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THE PROCESSES OF INFLAMMATION AND FIBROSIS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

T.A. Pertseva,
L.I. Konopkina,
D.S. Koval,
Yu.V. Guba

SE «Dnipropetrovsk medical academy of Health Ministry of Ukraine»
Department of internal medicine 1
V. Vernadsky str., 9, Dnipro, 49044, Ukraine
ДЗ «Дніпропетровська медична академія МОЗ України»
кафедра внутрішньої медицини 1
(зав. – д. мед. н., проф., Л.І. Конопкіна)
вул. В. Вернадського, 9, Дніпро, 49044, Україна
e-mail: dsmihailichenko@gmail.com

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Ключевые слова: *хроническое обструктивное заболевание легких, системное воспаление, фиброзирование*

Abstract. The processes of inflammation and fibrosis in patients with chronic obstructive pulmonary disease. Pertseva T.A., Konopkina L.I., Koval D.S., Guba Yu.V. *The aim of the study was to determine the categories of COPD patients with a predominance of fibrotic or inflammatory processes. The study included 37 stable COPD patients (men – 33 (89.2%), women – 4 (10.8%), mean age – 63.5±1.18 years, the level of forced expiratory volume for the first second after the test with bronchodilators (FEV_{1post}) – 46.7±5.81% of the proper value). To determine the categories of COPD patients with a predominance of inflammation or fibrosis, a cluster analysis was performed. For this purpose the most important indicators from a clinical point of view were selected: the number of exacerbations over the past year, dyspnea severity according to the mMRC scale, the level of FEV_1 post and reversibility level in absolute values, systemic inflammation markers levels (CAA, C-RP) and profibrotic cytokine TGF-β_1. Thus, according to the results of cluster analysis, two categories of patients were identified. The first category – COPD patients with a predominance of the inflammatory process with low dyspnea severity, high functional indicators (FEV_1 >50% of the proper value), high airway reversibility level, low level of profibrotic cytokine TGF-β_1, high levels of systematic inflammation markers (C-RP and CAA). The second category – COPD patients with a predominance of the fibrosis process, with a high dyspnea severity, low functional indicators (FEV_1 ≤50% of the proper value), low airway reversibility level, low levels of systematic inflammation markers (C-RP and CAA), and high profibrotic cytokine TGF-β_1 levels. The prevalence of inflammatory processes was observed mainly in COPD patients, who belong to clinical group C; the prevalence of fibrotic processes – mainly in patients of clinical group B.*

Реферат. Процессы воспаления и фиброзирования у больных хроническим обструктивным заболеванием легких. Перцева Т.А., Конопкіна Л.И., Коваль Д.С., Губа Ю.В. *Целью исследования было определить категории больных ХОЗЛ с превалированием процессов фиброзирования или воспаления. В исследование было включено 37 больных ХОЗЛ в стабильную фазу патологического процесса (мужчин – 33 (89,2%), женщин – 4 (10,8%), средний возраст – 63,5 ± 1,18 года, уровень объема форсированного выдоха за первую секунду после пробы с бронхолитиками ($ОФВ_{1пост}$) – 46,7 ± 5,81% должной величины). С целью определения категорий больных ХОЗЛ с превалированием процессов воспаления или фиброзирования был проведен кластерный анализ. Для этого были выбраны наиболее важные с клинической точки зрения показатели: количество обострений за прошлый год, выраженность одышки по шкале mMRC, уровень $ОФВ_{1пост}$ и прирост $ОФВ_1$ в абсолютных величинах, уровни маркеров системного воспаления (САА, С-РП) и профибротического цитокина ТФР-β_1. Согласно результатам кластерного анализа были выделены две категории больных. Первая категория – больные ХОЗЛ с преобладанием процесса воспаления с низкой выраженностью одышки, высокими функциональными показателями ($ОФВ_1$ > 50% должной величины), высоким уровнем обратимости бронхообструкции, низким уровнем профибротического цитокина ТФР-β_1, высокими уровнями маркеров системного воспаления (С-РП и САА). Вторая категория – больные ХОЗЛ с преобладанием процессов фиброзирования с высокой выраженностью одышки, низкими функциональными показателями ($ОФВ_1$ ≤ 50% должной величины), низким уровнем обратимости бронхообструкции, низкими уровнями маркеров системного*

воспаления (С-РП и САА), высоким уровнем профибротического цитокина ТФР-β1. Превалирование процессов воспаления наблюдалось преимущественно у больных ХОЗЛ, которые относятся к клинической группе С; превалирование процессов фиброзирования – преимущественно у больных ХОЗЛ клинической группы В.

Fibrosis and inflammation are key links in the pathogenesis of chronic obstructive pulmonary disease (COPD). First of all, COPD is characterized by a chronic inflammatory process which in the early stages of the disease may be reversible. Without excluding etiological factors and in the absence of proper treatment, the inflammation persists and becomes permanent. The main localization of inflammation is the small airways but it can be quite pronounced in the large bronchi, and in the pulmonary parenchyma, and in the pulmonary vessels [4, 13]. As the disease progresses, the inflammatory process becomes systemic with an increase in the levels of some markers of inflammation in the peripheral blood [3, 11].

Fibrosis, which is a consequence of chronic inflammation, leads to morphological changes in all structures of the bronchi which, in turn, cause functional changes. According to modern ideas, airway remodeling begins quite early – during the first year of persistent inflammatory process [9, 10].

In recent years, more and more attention is paid to personalized therapy of patients with COPD, which is usually chosen taking into account the clinical manifestations of the disease and the levels of functional indicators. However, since fibrosis and inflammation are the main pathogenetic processes that lead to irreversible changes in lung tissues, the choice of basic therapy should take into account the prevalence of a pathological process. Determination of this prevalence at different stages of the disease can be done by assessing the levels of serum biomarkers of fibrosis and inflammation [1, 7, 8, 15].

C-reactive protein (C-RP) remains one of the markers of inflammation available for determination in clinical practice. Although it is a non-specific, it is a sensitive clinical and laboratory indicator of inflammation which is synthesized in hepatocytes [11]. Another sensitive marker of inflammation in COPD is serum amyloid A (SAA), which, in contrast to C-RP, is produced not only in the liver but also directly in the inflammatory focus [6].

Of interest is also the possibility of non-invasive diagnosis of fibrosis of the lung tissue and bronchial wall using serum biomarkers. Thus, the transforming growth factor-β1 (TGF-β1) is one of the main factors leading to structural changes in the bronchial wall and the appearance of an irreversible component of airway obstruction [9, 13].

There is a small amount of data in the literature comparing the nature and severity of clinical manifestations of COPD, on the one hand, and the levels of serum biomarkers of fibrosis and inflammation, on the other [10].

Thus, the aim of our study was to establish the categories of patients with COPD according to the prevalence of markers of systemic inflammation or markers of fibrosis.

MATERIALS AND METHODS OF RESEARCH

We examined 37 patients with COPD with II-IV degree of ventilation disorders according to the GOLD classification [9] (clinical group B – 21 people (56.8%), clinical group C – 11 people (29.7%), clinical group D – 5 people (13.5%)) in the stable phase of the pathological process (men – 33 (89.2%), women – 4 (10.8%), mean age – 63.5±1.18 years, the level of forced expiratory volume in the first second after the test with a bronchodilator (FEV_{1post}) – 46.7±5.81% of the appropriate value.

The formulation of the clinical diagnosis of COPD was performed in accordance with international and national recommendations [1].

All subjects agreed to participate in the study.

Prior to inclusion in the study, all patients were in the stable phase of the disease for at least two months. None of the patients had severe exacerbations of COPD during the last year.

Criteria for exclusion of patients from the study were:

1) refusal to participate in the study;

2) the presence of bronchial asthma or other diseases with bronchoobstructive syndrome;

3) the presence of severe clinically significant cardiovascular pathology in the anamnesis and/or at the time of examination, which may lead to an increase in both markers of systemic inflammation and markers of fibrosis, in particular acute myocardial infarction, acute cerebrovascular accident;

4) liver disease (hepatitis, cirrhosis, severe liver failure) in the anamnesis and/ or at the time of examination, as they are characterized by an increase in the level of the marker TGF-β 1 in the serum;

5) increase in liver enzymes by more than 2.5 times, as high levels of liver enzymes indicate the presence of liver disease, which can lead to increased levels of TGF-β 1;

6) history of kidney disease and/or at the time of examination, in particular CKD, which may lead to increased levels of CAA and C-RP;

7) the presence of oncological diseases in the anamnesis and / or at the time of examination, which may lead to an increase in the level of CAA;

8) injuries and operations suffered during the last two years;

9) abuse of alcohol and/or drugs.

Thus, the patients included in the study did not have concomitant pathology that could affect markers of systemic inflammation or fibrosis.

Examination of patients included evaluation of complaints, including the severity of dyspnea by the mMRC scale (The Modified Medical Research Council Dyspnea Scale (mMRC)), medical history and physical examination. To determine the ventilatory function of the lungs, spirometry was performed on a "Master Screen Body/Diff" device ("Jaeger", Germany) with an estimate of the forced exhalation volume in the first second (FEV_1), forced vital capacity of the lungs (FVC), the ratio of FEV_1/ FVC before and after the test with a bronchodilator (salbutamol 400 mg), an increase in FEV_1 [5, 14].

To determine the severity of systemic inflammation in all subjects, the plasma level of C-RP (mg/l) was measured by immunoturbodimetric method and serum CAA level (pg/ml) by enzyme-linked immunosorbent assay. To determine the severity of the fibrosis process in all patients, the serum level of fibrosis marker TGF-β1 (ng/ml) was measured, which was determined by enzyme-linked immunosorbent assay. Collection of biological material was performed in the morning on an empty stomach [4, 6, 13].

The obtained results were processed using biometric analysis methods using the program "STATISTICA 6.1" ("StatSoftInc.", Serial N AGAR909E415822FA). The differences were assessed according to the criteria of Student, Mann-Whitney and Pearson. Statistical methods included parametric and nonparametric. The analysis of indicators with normal distribution was performed according to the mean value and the error of the mean, with abnormal distribution - according to the median and quartiles (Me [25-75]). Cluster analysis was used to determine the categories of patients with COPD with a predominance of fibrosis or inflammation [2]. Differences between groups at $p<0.05$ were considered significant.

RESULTS AND DISCUSSION

In order to determine the categories of patients with COPD with a predominance of inflammation or fibrosis, a cluster analysis was performed. For this purpose, the most clinically important indicators were selected: the number of exacerbations over the past year, the severity of dyspnea by the mMRC scale, FEV_1post levels and FEV_1 increase in absolute values, levels of systemic inflammatory markers CAA, C-RP and profibrotic cytokine TGF-β1.

Because the studied traits are measured in different units, the absolute values were standardized. Each variable had a mean (0) and standard (1) deviation. Hierarchical classification was chosen for the formation of clusters, as a rule of pooling – the method of single communication, as a measure of proximity – Euclidean distance. Tree-like clustering was carried out according to Ward's clustering strategy. The hierarchical cluster tree demonstrates the mechanism of sequential pooling of patients of two classes into one consecutive, indicating the distances between them. To determine the threshold distance, a diagram of the pooling process was used, which showed that the refractive point falls on the 35th clustering step, and the distance of pooling is 12. The number of clusters into which all patients were divided was determined by the formula: (n-m), where n is the total number of observations, and m is the step of the refractive point. Thus, the number of clusters was 2 (37-35=2).

The correctly chosen number of clusters was confirmed by constructing a dendrogram (Fig. 1). At the threshold distance 12 there are two intersections of the perpendicular with the "branches" of the dendrogram. The number of intersections determines the number of clusters, and the objects below the truncated branch are the composition of the clusters.

After forming a hypothesis to determine the number of clusters, the k-means method was used. The clustering algorithm showed that patients who belonged to different clusters had a significant difference between the levels of indicators ($p<0.05$), which indicates the correctness of the found cluster solution. According to cluster analysis, a significant difference was found. To visualize the differences between the indicators, their linear graphs were constructed (Fig. 2).

In order to determine those clinical features of COPD that are most consistent with the prevalence of systemic inflammation or fibrosis, it was appropriate to determine the level of clinical, functional and laboratory parameters in each cluster. No age and gender differences were found in the clusters. At the same time, they differed significantly in clinical and functional parameters and levels of biomarkers (Table).

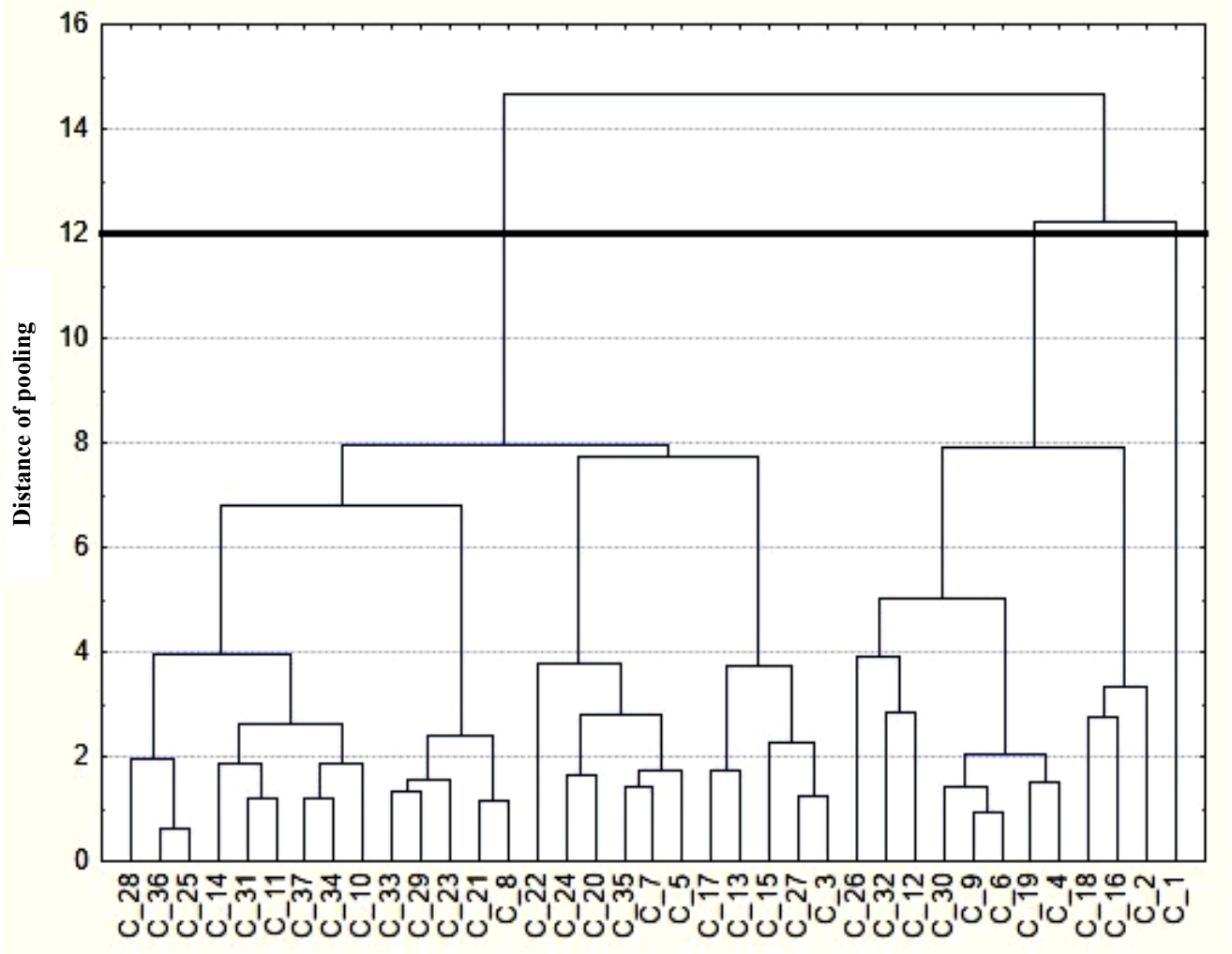

Fig. 1. Hierarchical tree

Cluster 1 included patients with relatively mild bronchoobstruction ($FEV_{1post.}$ ≥50% of the appropriate value), a high level of its reversibility (≥200 ml), low severity of shortness of breath (0 – 1 point by the mMRC scale), low levels of profibrotic cytokine TGF-β ≤6.0 ng/ml). At the same time, these patients had a high frequency of mild exacerbations (≥2 per year) and a significant severity of systemic inflammation both in terms of C-RP (>5.0 mg/l) and CAA levels (>500 ng/ml).

Cluster 2 included patients with more severe bronchoobstruction (FEV1post. ≤50.0% of the appropriate value), low reversibility (<200 ml), significant severity of shortness of breath (≥2 points by the mMRC scale), with a low frequency of mild exacerbations (≤1 per year) and low severity of systemic inflammation both at the level of C-RP (<5.9 mg/l) and at the level of CAA (<400.0 ng/ml). At the same time, these were patients with high levels of the profibrotic cytokine TGF-β1 (>6.0 ng/ml).

Thus, according to the results of cluster analysis, two categories of patients were identified: the first – with a predominance of inflammatory processes; the second - with a predominance of fibrosis processes.

When comparing the individual data obtained in the clusters and comparing them with the current classification of COPD by clinical groups [1], it was found that cluster 1 included mainly patients of clinical group C (10 (83.3%) people), cluster 2 – mainly patients of clinical group B (20 (80.0%) people). Patients of clinical group D were almost evenly distributed between the two clusters (2 patients entered cluster 1, 3 – cluster 2), although their total number was low and did not significantly affect the results of the study.

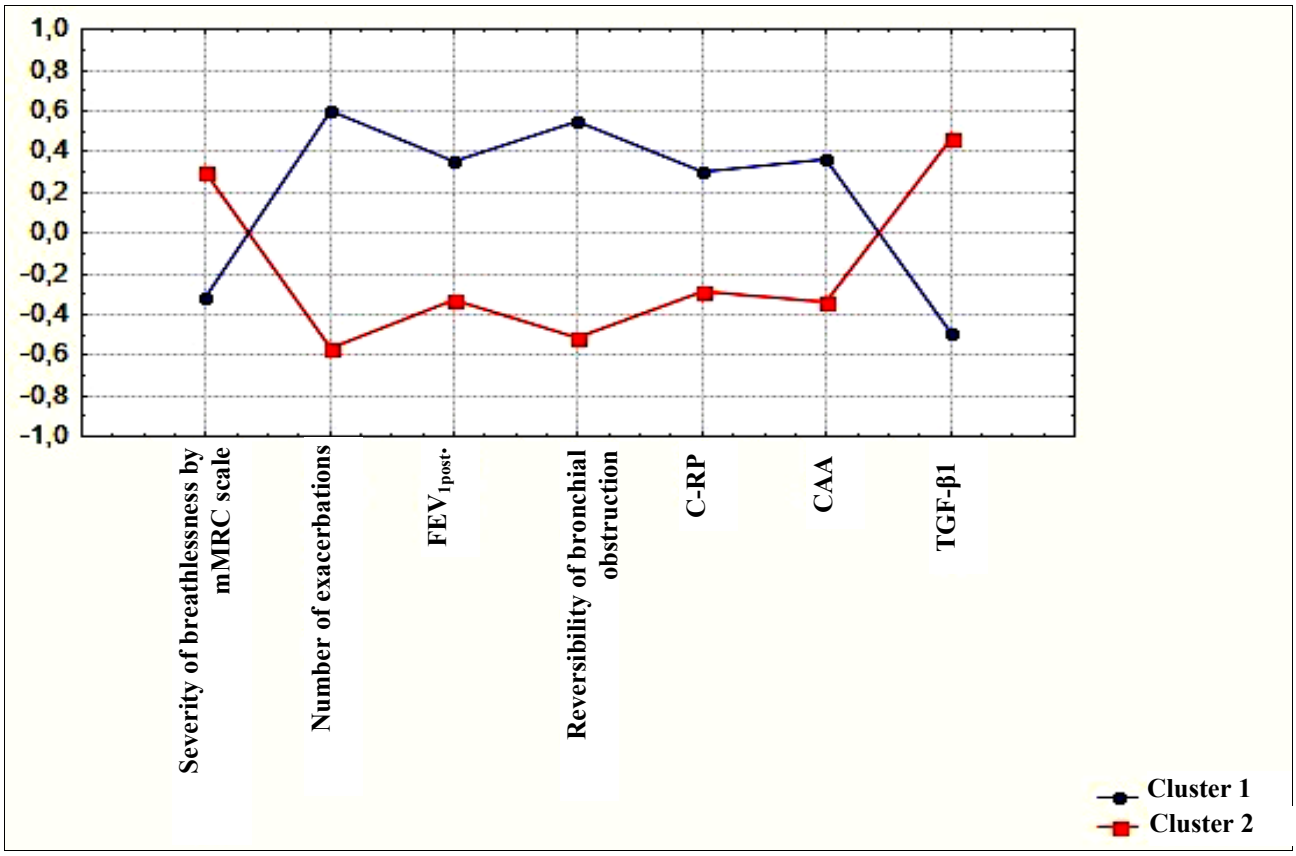

Fig. 2. Clusters of patients with COPD according to clinical and anamnestic data, indicators of lung ventilation function, markers of inflammation and fibrosis

Determining the categories of patients with COPD with a predominance of inflammation or fibrosis by determining the levels of markers of systemic inflammation (C-RP, CAA) and fibrosis (TGF-β1) allows to obtain the most reliable data for individualization of management tactics. Thus, according to some studies [3, 12], the use of inhaled glucocorticosteroids in the basic therapy of COPD helps to reduce the severity of systemic inflammation, and cholinolytics and long-acting β2-agonists control the level of TGF-β1 [9]. However, further research is needed to determine the impact of basic therapy of COPD patients on the severity of inflammation and fibrosis.

Levels of indicators of COPD patients included in the clusters

Indicators	Clusters		p
	1, n=12	2, n=25	
Gender: n (%) men women	 16 (88.8) 2 (11.1)	 17 (89.5) 2 (10.5)	0.863
Age (years), M±m	65.1±1.72	61.1±5.6	0.771
Number of exacerbations over the past year	2.0±0.22	1.1±0.15	0.001
Shortness of breath by mMRC, points	1 [1–1]	2 [1–3]	0.028
Level of $FEV_{1post.}$ (% of appropriate value)	58.3±4.2	45.5±2.8	0.029
Increase in FEV_1, ml	250±0.04	100±0.02	0.001
Level of C-RP, mg/l	9.25 [5.6–17.3]	4.8 [2.9–5.9]	0.037
Level of CAA ng/ml	695.3 [502.6–2980.1]	247.5 [217.8–406.3]	0.026
Level of $TGF\text{-}\beta_1$	3.6 [3.2–6.7]	11.8 [5.8–16.4]	0.001

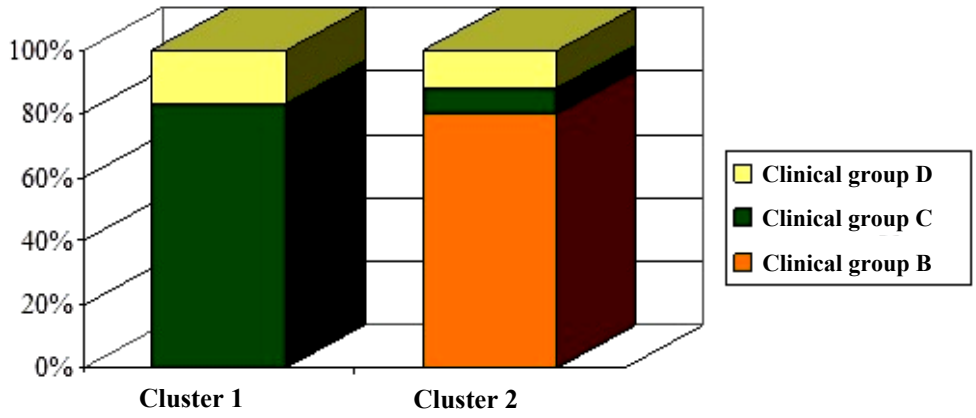

Fig. 3. Division of patients included in the clusters into clinical groups of COPD

CONCLUSIONS

1. Patients with COPD with a predominance of inflammation have a slight severity of shortness of breath, moderate bronchoobstruction (FEV1>50% of the appropriate value), high reversibility of bronchial obstruction, low profibrotic cytokine TGF-β1, high levels of markers of systemic inflammation (C-RP and CAA).
2. Patients with COPD with a predominance of the fibrosis process have a significant severity of shortness of breath, a significant level of bronchial obstruction (FEV1≤50% of the appropriate value), a low level of reversibility.
3. Bronchial obstruction, low levels of markers of systemic inflammation (C-RP and CAA), high levels of profibrotic cytokine TGF-β1.
4. The prevalence of inflammatory processes is observed mainly in patients with COPD who belong to clinical group C; prevalence of fibrosis processes – mainly in patients with COPD of clinical group B.

Conflict of interests. The authors declare no conflict of interest.

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