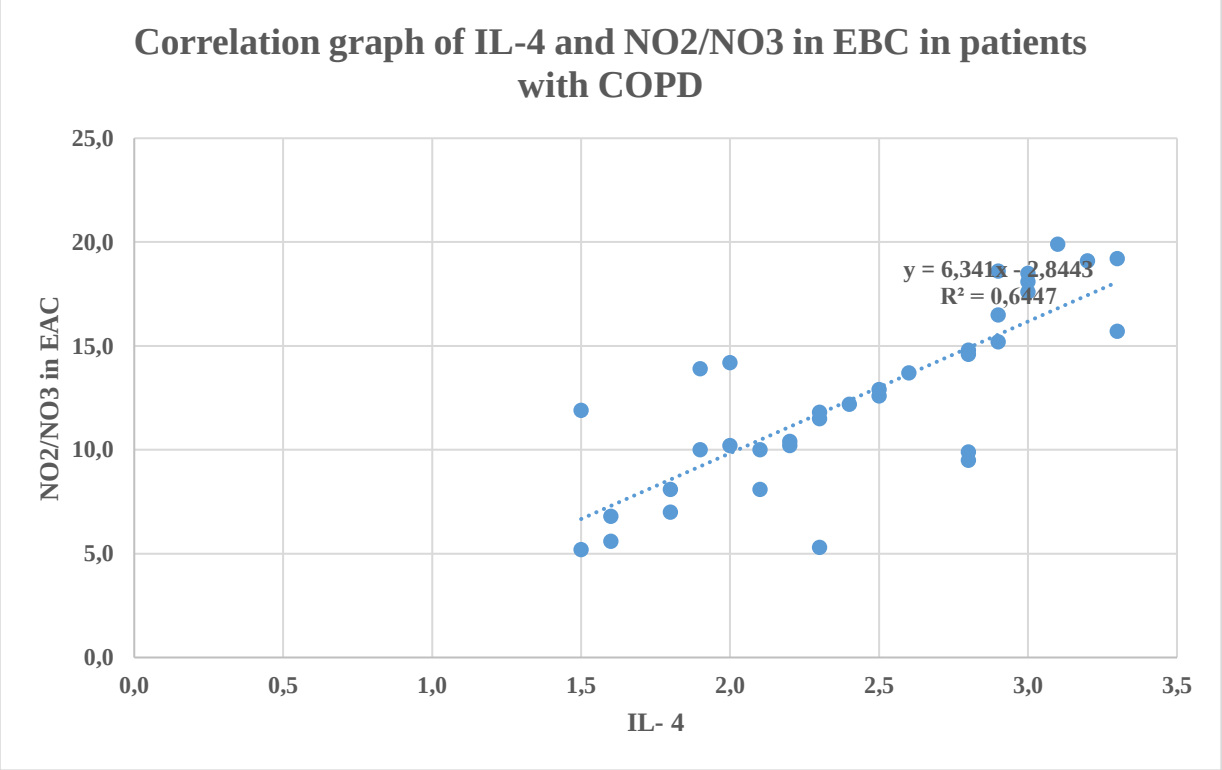


Figure 3.6.10. Correlation graph of IL-4 and NO2/NO3 in the EAV of COPD patients in the acute stage (P<0.05).

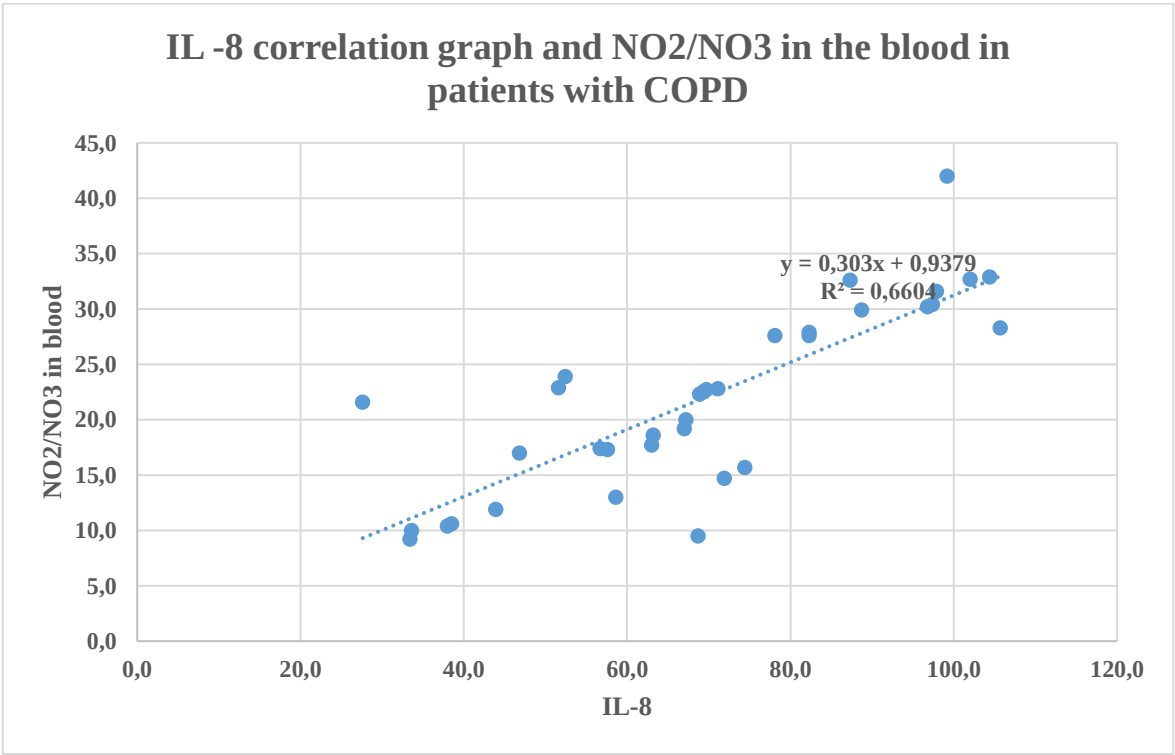


Figure 3.6.11. Correlation graph of IL-8 and NO2/NO3 in the blood of COPD patients in the acute stage (P<0.01).

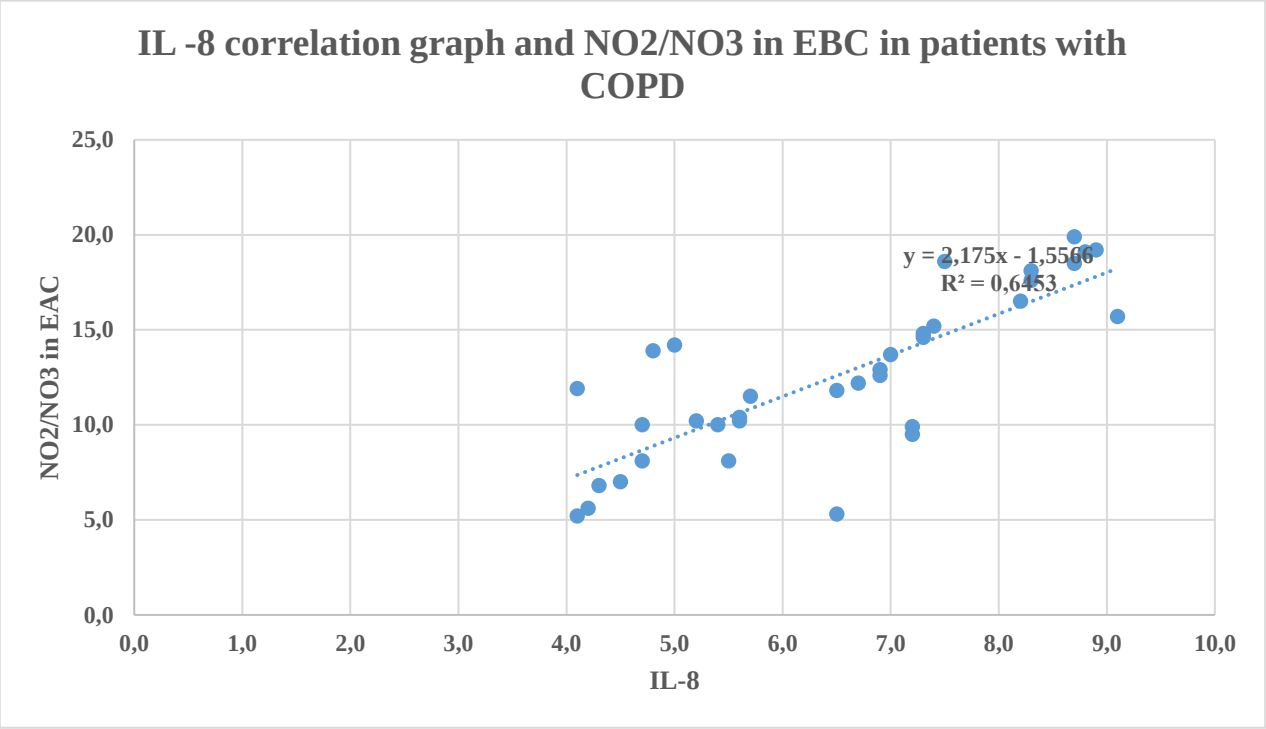


Figure 3.6.12. Correlation graph of IL-8 and NO2/NO3 in the EAC of COPD patients in the acute stage (P<0.05).

A study of the indicators of patients with COPD, shown in Figures 3.6.11 and 3.6.12, also shows the relative crowding of indicators with the number of deviations of approximately half of the points above and below relative to the trend line, while the identified relationship indicates a high direct correlation between the indicators IL -8 and NO 2/ NO 3 in the blood and EAC of COPD patients in the acute stage (r=0.81; r=0.80).

Data from patients with COPD shown in Figures 3.6.13 and 3.6.14 show uneven crowding of indicators in the form of an identically small deviation of points on both sides relative to the trend line. The data obtained indicate a high direct correlation between the indicators TNF - α and NO 2 / NO 3 both in the blood and EAC of patients with COPD in the acute stage (r = 0.83; r = 0.82), which indicates the validity of using these immunological and endothelial parameters in the diagnosis and determination of the course of the disease.

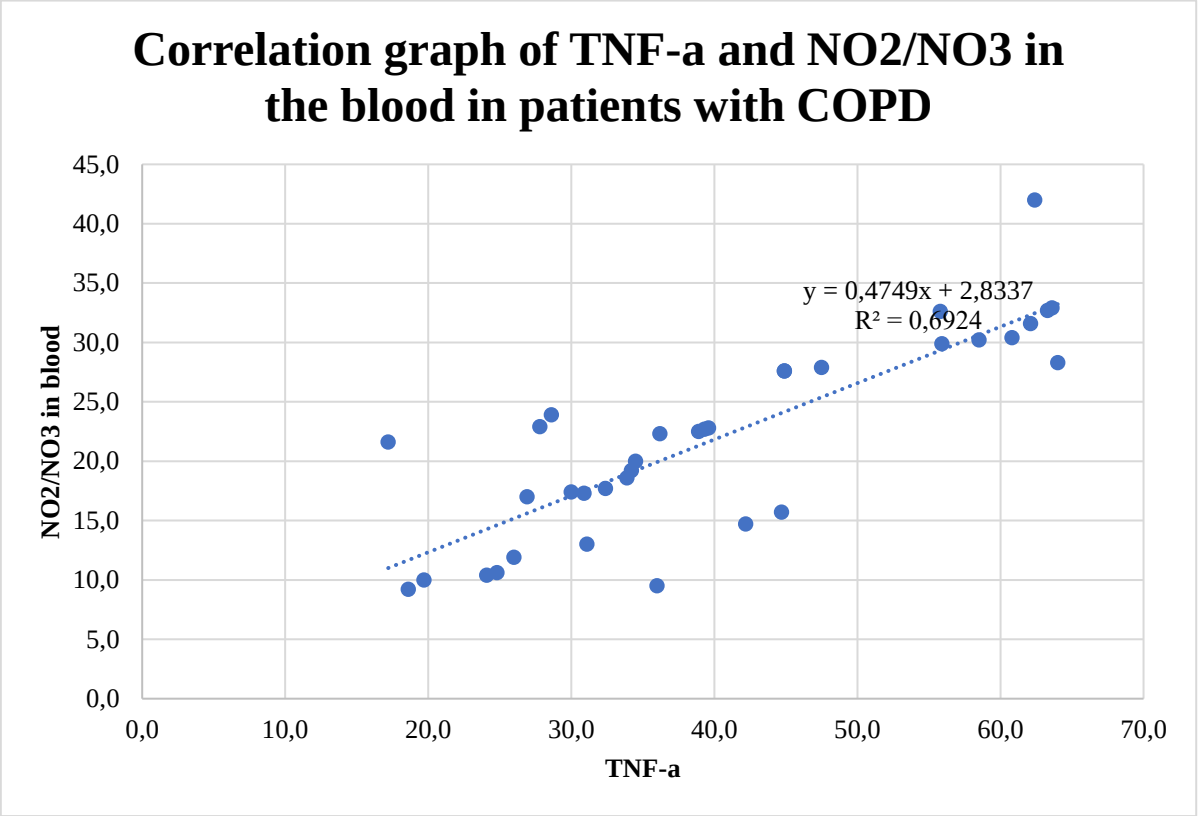


Figure 3.6.13. Correlation graph of TNF-α and NO2/NO3 in the blood of patients with COPD in the acute stage (P<0.05).

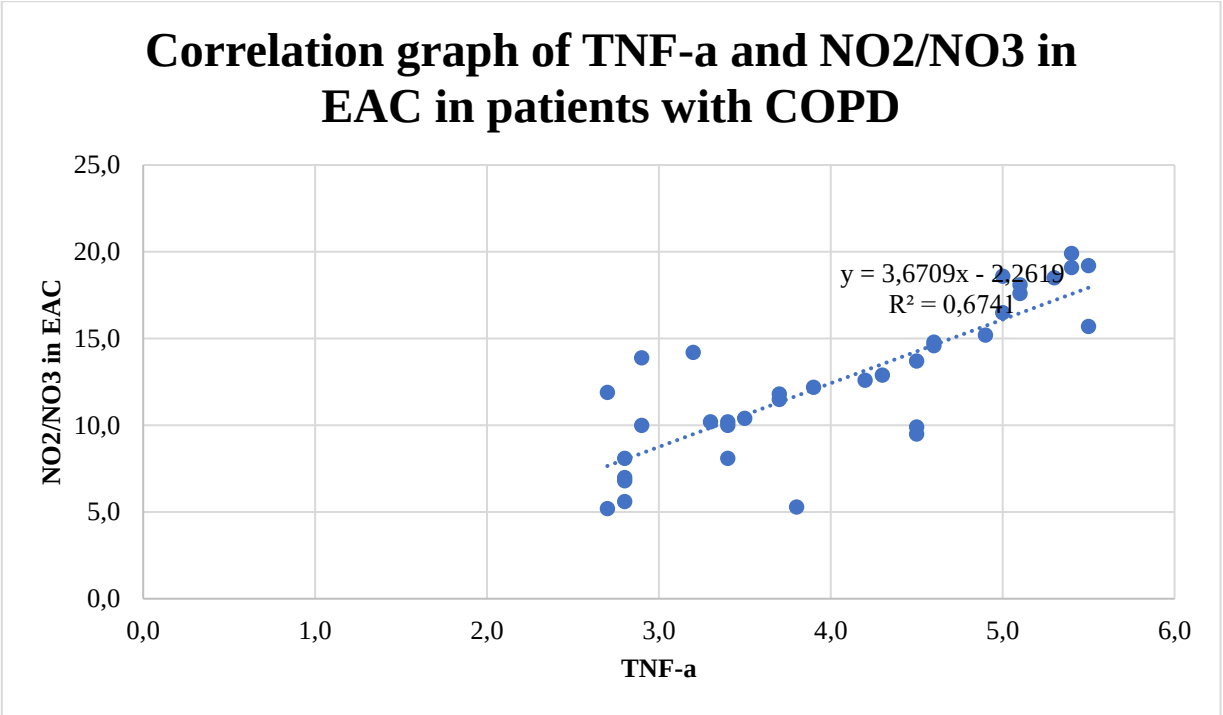


Figure 3.6.14. Correlation graph of TNF-α and NO2/NO3 in the EAC of COPD patients in the acute stage (P<0.05).

When studying the correlation relationships between IgE and NO 2/ NO 3 in the blood and EAC of patients with COPD in the acute stage , shown in Figures 3.6.15 and 3.6.16, a crowding of indicators was noted, with a relatively similar deviation from the trend line when studying indicators in both blood, and ECV of patients with COPD. The data obtained indicate a high direct correlation between the indicators IgE and NO 2/ NO 3 in the blood and EAC of COPD patients in the acute stage (r=0.80; r=0.81).

Thus, in the course of studying the relationship between immunological parameters and endothelial parameters in patients with COPD in the acute stage, a high strength of direct correlation was revealed, which confirms the dependence of the value of endothelial damage and cytokine immune parameters. When comparing the above data in the remission stage, similar indicators were revealed.

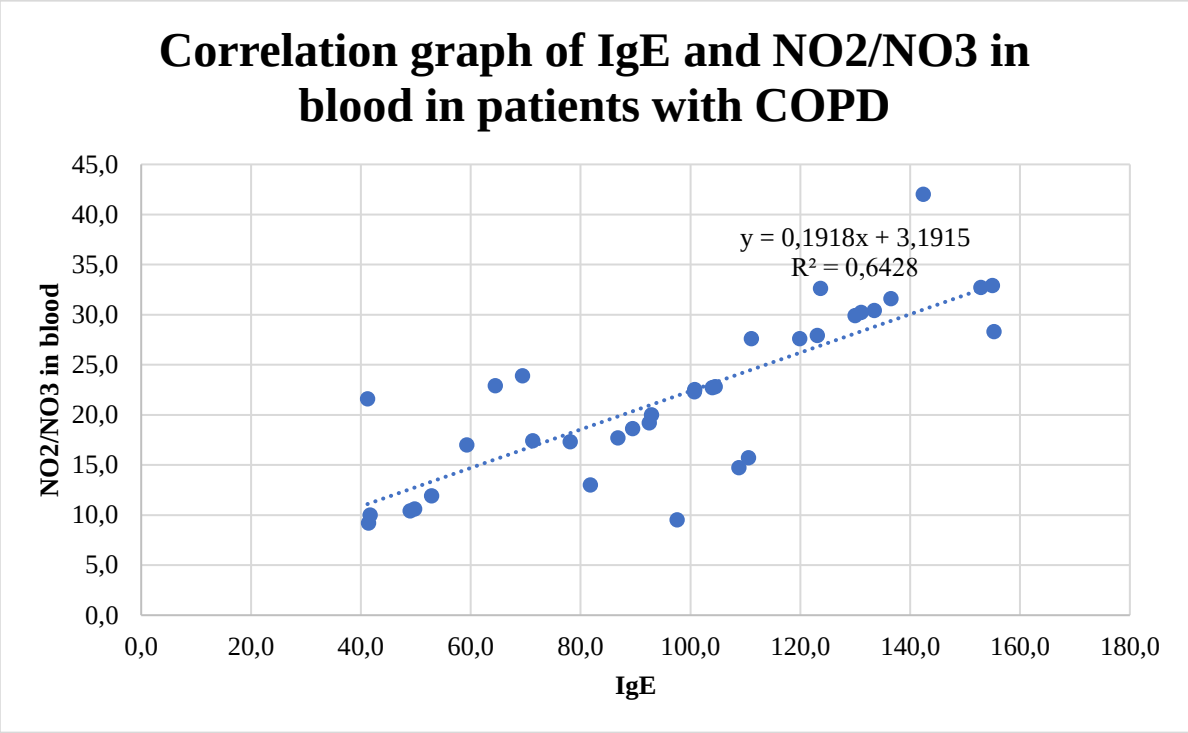


Figure 3.6.15. Correlation graph of IgE and NO2/NO3 in the blood of patients with COPD in the acute stage (P<0.05).

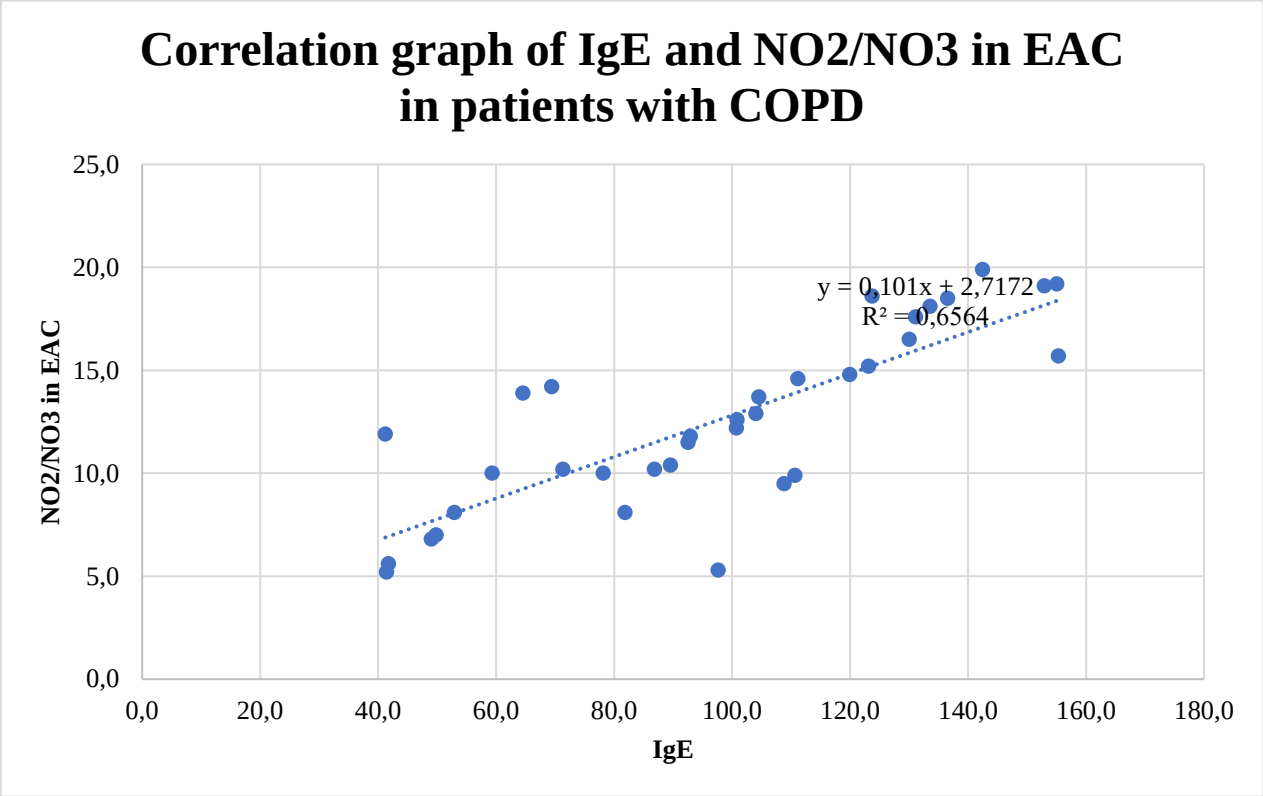


Figure 3.6.16. Correlation graph of IgE and NO2/NO3 in the EAC of patients with COPD in the acute stage (P<0.05).

The final stage of our correlation study was to study the relationship between immune and endothelial parameters in patients with BA + COPD.

The research data shown in Figures 3.6.17 and 3.6.18 show a high uniform crowding of indicators in the form of an almost identical small deviation of points relative to the trend line. The data obtained indicate a very high direct correlation between the indicators IL -4 and NO 2 / NO 3 in the blood and EAC of patients with COPD + BA in the acute stage (r = 0.88; r = 0.89), which indicates the validity of using these immunological parameters in the diagnosis and determination of the combined course of diseases.

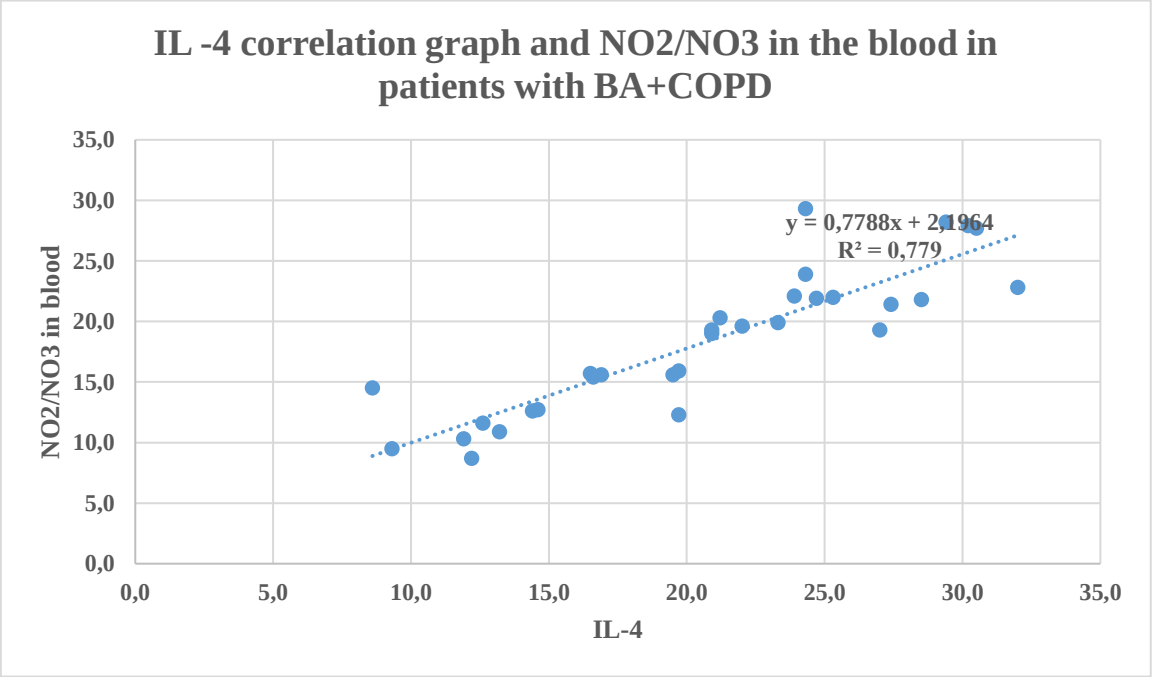


Figure 3.6.17. Correlation graph of IL-4 and NO2/NO3 in the blood of patients with COPD+BA in the acute stage (P<0.01).

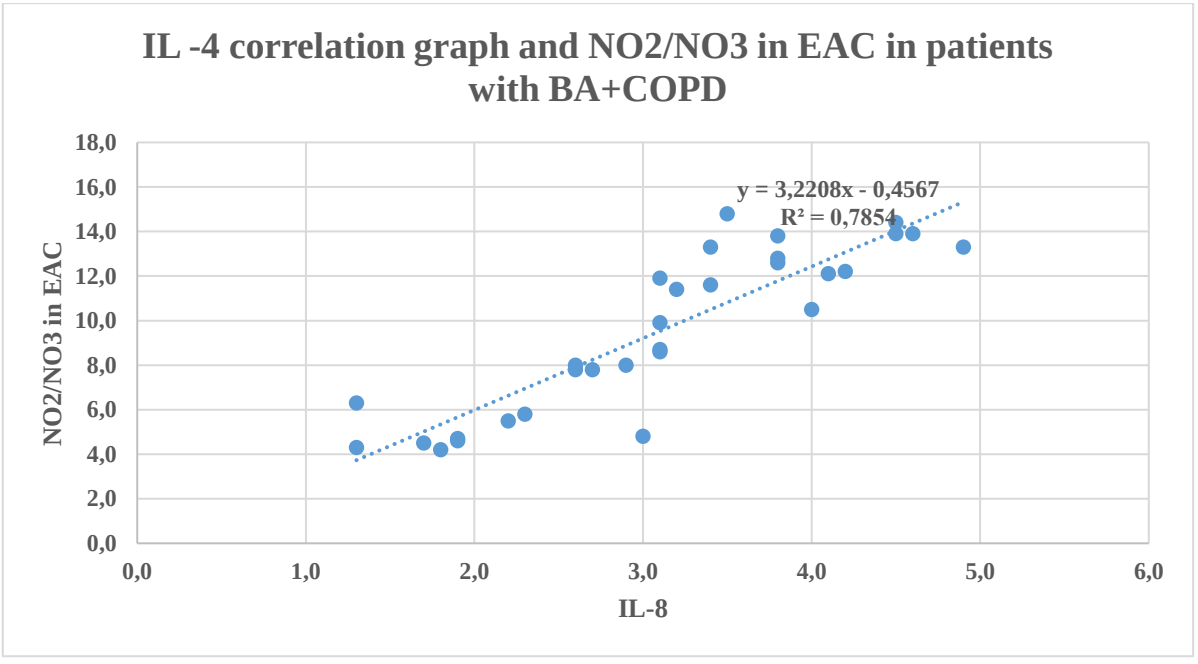


Figure 3.6.17 . Correlation graph of IL-4 and NO2/NO3 in the EAC of COPD+BA patients in the acute stage (P<0.01).

When studying the correlation relationships of IL -8 and the NO 2/ NO 3 ratio in the blood and EAC of patients with COPD + BA in the acute stage , shown in Figures 3.6.19 and 3.6.20, it was noted that on the background of crowded indicators, several points were observed that were at a great distance relative to the trend line

when studying indicators in both the blood and EAC of patients with COPD + BA. At the same time, the obtained correlation data ® indicate a high direct correlation between the indicators IL -8 and NO 2/ NO 3 in the blood and EAC of patients with COPD+BA in the acute stage (r=0.83; r=0.86).

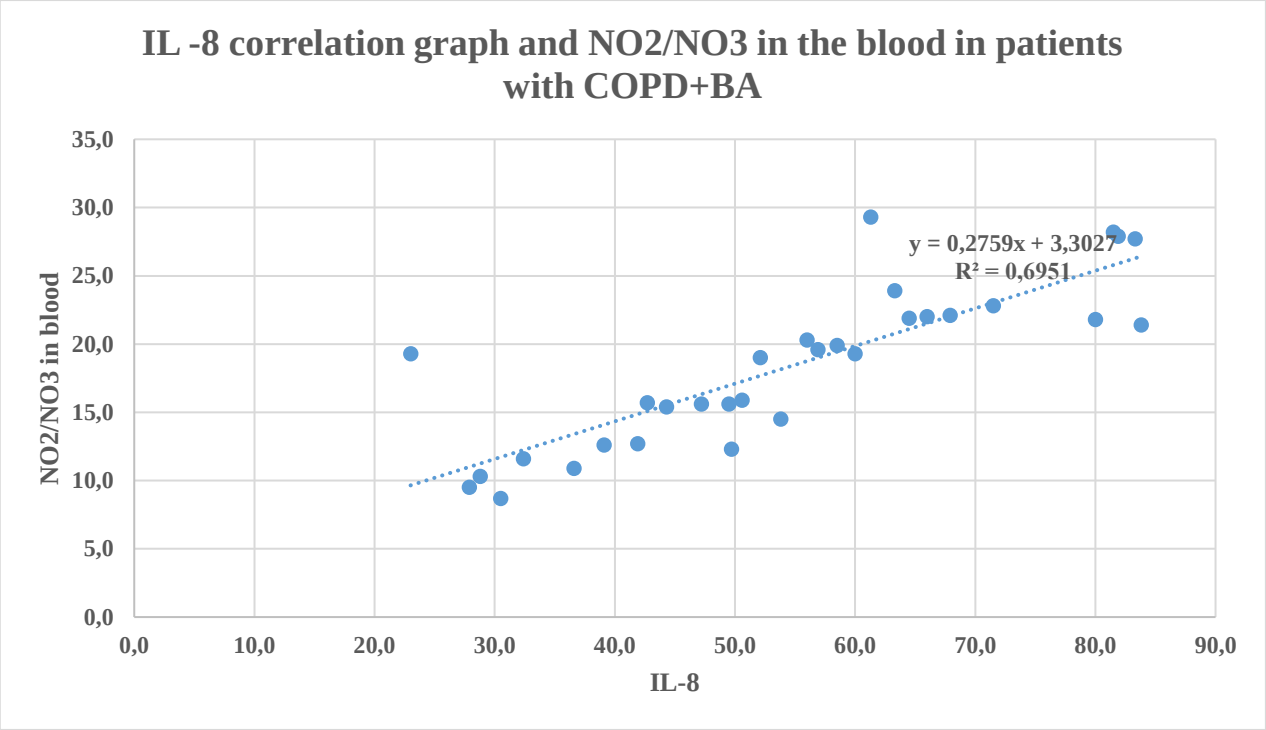


Figure 3.6.19. Correlation graph of IL-8 and NO2/NO3 in the blood of patients with COPD+BA in the acute stage (P<0.01).

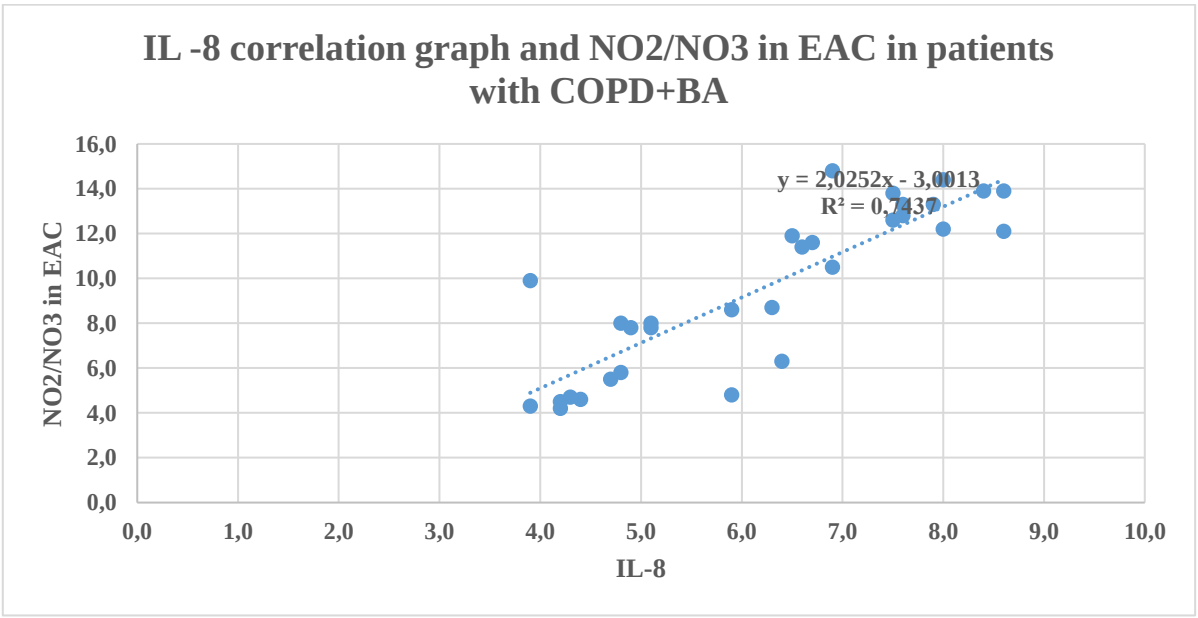


Figure 3.6.20 . Correlation graph of IL-8 and NO2/NO3 in the EAC of COPD+BA patients in the acute stage (P<0.01).

When studying the correlation relationships of IL -8 and the NO 2/ NO 3 ratio in the blood and EAC of patients with COPD + BA in the acute stage , shown in Figures 3.6.19 and 3.6.20, it was noted that on the background of crowded indicators, several points were observed that were at a great distance relative to the trend line when studying indicators in both the blood and EAC of patients with COPD + BA. At the same time, the obtained correlation data ® indicate a high direct correlation between the indicators IL -8 and NO 2/ NO 3 in the blood and ECV of patients with COPD+BA in the acute stage (r=0.83; r=0.86).

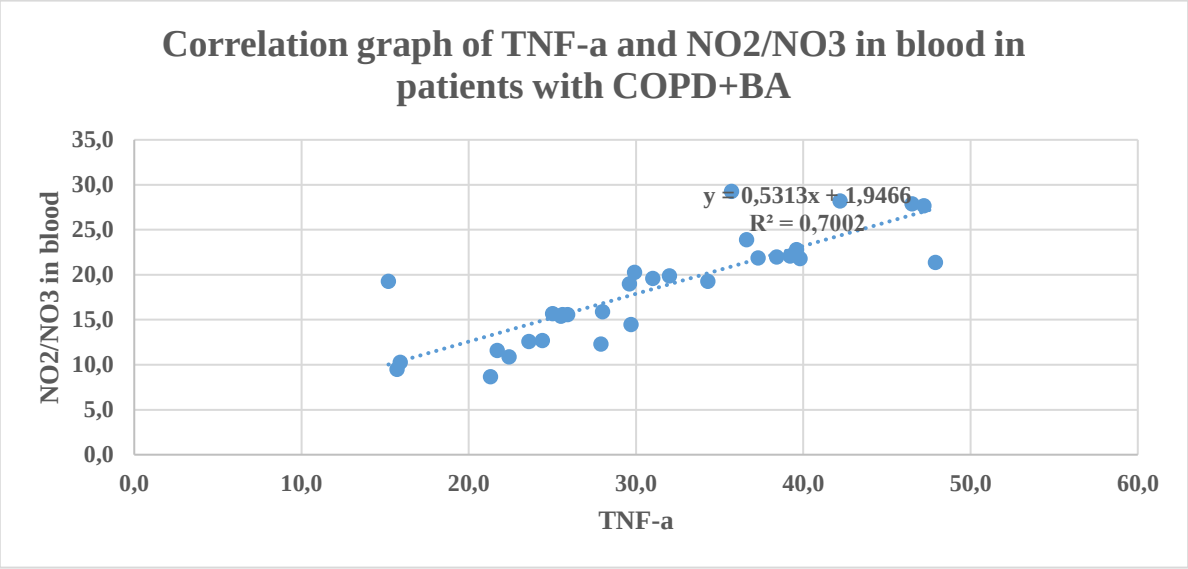


Figure 3.6.21. Correlation graph of TNF-α and NO2/NO3 in the blood of patients with COPD+BA in the acute stage (P<0.01).

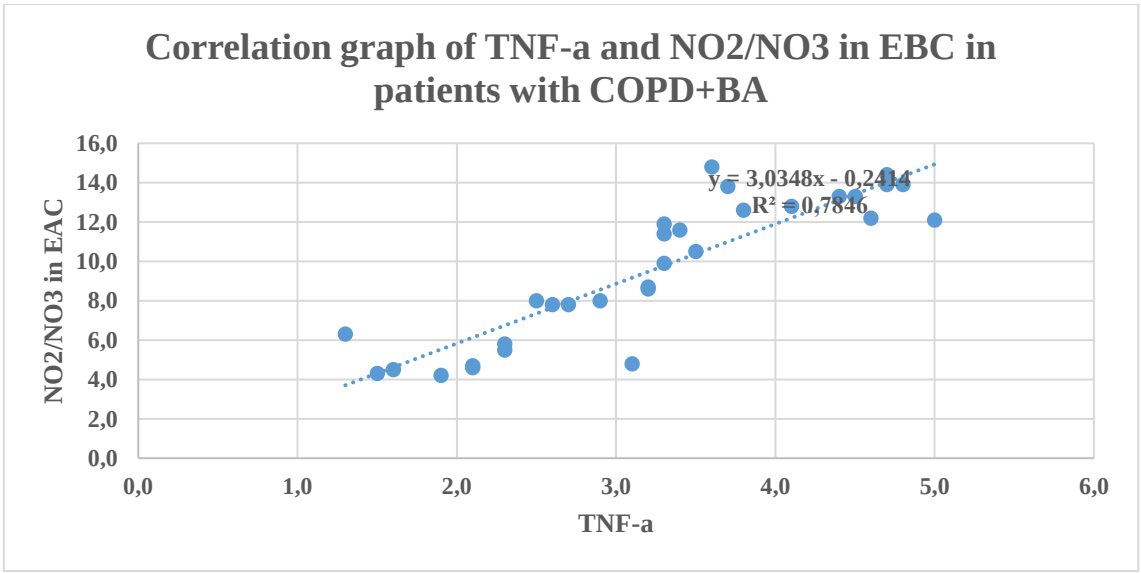


Figure 3.6.22 . Correlation graph of TNF-α and NO2/NO3 in the EAC of COPD+BA patients in the acute stage (P<0.01).

When studying the correlation relationships between TNF - α and the NO 2/ NO 3 ratio in the blood and EAC of patients with COPD + BA in the acute stage , shown in Figures 3.6.21 and 3.6.22, it was noted that on the background of crowded indicators, several points were observed that were at a great distance relative to the trend line when studying indicators in both the blood and EAC of patients with COPD + BA. At the same time, the obtained correlation data ® indicate a high direct correlation between the indicators TNF - α and NO 2/ NO 3 in the blood and EAC of patients with COPD+BA in the acute stage (r=0.84; r=0.89).

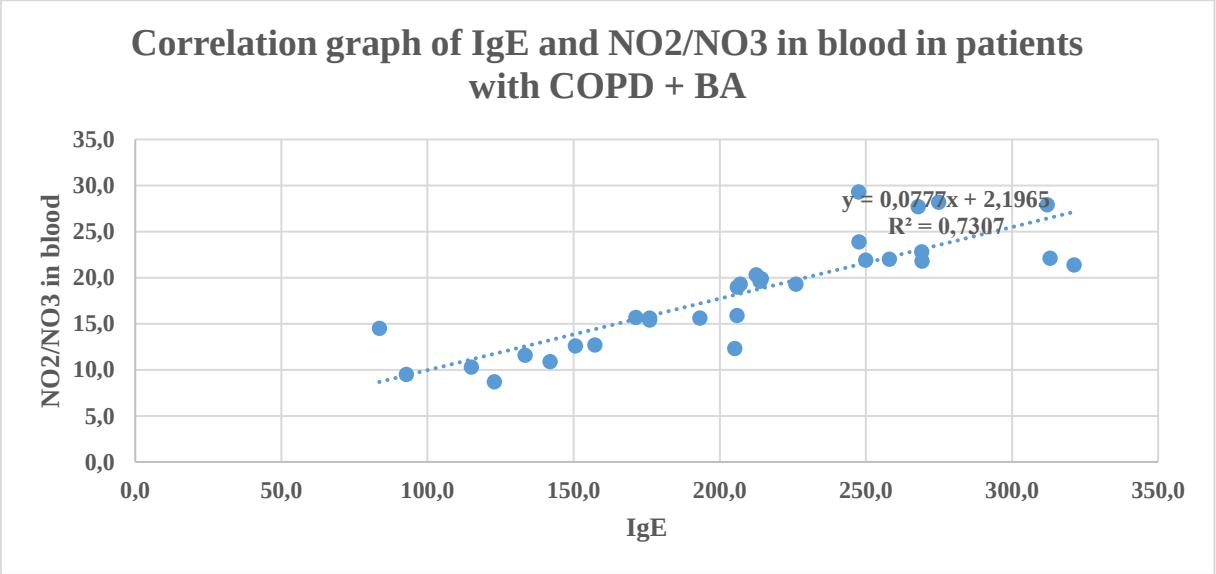


Figure 3.6.24. Correlation graph of IgE and NO2/NO3 in the blood of patients with COPD+BA in the acute stage (P<0.01).

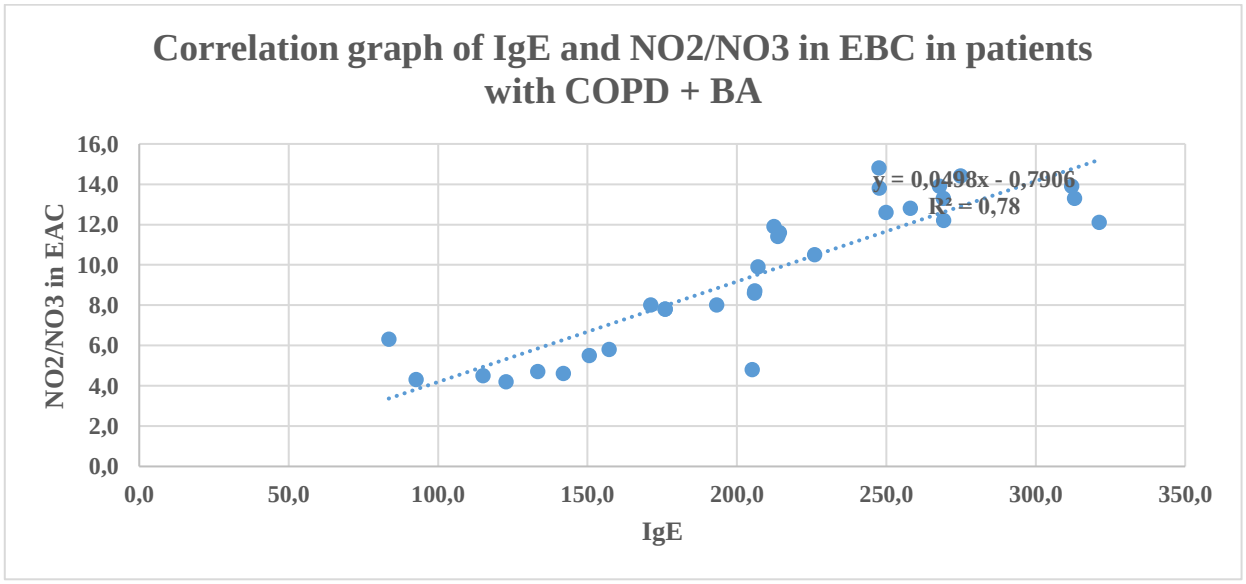


Figure 3.6.24 . Correlation graph of IgE and NO2/NO3 in the EAC of patients with COPD+BA in the acute stage (P<0.01).

The research data shown in Figures 3.6.23 and 3.6.24 show a high uniform crowding of indicators in the form of an almost identical small deviation of points relative to the trend line. The data obtained indicate a very high direct correlation between the indicators IgE and NO 2/ NO 3 in the blood and EAC of patients with COPD + BA in the acute stage (r=0.85; r=0.88), which indicates the validity of using these immunological parameters in the diagnosis and determination of the combined course of diseases.

Based on correlation studies of the indicators IL -4, IL -8, TNF - α , IgE with indicators of endothelial dysfunction in the groups of patients with asthma, COPD and COPD + asthma, the final correlation table was compiled **(Table 3.6.1 and 3.6.2)**

Table 3.6.1.

Correlation matrix of main immunological parameters and NO2 and NO3 in the blood in patients with asthma, COPD and COPD+BA

Indicators	NO 2 and NO 3 in the blood		
	BA (r)	COPD (r)	COPD+BA (r)
IL-4 in blood	0.90	0.80	0.88
IL-8 in blood	0.91	0.81	0.83
TNF-a in the blood	0.89	0.83	0.84
Total IgE in the blood	0.88	0.80	0.85

Table 3.6.2.

Correlation relationships (r) between cytokine parameters, IgE and NO2 and NO3 in EAC in patients with BA, COPD and COPD+BA

Indicators	NO 2 and NO 3 in EAC		
	BA (r)	COPD (r)	COPD+BA (r)
IL-4 in EAC	0.88	0.80	0.89
IL-8 in EAC	0.88	0.80	0.86
TNF-a in EAC	0.89	0.82	0.89
Total IgE in the blood	0.88	0.81	0.88

It is worth highlighting the very high strength of the direct correlation in patients with bronchial asthma between the indicators IL -4, IL -8 and endothelial indicators in the blood, which proved the significant role of immunological indicators in the course of the disease. It is also necessary to note the high strength of direct correlation in patients with asthma, COPD and COPD+BA between other immunological and endothelial parameters, which indicated a high relationship between impaired immunological and endothelial status in patients with chronic respiratory pathologies.

The studies showed that the patients had a disturbance in the immune response, which manifested itself in the overproduction of various interleukins, which had a direct relationship with the clinical picture of the disease. The clear direction of immune metabolism and their severity indicate the important pathogenetic role of immune mechanisms, which leads to a delay in the recovery processes of asthma, COPD and asthma + COPD in the development and progression of changes in the state of the immune and endothelial systems.

CHAPTER 4. INSTRUMENTAL ASSESSMENT OF THE SEVERITY OF BA, COPD AND BA+COPD DEPENDING ON THE SEVERITY OF THE DISEASE

4.1. The state of saturation, forced expiratory volume and peak expiratory flow among patients with asthma, COPD and their combination

Before and after treatment, all patients were prescribed instrumental studies such as pulse oximetry, spirometry, and peak flowmetry. The data obtained were compared between 3 groups of patients, where it was clearly visible that patients with BA and COPD had statistically insignificant differences among themselves, however, it was noted that the saturation among patients with BA was relatively high in comparison with patients with BA + COPD (Figure 4.1.1.).

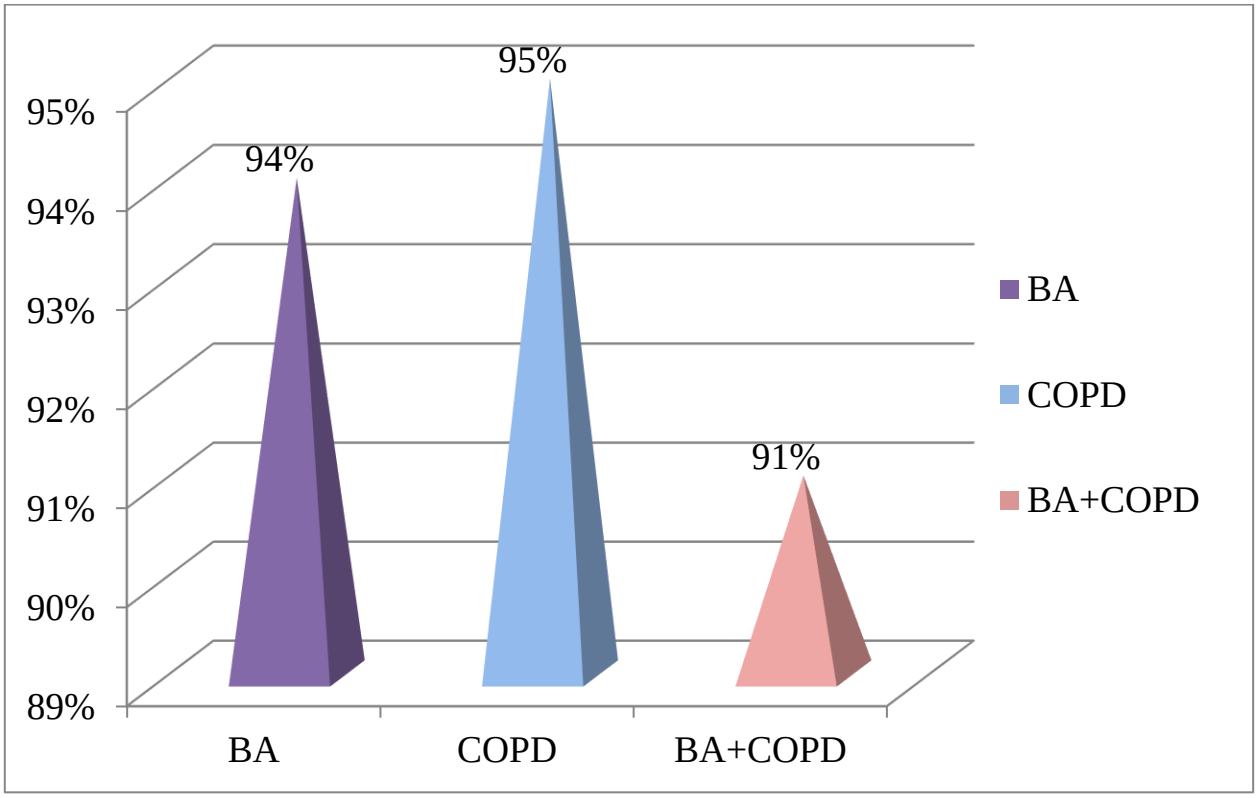


Figure 4.1.1. Comparative characteristics of saturation (SpO2) in patients with asthma, COPD and asthma + COPD during exacerbation

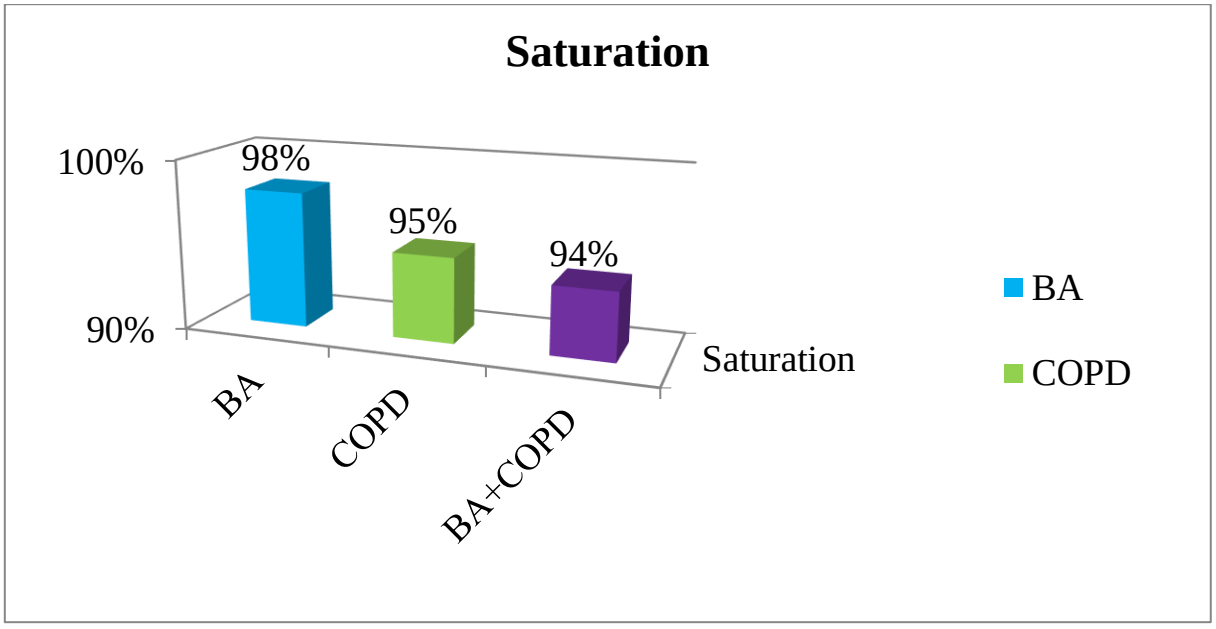


Figure 4.1.2 . Comparative characteristics of the saturation index (SpO2) in patients with asthma, COPD and asthma + COPD during remission.

When comparing saturation indicators among patients with BA and BA+COPD , as well as COPD and BA+COPD, a statistically significant difference in indicators was revealed (P <0.05; P <0.01), in particular among patients with

extremely severe COPD and BA+COPD difference was 3.9±0.2%, and the difference in saturation between patients with severe BA and BA+COPD was 4.7±0.3%.

Upon further examination, all patients underwent peak flowmetry; for this, the patient, after taking the maximum possible deep breath, immediately (without holding the breath at the peak of inspiration) exhales sharply into the peak flow meter. The measurement was repeated 3–5 times, the result was considered the highest PEFR value obtained in l/min. The difference between the results of subsequent measurements should not exceed 40 ml/min. Daily variability of PEFR was calculated by dividing between the maximum ($PEFR_{max}$) and minimum ($PEFR_{min}$) values.

$$(P_{max} - PEFR_{min}) / PEFR_{max} \times 100\% \text{ or}$$

$$(PEFR_{max} - PEFR_{min}) / (PEFR_{max} + PEFR_{min})/2 \times 100\%$$

The final result was taken as the average value over a period of 1–2 weeks.

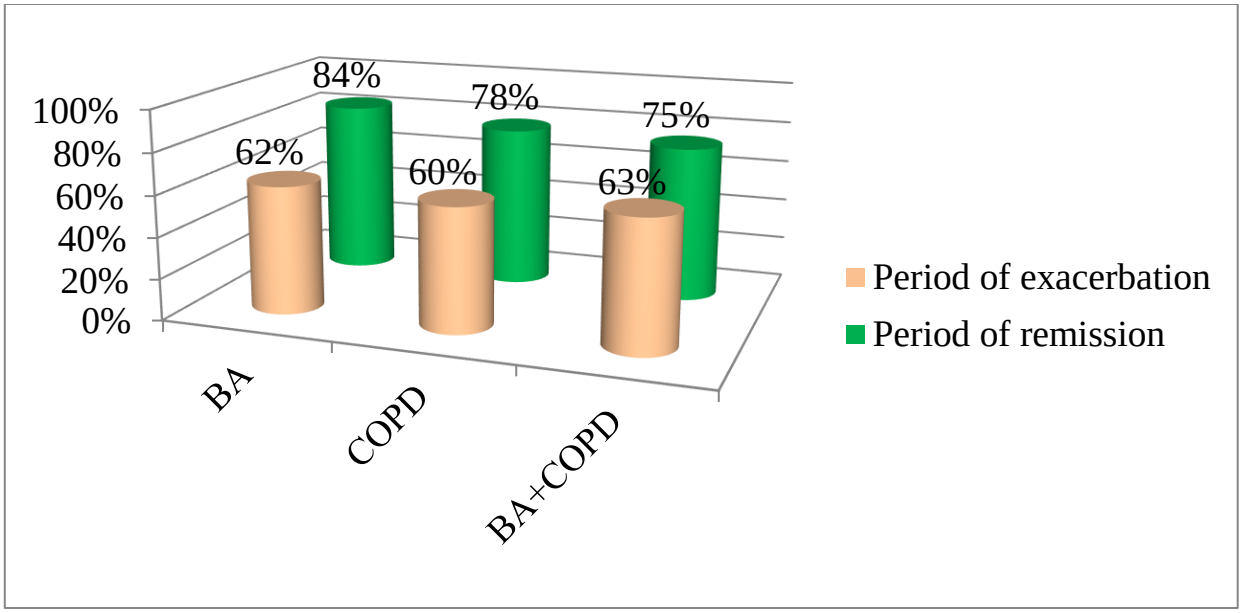


Figure 4.1.3. Comparative characteristics of peak flow metry (PFM) in patients with asthma, COPD and COPD+BA depending on the stage of the disease

In Figure 4.1.3, it can be noted that patients with BA and BA+COPD had high PEFR rates, while there was a statistically significant difference in the rates ($P < 0.01$), which requires timely correction of this condition.

Next, all patients underwent a spirography study in the morning on an empty stomach, and such indicators as VCL%, FEV1%, MEFR %, MEFR 75%, MEFR 50%, MEFR 25% were determined (Table 4.1.1.).

Table 4.1.1.

Spirography indicators among patients with asthma

Asthma severity	vital capacity	FEV1	MEFR 25%	MEFR 50%	MEFR 75%
Intermittent	68.8±3.1	69.2±3.0	52.8±2.3	42.6±1.8	41.6±1.6
Mild persistent	62.6±2.7	63.8±2.4	44.3±2.0	32.6±1.5	28.5 ± 1.4
Moderately persistent	55.5±2.1	58.0±2.8	31.5±1.4	21.7±1.0	17.2±0.8
Heavy	50.2±2.2	53.0±2.3	27.4±1.1	12.7±0.6	9.7 ±0.5

Table 4.1.2

Indicators of spirography among patients with COPD

COPD severity	vital capacity	FEV1	MEFR 25%	MEFR 50%	MEFR 75%
Lightweight	61.5±2.8	58.2±2.1	44.1±1.9	28.7±1.3	25.5±1.2
Average	53.2±2.3	51.2±1.9	29.1±1.3	20.5±1.1	16.2±0.7
Heavy	48.5±2.0	42.3±1.7	24.1±1.0	15.1±0.7	10.2±0.6

Table 4.1.3

Indicators of spirography among patients with asthma + COPD

Severity of asthma + COPD	vital capacity	FEV1	MEFR 25%	MEFR 50%	MEFR 75%
Intermittent	64.5±2.8	65.3±2.7	48.2±2.3	35.1±1.7	37.5 ± 1.8
Mild persistent	57.3±2.4	59.2±3.1	35.3±1.6	25.2±1.2	21.2±1.0
Moderately persistent	48.1±2.4	50.1±2.4	29.4±1.2	18.7±0.9	12.9±0.6
Heavy	38.7±1.8	39.0±1.7	24.1±1.0	13.2±0.6	8.5±0.4

Then all the above studied indicators among patients of the 3 groups were compared with each other (P 1, P 2, P 3) (Table 3.5.6.).

Thus, when studying spirography among patients with BA, it was revealed that among patients with moderate BA, vital capacity was reduced to 55.5%, while among patients with intermittent BA this figure was 53.2% (Table 4.1.2), in addition the indicators FEV1, MEFR 25%, MEFR 50% and MEFR 75% were also reduced, but when comparing these indicators among patients with COPD and BA + COPD, the above indicators were significantly reduced, in particular, among patients with comorbid VC, patients with moderate BA + COPD were equal to 48.1 (Table 4.1.3), FEV1 45.1, MEFR 25% 25.1, MEFR 50% 17.2, MEFR 75% 14.5% (Table 4.1.4).

Table 4.1.4

Comparative characteristics of spirography parameters in patients of the compared groups

Asthma severity	BA	COPD	COPD+BA	P1	P2	P3
vital capacity	55.5±2.1	53.2±2.3	48.1±2.4	> 0.5	<0.05	> 0.5
FEV $_1$	58.0±2.8	51.2±1.9	45.1 ± 2.1	<0.05	<0.01	> 0.5
MEFR 25%	44.3±2.0	31.2 ± 1.4	25.1 ± 1.0	<0.001	<0.001	<0.05
MEFR 50%	32.6±1.5	20.5±1.1	1 7.2 ± 0.8	<0.001	<0.001	<0.05
MEFR 75%	28.5 ± 1.4	16.2±0.7	1 4.5 ± 0.5	<0.001	<0.001	> 0.5

Note: P – reliability of differences between the compared groups, P 1 – reliability of differences between BA and COPD, P 2 – reliability of differences between BA and BA + COPD, P 3 – reliability of differences between COPD and COPD + BA.

State of induced sputum in patients with asthma, COPD and their combination.

During the study we decided to study the content of sputum acquired by alternate inhalation of 3.4 and 5% hypertonic sodium chloride solution using an ultrasonic nebulizer (OMRON NE-U-17, Japan) to perform a cytogram in patients with asthma, COPD and their combination in 5-minute sessions under ERF control, with sequential counting of at least 400 cells in 100 fields of view.

Induced sputum was assessed using a unified method no later than 2 hours after its isolation. Based on the results obtained, 3 types of cellular phenotypes were determined.

1. Lymphocytes;
2. Neutrophils;
3. Eosinophils.

In the group of patients with severe bronchial asthma, an eosinophilic inflammatory biophenotype was detected in 68.9% of cases, neutrophilic biophenophyte in 20.6%, lymphocytic biophenotype of inflammation in 10.3% of cases. In the group of patients with COPD, 57.1% of cases were neutrophilic

biophenotype , lymphocytic the biophenotype was in 31.4%, and only 11.5% had an eosinophilic type of inflammation.

In combined pathology, in most cases (58.1%) a mixed (eosinophilic-neutrophilic) biophenotype of inflammation was observed. The lymphocytic type was observed in 25.8% of cases.

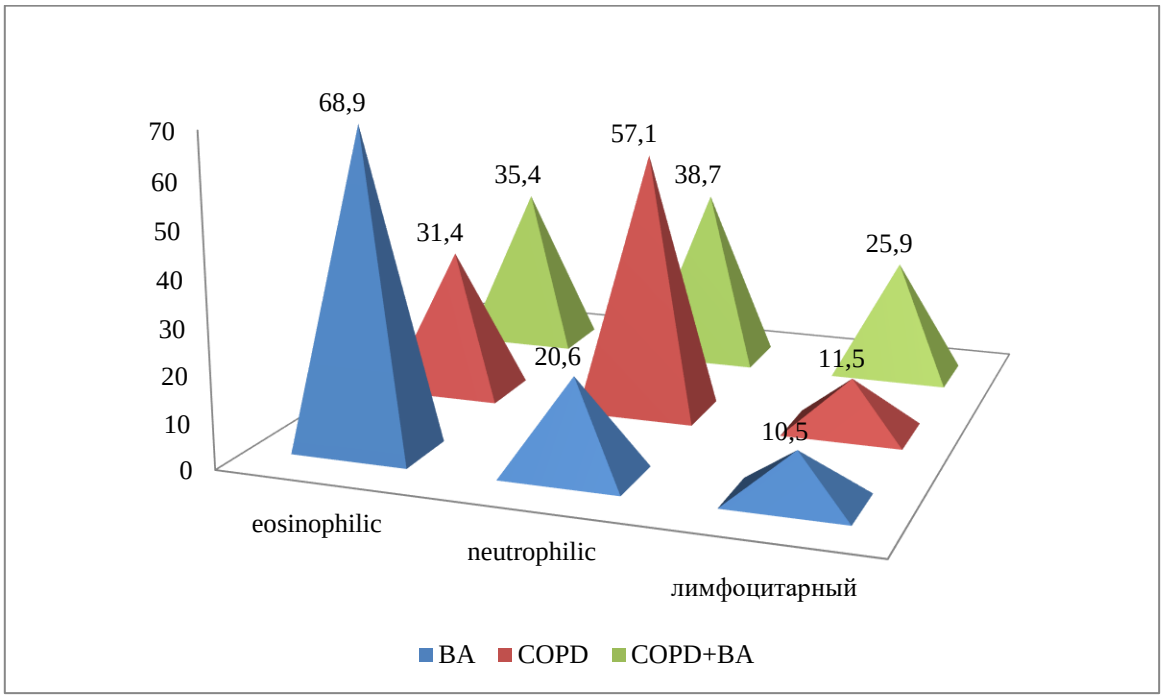


Fig.4.1.1. Assessment of the cellular composition of induced sputum

When studying the average indicators of the cellular composition of induced sputum, the following indicators were revealed: in the group of patients with asthma (n = 35) eosinophils 11.2 ± 2.24%, neutrophils 81.3 ± 16.26% and lymphocytes 11.4 ± 2.28 %, among patients with COPD eosinophils 9.2±1.84%, neutrophils 87.2±17.44% and lymphocytes 44.5±8.9%, and with combined pathology (BA+COPD) a significant increase in eosinophils and neutrophils: eosinophils 12.2±2.44%, neutrophils 88.1±17.62% and lymphocytes 11.0±2.2% (Table 3.5.7).

Table 4.1.7.

Cellular composition / Groups of patients	Eosinophils,%	Lymphocytes,%	Neutrophils,%	P - value
BA	7.1±0.4	11.4±0.6	62.1±3.7	P<0.0 5
COPD	4.2±0.2	44.5±1.8	47.2±2.8	P<0.01
COPD+BA	9.0±0.5	11.0±0.7	74.6±4.9	P<0.01

The results of the study showed that in the group of patients with BA in combination with COPD, a significantly increased level of neutrophils and eosinophils was detected . Patients with COPD had a statistically significant high level of neutrophils (P=0.05).

Thus, in the course of our study it was revealed that patients with concomitant pathology are a high-risk group, since saturation indicators among patients with severe BA + COPD were 70.8 ± 14.16, while patients with BA and COPD had 74.8±14.9; 73.8±14.7, respectively. The indicators VCL%, FEV1%, MEFR %, MEFR 75%, MEFR 50%, MEFR 25% were also more impaired among this category of patients than among patients with asthma and COPD (Table 3.5.6.), and also as already mentioned indicators of the cellular composition of induced sputum were significantly impaired (Table 3.5.7), which confirms the literature sources we studied.

4.2. Program for early and differentiated diagnosis of bronchial asthma, chronic obstructive pulmonary disease and their combinations

A distinctive feature of modern medicine is the priority of modern technologies in the diagnosis and treatment of diseases, which is achieved through modern technical means.

In this regard, we have developed and introduced into clinical practice an electronic computing program to determine the severity of the disease and determine the respiratory function in patients with asthma, COPD, and their combination. This

program is based on the St George's Hospital Questionnaire (SGRQ). The program is designed to improve the early differential diagnosis of asthma, COPD and COPD+BA. Thanks to the SGRQ questionnaire , it is possible to identify indicators of symptom components, disease activity and the impact of the disease on the lifestyle of patients .

When loading the program, a window automatically opens in which a menu displaying the questionnaire is displayed.

After entering the patient's passport data (full name, age, gender, address, diagnosis) into the program for determining the severity of the disease, the questionnaire was filled out - similar to the answers when solving test tasks, into a personal computer. This questionnaire went through a full cycle of language adaptation and was modified when counting components. The questionnaire consists of 3 parts, which assess the frequency and severity of existing symptoms, physical activity and the impact of the disease on the emotional state of the patient. The "Symptoms" component is calculated from positive answers to questions 1-8, the "Activity" component is calculated from questions 11 and 15, and the "Influence" component is calculated from positive answers to questions 9-10, 14.

The sum calculated by answering all questions gives an overall assessment of the patient's health status.

The questionnaire was filled out by the patient himself; if necessary, we asked clarifying and additional questions; there were practically no difficulties during the survey.

After completing the entry of answers to the survey questions and clicking the OK button, a calculation is carried out and a conclusion is drawn : mild degree of the disease (from 0 to 20 points), moderate degree (from 21 to 40 points) and severe degree (from 41 to 60 points).

The grade for this program is assessed based on the following criteria. Mild disease from 0-20 points, moderate degree from 21-40 points and severe degree from 41-60 points.


ПРОГРАММА ДЛЯ ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКИ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНИ ЛЕГКИХ И БРОНХИАЛЬНОЙ АСТМЫ
0
1.Сколько раз в году у вас появляется кашель?
Нет
Однократно
Редко
Иногда
Часто
2.Как часто у вас начинает отделятся мокрота (в течении года)?
Нет
Однократно
Редко
Иногда
Часто
3.Проявляется ли у вас одышка в течении года?
Нет
Однократно
Редко
Иногда
Часто
4.Как часто у вас бывают приступы хриплого дыхания?
Нет
Однократно
Редко
Иногда
Часто
5.Сколько раз в течение года у вас бывают тяжелые приступы или обострения заболеваний дыхательной системы?
Ни одного приступа
1 приступ
2 приступа
3 приступа
Более 3 приступов
6.Сколько длился самый тяжелый приступ? (если тяжелых приступов не наблюдалось, сразу переходите на 7 вопрос)
Менее суток
1-2 дня
3 дня и более
Неделю или больше
7.Сколько, в среднем, в неделю у Вас было дней, когда Вас не беспокоили органы дыхания (когда заболевание дыхательной системы проявлялось мало) в течение года?
Все дни были благоприятными
Почти все дни были благоприятными
3-4 благоприятных дней
1-2 благоприятных дней
Благоприятных дней не было
8.Как бы Вы описали состояние Вашей дыхательной системы?
Не создает проблем
Создает мне немного проблем
Создает мне довольно много проблем
Это главная моя проблема
9.Влияет ли ваша болезнь на вашу работу?
Проблемы с легкими не влияют на мою работу
Проблемы с легкими заставили меня прекратить работать
Проблемы с легкими мешают моей работе или заставили меня поменять работу.
10.Вопросы о видах деятельности, которые в настоящее время обычно вызывают у Вас одышку.
При занятиях спортом или подвижными играми
При подъеме на один лестничный пролёт
При умывание или одевание
При подъеме в гору, на возвышенность
При ходьбе по дому
В покое сидя или лежа
11.Дополнительные вопросы о кашле и одышке, беспокоящих Вас в последнее время:
Я быстро утомляюсь и теряю силы
Я задыхаюсь, когда наклоняюсь
Я устаю от кашля
Кашель или одышка мешают мне спать
Я задыхаюсь, когда разговариваю
Кашель причиняет мне боль
12. Вопросы о других проблемах, доставляемых Вам заболеванием дыхательной системы в последнее время:
Мне кажется, что все действия требуют слишком много усилий
Я чувствую, что не могу контролировать мое заболевание дыхательной системы
Физические трудности небезопасны для меня
Я пугаюсь или даже паникую, когда не могу продышаться, перевести дыхание
Я стал обессиленным или инвалидом из-за этого заболевания
Мое заболевание дыхательной системы причиняет неудобства моей семье, друзьям или соседям
Я не ожидаю улучшения течения своего заболевания дыхательной системы
Мой кашель или проблемы с дыханием смущают меня на людях
13.Вопросы о Вашем лечении (если Вы не получаете лечение по заболеванию дыхательной системы, то переходите сразу к вопросу 15).
Мое лечение нарушает мой привычный образ жизни.
Я стесняюсь принимать лекарства, пользоваться ингаляторами в присутствии других людей
Лечение вызывает у меня неприятные побочные эффекты
Мое лечение не особенно мне помогает
14.Выберите предложение, которое лучше всего описывает влияние легочного заболевания на Вашу жизнь.
Я могу делать все, что мне нравится
Не позволяет большинство дел, которыми мне бы хотелось заниматься
Я вынужден прекратить одно-два дела, которыми мне хотелось заниматься
Я вынужден прекратить заниматься всем, чем бы мне хотелось заниматься
15.Когда у вас начались проблемы с дыхательной системой?
Это у меня с детства.
После 40 лет и старше (я курильщик со стажем.)
После сильного переохлаждения.
OK
ПРОГРАММА ДЛЯ ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКИ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БО
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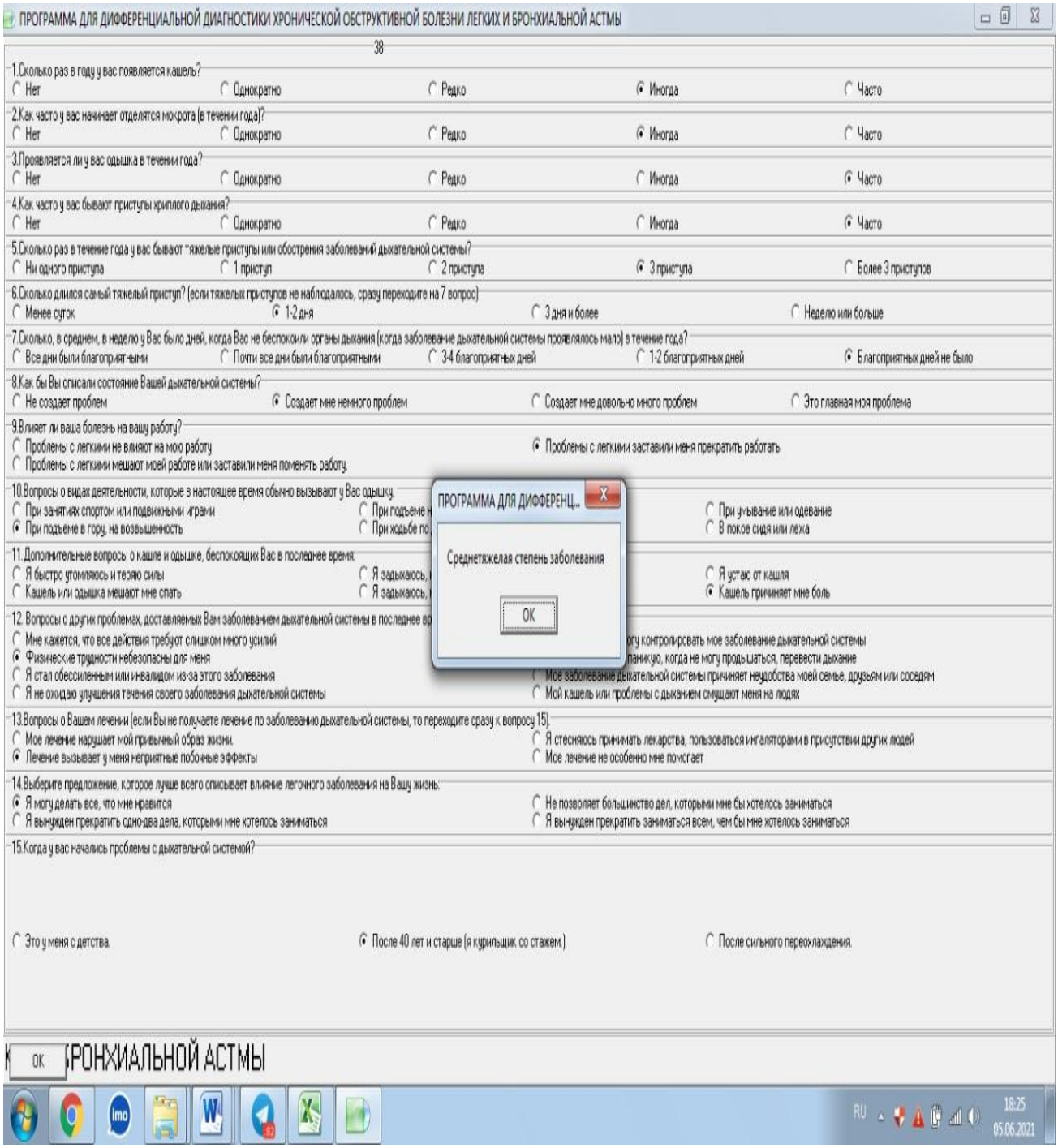


Figure 4.1. Program for differential diagnosis of COPD, asthma and their combinations.

Using this program, it was revealed that in the group of patients with BA, 3 (8.57%) patients were diagnosed with a mild degree of the disease, 5 (14.28%) patients with a moderate degree of the disease and 27 (77.1%) patients with a severe degree of the disease (Figure 4.2).

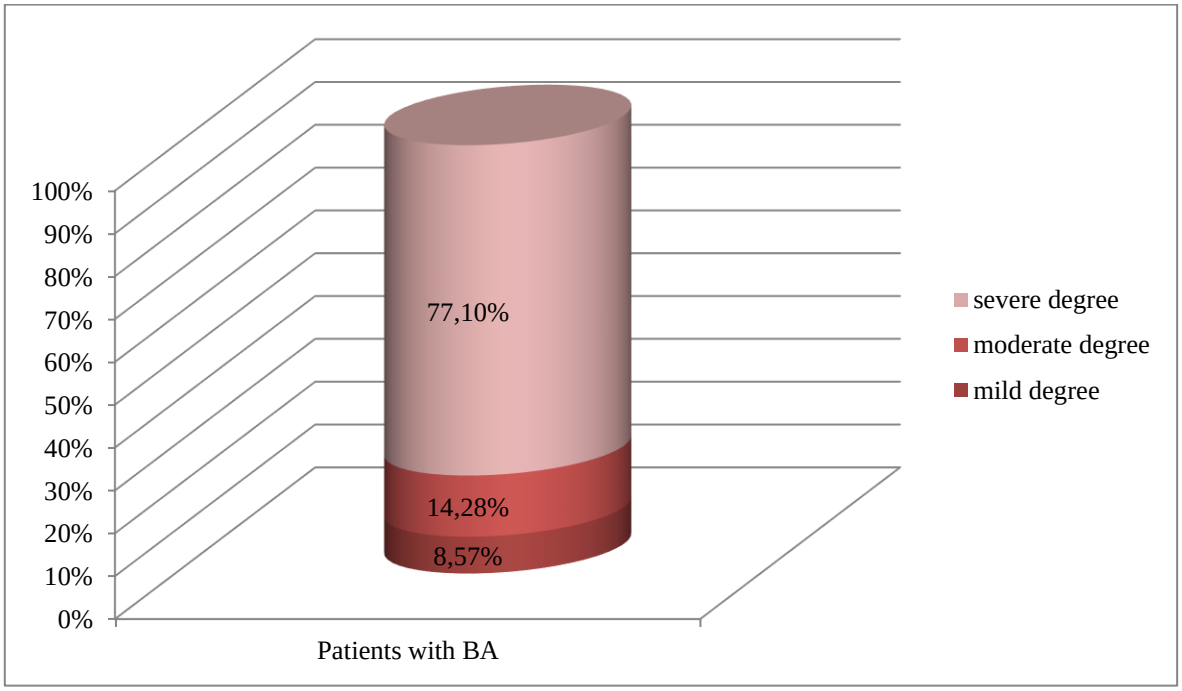
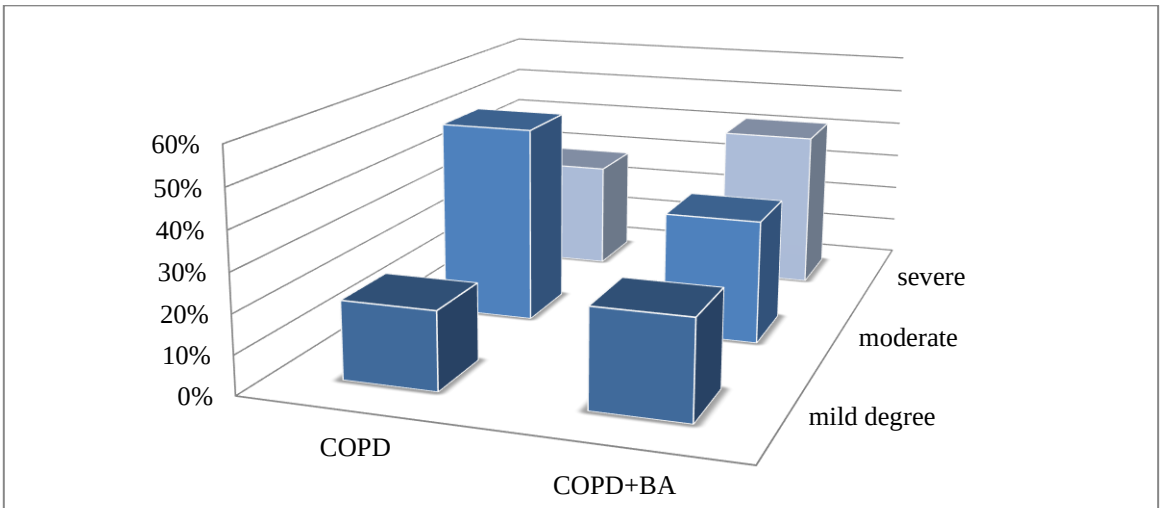


Figure 4.2. Analysis of patients with asthma according to the program of differential diagnosis of COPD, asthma and their combinations.

When conducting a study in a group with COPD (n = 35), 7 (20%) patients had mild disease, 18 (51.4%) patients had moderate disease, and 10 (28.6%) patients had severe disease (Fig. 4.3).



	COPD	COPD+BA
mild degree	20%	25%
moderate	51,40%	32%
severe	28,60%	41,90%

Figure 4.3. Analysis of patients with COPD and BA+COPD according to the program of differential diagnosis of COPD, BA and their combinations.

In the group with comorbid BA and COPD (n =31), 8 (25%) patients with mild disease, 10 (32%) with moderate disease, and 13 (41.9%) patients with severe disease were identified (Fig. 4.3).

The analysis of the use of the program for the differential diagnosis of COPD, BA and BA + COPD showed that among patients with BA, severe BA predominated (77.1%), with COPD the average degree was more often observed (51.4%) and with a combination of BA + COPD more often there were severe patients (41.9%), which indicates later hospitalization of this category of patients and the need for optimal corrective measures

Thus, the use of a program for differential diagnosis of COPD, asthma and their combinations to determine the degree of severity makes it possible to provide timely, highly qualified assistance**.**

CONCLUSION

Thus, the relevance of the above problem is associated with its increasing importance in pulmonological practice due to the increase in severe forms of BA and COPD. However, despite the results of many studies, significant questions about the clinical and laboratory features of the diseases being compared, both in isolated cases and in their combined course, in the pathogenetic and applied aspects remain unresolved. All this creates difficulties in the practical work of both general practitioners and highly specialized specialists.

The role of the laboratory and instrumental studies we studied in BA and COPD has not been studied in many publications and requires detailed consideration. Although studying the connection and characteristics of inflammatory and immune processes in asthma, COPD and their combinations will help clarify questions about these pathologies, which would help the early detection of these conditions and the provision of timely qualified assistance.

The main goal of this study was to improve diagnostic procedures for BA and COPD based on examination and in-depth study of immune and inflammatory processes in these diseases and to develop an algorithm for early and differentiated diagnosis of bronchial asthma, chronic obstructive pulmonary disease and their combinations (if they are comorbid) .

The distribution of severity of patients with asthma and COPD is based on functional criteria, in particular spirometry, peak flowmetry and saturation parameters.

The patients with asthma we selected were in the acute stage. The total number of patients was 35 people, of which 2 people (5.7%) had a mild persistent course of the disease, 4 people (11.4%) had a moderate degree, 29 people (82.8%) had a severe degree of the disease. The average age of patients with asthma was 47.14 ± 9.4 years.

Among 35 patients with COPD, stage 1 of the disease was detected in 3 people (8.5%), stage 2 in 4 people (11.4%), stage 3 in 17 people (48.6%), 11 people (31.4%) had stage 4 of the disease. All patients, like those with asthma, were in the stage of exacerbation of COPD. The average age of the patients was 61.4 ± 12.28 years.

Of the 121 patients we studied, 101 patients in the pulmonology departments were classified into the group of asthma, COPD (BA+COPD) with an average age of 73.7±9.3 years.

Clinical, laboratory, immunological and instrumental comparisons were based on taking into account the severity of BA and COPD, taking into account the phase of the disease. And it is this clinical and immunological component that served as the matrix for the distribution and assessment of the severity of laboratory and instrumental indicators. In this regard, the laboratory changes we obtained , observed in asthma and COPD, acquired the meaning of corresponding laboratory syndromes, taking into account general inflammatory and immune processes. In general, according to the results obtained, changes in laboratory parameters for BA and COPD were noted in 45.7% and 51.4% of patients, respectively . Laboratory syndromes occurred separately, but often in combination with each other. In addition, a combination of three syndromes was noted, which in turn indicated a severe course of the disease. Assessing the severity of laboratory abnormalities identified during the initial examination of hospitalized patients had not only diagnostic (severity of exacerbation) but also prognostic significance.

In general, the influence of the severity of the disease on deviations of laboratory parameters from the norm that we identified was quite natural . The following laboratory studies of these syndromes in BA and COPD turned out to be quite informative: leukocytosis, eosinophilia , accelerated ESR, hyperimmunoglobulinemia E blood.

In patients with asthma and COPD, the rate of inflammatory disorders was 54.3% and in patients with asthma 48.5%, which was minimal and corresponded to the literature sources we studied. The proportion of immune changes differed significantly, prevailing in patients with asthma (55.9%) and in patients with COPD was 40.6%, and in the combined group - 45.8%. The involvement of all laboratory syndromes in the process was observed in patients with asthma in 15.4%, in COPD in 13.1%, and in patients with a combination of diseases in 29.2%. Moreover, as their frequency increased, an increase in this indicator was observed : from 9.3% with mild

BA to 35.7% with severe BA, with COPD - from 9.4% at stage 1 to 18.4% at stage 4 . In contrast, laboratory parameters of immune status differed significantly between asthma and COPD. This was mainly due to the frequency of hyperimmunoglobulinemia E and eosinophilia , especially in sputum: in asthma they were 2 times higher than in COPD ($p < 0.01$).

Comparison approves the results of laboratory assessment of the “mirror” for BA and COPD the correctness of what we discovered two leading pathological processes that are present in these diseases , but specifically inflammatory and immune.

Taking into account the differences in the pathogenesis of BA and COPD, as well as the resulting pathological conditions, reflecting their influence on the main inflammatory processes in these pathologies.

In the hierarchy of laboratory tests that have differential diagnostic value, priority is given to assessing the status of the general inflammatory syndrome in COPD, primarily the characteristics of the immune status, in particular for BA and, ultimately, the severity of metabolic disorders [39].

Thus, including within the framework of classical methods , coordinated with the clinic and anamnesis of patients with asthma and COPD, is carried out appropriately by multidisciplinary painstaking diagnostic laboratory testing that allows detect features of the laboratory picture given the data diseases .

The main characteristics of the leading laboratory manifestations of the inflammatory reaction in patients with bronchial asthma were a sharp deviation in laboratory parameters (Chapters 3 and 4). This approves that the worsening of the course with a combination of asthma and COPD is associated with the complication and severity of laboratory joint inflammatory pathology and urgently requests early diagnosis

A significant frequency of some biochemical disorders is more pronounced in the combined group of patients than in patients with isolated forms of BA and COPD. This may be due not only to the ongoing effects of lung disease, but also to extrapulmonary factors, that is, the older age of patients with diabetes and

atherosclerosis. The immunogram formula for BA in combination with COPD is characterized by indicators similar to those for isolated forms of the disease.

The leading component in this study was hyperimmunoglobulinemia E, which was twice as high as in patients with isolated COPD, highlighting the influence of asthma.

Thus, laboratory characteristics describing the main disorders in COPD, asthma and their combination (general inflammation, metabolic and immune changes) not only do not contradict early studies and conclusions , but also confirm them in certain sections of our work.

Inflammatory, immune and metabolic processes are closely interrelated and have a systemic nature in asthma and COPD and are characterized by certain laboratory and clinical abnormalities that are subject to careful study. The frequency of changes in inflammation indicators in bronchial asthma was 47.3%, in COPD - 50.1%, and in the simultaneous presence of both pathologies - 89.4%, which is explained by the similarity of the processes in these diseases . BA and COPD differ in the presence of common changes in inflammatory processes , in fact there is a greater correlation between them depending on the severity, phase of the disease and the combination of concomitant diseases.

However, the severity and nature of laboratory changes depend on the specificity of pathogenetic factors . Basic laboratory parameters in patients with BA and COPD can be influence more on the prognosis of this pathology, as well as to diagnose these diseases in the early stages, especially when they occur with immune reactions.

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FOR NOTES

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