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Markers Of Progression of Chronic Obstructive Pulmonary Disease

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Annotation
Chronic obstructive pulmonary disease (COPD) is a pressing problem in the modern world. Every year, COPD increasingly leads to temporary disability and death. This is why it is so important to predict the progression of COPD in time. Progression of the disease can lead to severe shortness of breath, frequent exacerbations of COPD, respiratory failure and death.
This literature review examines radiological and functional markers, clinical manifestations, sputum and blood markers, and the lung microbiome. All of this may be useful for predicting the risk of COPD progression.
Key words: COPD, disease progression, markers, prognosis, FEV1, CT, sputum, CRP, ET-1, nitric oxide, slCAM-1, slCAM-3, TGF-β1, bFGF, SP-D, IL-6, fibrinogen, lung microbiome

Currently, chronic obstructive pulmonary disease (COPD) is considered one of the most common diseases of the respiratory system among the adult population. This disease can lead to temporary disability and mortality of patients [24, 35, 44, 51]. WHO estimates that moderate to severe COPD affects 65 million people worldwide [3]. In 2016, there were 251 million cases of this disease worldwide, according to the Global Burden of Disease Study [9]. Currently, the global incidence of chronic obstructive pulmonary disease is estimated at 10% among adults over 40 years of age [12].

This figure is growing every year. The increasing prevalence of chronic obstructive pulmonary disease is observed in both developed and developing countries. In addition, there is an annual increase in mortality from this disease around the world. The World Health Organization annually publishes mortality statistics from various diseases, including COPD. According to WHO data, if back in 2002 this disease was the fifth leading cause of death [3], then at the moment COPD is the third leading cause of death worldwide. This disease accounts for approximately 6% of the total number of deaths, respectively [1]. All these data indicate a rapid increase in mortality from chronic obstructive pulmonary disease. That is why chronic obstructive pulmonary disease is considered one of the most pressing problems in healthcare.

In addition, COPD is considered a socially and economically significant problem (Mannino D. M., 2007). This is due to the fact that as a result of this disease, there is a steady decline in the quality of life of patients, causing early disability in 13% [44, 50], which, accordingly, leads to increased costs from the healthcare system for lifelong use of medications, expensive emergency medical assistance, long periods of incapacity and disability payments [8].

That is why it is so important to diagnose this disease in time and predict the progression of COPD in time. There are currently a large number of putative biomarkers that can help diagnose COPD, clarify COPD phenotypes, and monitor response to treatment [15, 43, 10].

Biomarkers are any clinical signs, functional and radiological studies, laboratory test markers that can characterize disease activity and will be useful in diagnosing and monitoring disease processes, as well as response to therapy.

Currently, many scientists around the world are identifying biological markers that would help predict the progression of chronic obstructive pulmonary disease in advance. Providing reliable evidence to validate biomarkers prior to clinical implementation remains a critical challenge. Important questions that many scientists around the world are trying to address are: the accuracy and reliability of biomarkers for a clinical condition of interest, assessment of clinical utility and cost-effectiveness, and real-world effectiveness compared to other biomarkers [52].

The progression of chronic obstructive pulmonary disease can vary: some patients may experience a relatively stable course, while other patients will suffer a steady progression that can lead to severe shortness of breath, frequent exacerbations of COPD, respiratory failure, and death. Early identification of people with chronic

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obstructive pulmonary disease who are at higher risk of progression will allow more individualized treatment to slow disease progression, the development of complications and reduce the risk of mortality from this disease.

Symptoms and exacerbations

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), it is recommended to include an assessment of symptoms (worsening cough and shortness of breath) and history of exacerbations along with measurement of forced expiratory volume in 1 second [23]. The ECLIPSE study confirmed that patients with 2 or more exacerbations per year and more severe airflow limitation are at higher risk of developing future exacerbations and disease progression [49].

External respiration function

Traditionally, the diagnosis and determination of the severity of chronic obstructive pulmonary disease is based on spirometry data. Indicators of external respiratory function, especially forced expiratory volume in 1 second (FEV 1), reflect the severity of chronic obstructive pulmonary disease, and a gradual change in FEV1, which is determined over a long period of time, is considered a generally accepted indicator of the progression of this disease. FEV1 measurement has always been considered the gold standard, but FEV1 has been found to have poor correlation with clinical parameters. It was found that patients who have the same FEV1 values may have different pathological changes, for example, the severity of emphysema, changes in the caliber of small bronchi [13]. In addition, to evaluate the progression of COPD through FEV1 decline, studies are conducted that typically last ≥ 3 years, resulting in high study costs and physical burden, while limiting the number of new drugs that can be used to treat COPD [48]. As a result, although FEV1 and other indicators of pulmonary function can be used for prognostic purposes, the results will nevertheless be more accurate if FEV1 is assessed in combination with other indicators to determine the prognosis of the disease [16]. Thus, more sensitive indicators are needed to assess the severity and progression of COPD.

Radiological markers

Imaging biomarkers that are visualized on high-resolution computed tomography (CT) chest scans have been found to be useful predictors of disease progression.

With high-resolution CT, it is possible to evaluate emphysema and airway changes that are observed in COPD using quantitative indicators [32]. Examination of emphysema and inspiratory and expiratory small bronchi changes provides information about the COPD phenotype [22], and changes in lung density over time can be used as an endpoint for COPD progression [17].

Large cohort studies have correlated quantitative CT measurements with COPD progression outcomes. Studies have found an association of accelerated decline in lung function with more severe emphysema, which has been quantified using CT [27]. The MESA (Multi-Ethnic Study of Atherosclerosis) study showed that the presence of centrilobular and panlobular emphysema on CT correlates with increased dyspnea and decreased exercise capacity [42]. A cross-sectional study found a correlation of airway wall thickness with decreased lung function and increased symptoms in smokers [20]. In the COPDGen study of 1002 people, exacerbations of the disease were more likely to occur in those people who had a more severe emphysema index on CT and who had increased airway wall thickness [25]. A higher emphysema index on CT was associated with an increased risk of respiratory [26, 29] and COPD-specific mortality [54]. There was no association between airway wall thickness and mortality [29]. Thus, detection of emphysema and changes in the airways on CT can predict the progression of chronic obstructive pulmonary disease.

Sputum

Sputum (spontaneous and induced) is an important diagnostic material for assessing airway inflammation in COPD. Whether sputum can be considered as a biomarker to assess the severity and progression of COPD is currently being studied. Sputum biomarkers during disease stabilization and exacerbation were found to be associated with the severity of chronic obstructive pulmonary disease.

Increased levels of neutrophils were found in the sputum of COPD patients. At the same time, a significant correlation was established between the number of neutrophils in sputum and the stage of COPD, but in the ECLIPSE study this indicator was weakly associated with lung function [21]. In later stages of the disease, lymphocytes are detected in the sputum, with an increase in the concentration of type 1 CD8+ T cells. Also, some patients with COPD experience an increase in the content of eosinophils, which is related to the effectiveness of glucocorticosteroids (GCS) and bronchodilators [2].

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There was an association of higher levels of neutrophils, elastase, interleukin (IL)-8 and matrix metalloproteinase (MMP)-9 in spontaneous sputum in COPD patients with greater decline in pulmonary function (FEV 1) [34]. Inflammatory mediators in induced sputum during stabilization may predict future risk of exacerbations. A review by Koutsoker and co-workers suggested that sputum levels of several mediators [including sputum IL-6, IL-8, and myeloperoxidase (MPO)] may be associated with exacerbation rates, although more confirmatory studies are needed [31]. Tuffeson E. and his colleagues studied the level of leukotriene B 4 and found that in sputum this indicator increases before an exacerbation. Therefore, this indicator has been proposed as a possible biomarker of exacerbation risk [46].

Many patients with COPD can expectorate valid sputum spontaneously, but this sputum may contain large amounts of dead cells, which could potentially lead to misleading results in sputum cell counting and inflammatory mediator testing [45]. To overcome this, sputum can be induced using a hypertonic saline in stable patients with COPD. These samples provide a lot of information about inflammatory cells and mediators [14]. However, in this case there are some problems. Induced sputum samples are predominantly obtained from the proximal airways and may not reflect the peripheral inflammation that contributes to the clinical symptoms of COPD. In addition, processing of sputum during examination can change proteins so that they are not recognized by antibodies [30]. Due to many technical and clinical confounding factors, induced sputum is still being investigated as a source of clinically useful biomarkers [15].

Blood biomarkers

Blood samples are a convenient source of biomarkers for lung diseases, including chronic obstructive pulmonary disease. Currently, many scientists around the world are searching for blood biomarkers, with the help of which it would be possible to predict the progression of chronic obstructive pulmonary disease.

1) C-reactive protein (CRP)

Studies have shown that in stable COPD there is a low level of systemic inflammation with an increase in the level of CRP in the blood, while a higher level of CRP is observed during exacerbation of the disease [38]. Some studies have shown that baseline CRP levels correlate with subsequent decline in lung function [33]. Increased levels of CRP over time are associated with a decrease in FEV1 in patients with COPD [39], the risk of hospitalization and mortality [18], so the level of CRP in the blood in patients with stable COPD may be a prognostic marker of hospitalization and death from COPD.

In studies by J.R. Hurst et al., who studied the role of 36 biomarkers (CRP, IL-6, TNF-α, etc.) in patients with COPD outside and during an exacerbation of the disease, they showed that CRP (or any other marker separately) without clinical signs was not a sufficiently sensitive and specific biomarker for exacerbation and progression of COPD [28]. At the same time, CRP was the most informative of the 36 biomarkers studied. The level of biomarkers in the blood plasma did not depend on the severity of the exacerbation. The combination of CRP with any major clinical sign of exacerbation increased its diagnostic accuracy [28].

Thus, CRP can be used to predict the progression of COPD, but it is not a sensitive and specific biomarker. Therefore, it is better to combine it with other clinical signs and markers.

2) Endothelin-1 (ET-1)

Currently, endothelium-1 is considered as a marker of COPD progression by many scientists around the world. One of such studies is the study by N.I. Kubesheva et al., which revealed that the serum concentration of ET-1 in all examined patients was statically significantly higher than in healthy people. At the same time, no relationship was found between the concentration of ET-1 in the acute phase and during a stable course. But it was found that the concentration of ET-1 increases depending on the severity of COPD. For example, the concentration of ET-1 in the blood in patients with grade III severity was 1.4 times higher than in patients with grade II. The maximum concentration of ET-1 in the blood was found in patients with severe disease in the acute stage. Negative relationships were also revealed between the serum ET-1 content and the inspiratory capacity value in all examined patients. Endothelin-1 plays an important role in the pathogenesis of bronchial obstruction and the progression of chronic obstructive pulmonary disease [6].

3) Nitric oxide metabolites

In a study by N.I. Kubesheva et al. also looked at the level of nitric oxide metabolites in the blood serum of patients with COPD. Serum levels of nitric oxide metabolites in patients were significantly higher than in healthy nonsmoking volunteers. During the study, no significant differences were found in the concentration of nitric oxide products in the blood serum during a stable period and during exacerbation in patients of the

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GOLD II and GOLD III groups. A progressive increase in the content of nitric oxide metabolites in the blood circulation has been recorded in patients with chronic obstructive pulmonary disease with increasing severity of bronchial obstruction. The serum concentration of nitric oxide metabolites in patients with exacerbation of severe COPD and during the stable period was 1.8 times higher than in patients with severity II during the exacerbation and stabilization period. It was found that nitric oxide metabolites in blood serum can also be a marker of the progression of chronic obstructive pulmonary disease [6].

4) Cell adhesion molecules slCAM-1 and slCAM-3

In a study by N.I. Kubesheva et al. found that the concentration of cell adhesion molecules slCAM-1 and slCAM-3 in the blood serum of all examined patients with COPD was significantly higher than in the group of healthy people. It was found that an increase in the concentration of cell adhesion molecules slCAM-1 and slCAM-3 is associated with the progression of COPD severity. Their content in patients with grade III severity was statically significantly higher than in patients with grade II severity of the disease. In addition, increased concentrations of these soluble proteins in the blood circulation were associated with worsening bronchial conduction in COPD. The scientists also found that during exacerbation and in the stable phase of the disease, the concentrations of the studied soluble proteins in the blood within each group did not differ significantly. Thus, it was found that changes in the content of cell adhesion molecules slCAM-1 and slCAM-3 do not depend on the stage of COPD [6].

5) Transforming growth factor β1 (TGF-β1) and fibroblast growth factor b (bFGF)

In the study by Kalinina E.V. and Lobanova E.G. It was found that the production of TGF-β1 and bFGF differs in patients with COPD with varying degrees of progression of bronchial obstruction. In patients with FEV1 ≥ 80%, the serum levels of the studied cytokines were reduced; in patients with FEV1 < 80%, but ≥ 50% of predicted, the synthesis of TGF-β1 continued to decrease, but the bFGF content remained at the level of indicators that are characteristic of mild bronchial obstruction. In patients with FEV1 < 50% of predicted, i.e. in patients who have severe bronchial obstruction, there was a significant decrease in the concentration of TGF-β1 and an increase in the content of bFGF ($p < 0.01$). It was found that if there is a lack of the required level of synthesis of the inflammatory response limiting factor - TGF-β1, in combination with increased production of bFGF, which stimulates the proliferation of fibroblasts and collagen synthesis, replacement of lung tissue with fibrous tissue is observed.

In order to prove the prognostic significance of these indicators, patients with COPD were monitored for a year. As a result of dynamic observation of patients with COPD, who had a decrease in the content of TGF-β1 and an increase in bFGF in the blood serum to levels unfavorable for this disease, a deterioration in respiratory function was observed, which was poorly corrected by treatment. These data showed that TGF-β1 and bFGF markers in the blood are reliable, informative diagnostic criteria that can be used to assess the progression of bronchial obstruction.

The results of the study made it possible to determine the level of secretion of TGF-β1 and bFGF in the blood serum to predict the risk of COPD progression [5].

6) Surfactant protein D (SP-D)

D. D. Sin et al. published data on one of the probable biomarkers of COPD - surfactant protein D (SP-D). This marker is relatively specific to the lungs and is detected in blood serum [41]. SP-D synthesis mainly occurs in lung tissue. This is shown in many works [11, 36]. It was found that SP-D increases in the blood in response to pathological changes in the lungs, and also decreases with the administration of inhaled corticosteroids and the combination of inhaled corticosteroids with long-acting β2-agonists. That is why this marker can be used as a lung-specific COPD marker [11, 40]. It was found that the level of serum SP-D does not depend on gender, i.e. its levels are approximately the same in men and women with COPD. It was also found that in more severe stages of COPD (according to GOLD), there is no significant increase in serum SP-D levels. Although SP-D concentrations do not correlate with disease severity, peak serum levels are associated with the risk of exacerbations and progression of emphysema [2].

At this time, it is important to determine whether SP-D is associated with decreased pulmonary function and progression of emphysema, airway disease, and systemic manifestations (such as fatigue, muscle loss, and systemic inflammation). If a link is found, it could be suggested that SP-D is a viable biomarker that may determine COPD disease progression.

7) Expression of the receptor for IL-6 on the surface of immunocompetent cells

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During the study by Vitkina T.I. et al. calculated the percentage of immune system cells that carry IL-6R on their surface in the blood of healthy individuals and patients with COPD. When considering the expression pattern of IL-6R in patients with COPD, a trend towards an increase in the content of CD126+ cells was found in comparison with the control group. At the same time, in patients with COPD, changes in the level of IL-6R expression were detected depending on the severity of the disease. As COPD worsened, there was an increase in the number of T lymphocytes, T helper cells, granulocytes and monocytes that carry IL-6R on their surface, indicating the important role of this marker in predicting the risk of COPD progression [4].

8) Fibrinogen

Dahl M. and colleagues examined the relationship between fibrinogen and COPD. At baseline, an inverse relationship was observed between fibrinogen and % predicted FEV 1 in a cohort of 8955 individuals randomly selected from the Copenhagen population; In patients with high levels of fibrinogen in the blood, an excess annual decrease in FEV 1 was observed compared with low levels of fibrinogen [19]. It was found that patients with the highest baseline fibrinogen were also more likely to be hospitalized with an exacerbation of COPD during the 6-year follow-up period. Valvi and colleagues further studied 20,192 individuals from the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS) cohorts, showing that baseline fibrinogen levels predicted future cases of COPD and COPD-related hospitalization [47]. . Fifteen-year follow-up data from the Coronary Artery Risk Development in Young Adults (CARDIA) study of 2132 participants showed that higher fibrinogen leads to greater loss of FEV 1 and forced vital capacity (FVC) and the development of abnormal FEV 1 or FVC, regardless of status smoking. Evidence provided by such general population cohort studies suggests that increased fibrinogen predicts more rapid decline in lung function at the population level, although definitive evidence of predisposition to COPD is lacking. Thus, fibrinogen has emerged as a promising biomarker in COPD. Fibrinogen is likely to be a useful biomarker for predicting the risk of progression of chronic obstructive pulmonary disease.

9) Combination of markers: fibrinogen, C-reactive protein (CRP), surfactant protein D (SP-D), soluble receptor for advanced glycation end products (sRAGE) and club cell secretory protein (CC16)

Based on the literature, Rachel L. Zemans and colleagues evaluated the effectiveness of five biomarkers—sRAGE, SP-D, fibrinogen, CC16, and CRP—either individually or in combination in predicting airflow limitation, emphysema severity, exacerbations, and decline in FEV 1 , emphysema progression and mortality in the COPDGene and ECLIPSE cohorts. As a result, it was found that the combination of all five biomarkers together gave the most accurate results in predicting the risk of COPD progression than all of the above markers individually [53].

Lung microbiome

During microbiological examination of sputum N.A. Lyubavina and colleagues isolated from 1 to 6 types of microorganism cultures from patients with COPD. At the same time, a monoculture of microorganisms was found in 28% of crops, associations of two species - in 27%, three species - in 20%, four or more species - in 25% of cases. It was found that the microbiome of the respiratory tract in patients with COPD included: α-hemolytic, β-hemolytic and non-hemolytic streptococci (25, 5 and 10%, respectively), enterobacteria (10%), candidates (16%), Staphylococcus aureus (7 %), pneumococcus (5%), moraxella (5%), diphtheroids (5%), Pseudomonas aeruginosa was isolated from 1 person.

In COPD patients, an inverse relationship was found between the number of types of microorganisms detected during microbiological examination of sputum and the FEV1 value, as well as a direct correlation with the level of peripheral blood leukocytes [7]. Chronic bacterial respiratory tract infection is more common in patients with severe COPD [37]. Although few studies to date have applied the lung microbiome to outcomes of COPD progression, the association between bacterial burden and lung function may suggest a role for chronic bacterial colonization in disease progression.

Conclusions

COPD is a heterogeneous and complex chronic lung disease with extrapulmonary manifestations. Progression of the disease can lead to irreversible consequences and even death of patients. To avoid this, markers are needed that will help predict the risk of COPD progression. The search for appropriate biomarkers in COPD is currently underway. Every year the number of markers that can help predict the progression of the disease is growing. At the moment, the world already knows a large number of these markers, but many of them still require confirmation of their effectiveness. Much more research is currently needed to evaluate biomarkers in

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relation to disease progression outcomes in COPD. Overcoming methodological challenges in sampling and quality control will allow the development and use of more reliable but easily accessible biomarkers in the assessment of all patients with COPD that will help predict the risk of progression to COPD.

References

1) 10 ведущих причин смерти в мире. URL: https://www.who.int/ru/news-room/fact-sheets/detail/the-top-10-causes-of-death
2) Анаев Э. Х. Биологические маркеры при хронической обструктивной болезни легких //Практическая пульмонология. – 2018. – №. 1. – С. 26-32.
3) Бремя хронических обструктивных болезней легких. URL: https://www.who.int/respiratory/copd/burden/ru/
4) Виткина Т. И., Сидлецкая К. А., Денисенко Ю. К. Изменение экспрессии рецептора к IL-6 на поверхности иммунокомпетентных клеток при прогрессировании хронической обструктивной болезни легких //Медицинская иммунология. – 2017. – Т. 19. – №. 2. – С. 191-196.
5) Калинина Е. П., Лобанова Е. Г. Диагностический критерий прогрессирования хронической обструктивной болезни легких //Сибирский научный медицинский журнал. – 2010. – Т. 30. – №. 1. – С.5-7.
6) Кубышева Н. И. и др. Значение растворимых молекул клеточной адгезии, метаболитов оксида азота, эндотелина-1 и их ассоциаций как маркеров прогрессирования воспаления при ХОБЛ //Современные технологии в медицине. – 2017. – Т. 9. – №. 2. – С.105-115.
7) Любавина Н. А. и др. Сывороточное содержание растворимых антигенов адгезии как маркер прогрессирования хронической обструктивной болезни легких //Современные технологии в медицине. – 2011. – №. 1. – С.67-71.
8) Федеральные клинические рекомендации по диагностике и лечению хронической обструктивной болезни легких (2014). URL: http://www.pulmonology.ru/ publications/guide.php.
9) Хроническая обструктивная болезнь легких (ХОБЛ). URL: https://www.who.int/ru/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd).
10) Agusti A., Sin D. D. Biomarkers in COPD //Clinics in chest medicine. – 2014. – Т. 35. – №. 1. – С. 131-141.
11) Apweiler R. et al. Approaching clinical proteomics: current state and future fields of application in fluid proteomics //Clinical chemistry and laboratory medicine. – 2009. – Т. 47. – №. 6. – С. 724-744.
12) Argyriou E., Atmatzidou V., Bellou A. Economic and social burden of chronic obstructive pulmonary disease // Ann Transl Med. -2016. -Т.4– №. 22. - С.1021
13) Barnes P. J., Ito K., Adcock I. M. Corticosteroid resistance in chronic obstructive pulmonary disease: inactivation of histone deacetylase //The Lancet. – 2004. – Т. 363. – №. 9410. – С. 731-733.
14) Beeh K. M. et al. Long-term repeatability of induced sputum cells and inflammatory markers in stable, moderately severe COPD //Chest. – 2003. – Т. 123. – №. 3. – С. 778-783.
15) Casaburi R. et al. The COPD biomarker qualification consortium (CBQC) //COPD: Journal of Chronic Obstructive Pulmonary Disease. – 2013. – Т. 10. – №. 3. – С. 367-377.
16) Celli B. R. et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease //New England Journal of Medicine. – 2004. – Т. 350. – №. 10. – С. 1005-1012.
17) Coxson H. O. et al. The presence and progression of emphysema in COPD as determined by CT scanning and biomarker expression: a prospective analysis from the ECLIPSE study //The lancet Respiratory medicine. – 2013. – Т. 1. – №. 2. – С. 129-136.
18) Dahl M. et al. C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease //American journal of respiratory and critical care medicine. – 2007. – Т. 175. – №. 3. – С. 250-255.

ISSN NO: 2770-2936
May 2024

19) Dahl M. et al. Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease //American journal of respiratory and critical care medicine. – 2001. – Т. 164. – №. 6. – С. 1008-1011.
20) Dijkstra A. E. et al. Low-dose CT measurements of airway dimensions and emphysema associated with airflow limitation in heavy smokers: a cross sectional study //Respiratory research. – 2013. – Т. 14. – №. 1. – С. 1-9.
21) Faner R. et al. Lessons from ECLIPSE: a review of COPD biomarkers //Thorax. – 2014. – Т. 69. – №. 7. – С. 666-672.
22) Galbán C. J. et al. Computed tomography–based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression //Nature medicine. – 2012. – Т. 18. – №. 11. – С. 1711-1715.
23) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Medical Communications Resources, Inc., 2014. Accessed 12 July 2014. Available online: www.goldcopd.com
24) GOLD (Global Initiative for Chronic Obstructive Lung Disease) [Internet]. Global strategy for the diagnosis, management, and prevention of COPD. 2017 [cited 2018 May 29]. Available from: http: // goldcopd.org/ download/326/
25) Han M. L. K. et al. Chronic obstructive pulmonary disease exacerbations in the COPDGene study: associated radiologic phenotypes //Radiology. – 2011. – Т. 261. – №. 1. – С. 274-282.
26) Haruna A. et al. CT scan findings of emphysema predict mortality in COPD //Chest. – 2010. – Т. 138. – №. 3. – С. 635-640.
27) Hoesein F. A. A. M. et al. CT-quantified emphysema in male heavy smokers: association with lung function decline //Thorax. – 2011. – Т. 66. – №. 9. – С. 782-787.
28) Hurst J. R. et al. Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease //American journal of respiratory and critical care medicine. – 2006. – Т. 174. – №. 8. – С. 867-874.
29) Johannessen A. et al. Mortality by level of emphysema and airway wall thickness //American journal of respiratory and critical care medicine. – 2013. – Т. 187. – №. 6. – С. 602-608.
30) Keatings V. et al. Analysis of fluidphase mediators //European Respiratory Journal. – 2002. – Т. 20. – №. 37 suppl. – С. 24s-39s.
31) Koutsokera A. et al. Pulmonary biomarkers in COPD exacerbations: a systematic review //Respiratory research. – 2013. – Т. 14. – №. 1. – С. 1-12.
32) Litmanovich D. E. et al. Multidetector computed tomographic imaging in chronic obstructive pulmonary disease: emphysema and airways assessment //Radiologic Clinics. – 2014. – Т. 52. – №. 1. – С. 137-154.
33) Man S. F. P. et al. C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease //Thorax. – 2006. – Т. 61. – №. 10. – С. 849-853.
34) Paone G. et al. Analysis of sputum markers in the evaluation of lung inflammation and functional impairment in symptomatic smokers and COPD patients //Disease markers. – 2011. – Т. 31. – №. 2. – С. 91-100.
35) Pavlov P., Ivanov Y., Glogovska P., et al. New epidemiology data on COPD in the Pleven region // Thoracic Med. -2012. -Т. 2 – №. IV. -С. 44–50.
36) Pontén F. et al. A global view of protein expression in human cells, tissues, and organs //Molecular systems biology. – 2009. – Т. 5. – №. 1. – С. 337.
37) Rangelov K., Sethi S. Role of infections //Clinics in chest medicine. – 2014. – Т. 35. – №. 1. – С. 87-100.
38) Samy N. et al. Clinical utility of biomarkers as predictors of lung function in chronic obstructive pulmonary disease //NY Sci. J. – 2010. – Т. 6. – С. 25-32.
39) Shaaban R. et al. Change in C-reactive protein levels and FEV1 decline: a longitudinal population-based study //Respiratory medicine. – 2006. – Т. 100. – №. 12. – С. 2112-2120.
40) Sin D. D. et al. Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease //Thorax. – 2005. – Т. 60. – №. 12. – С. 992-997.

ISSN NO: 2770-2936
May 2024

41) Sin D. D. et al. The effects of fluticasone with or without salmeterol on systemic biomarkers of inflammation in chronic obstructive pulmonary disease //American journal of respiratory and critical care medicine. – 2008. – Т. 177. – №. 11. – С. 1207-1214.
42) Smith B. M. et al. Pulmonary emphysema subtypes on computed tomography: the MESA COPD study //The American journal of medicine. – 2014. – Т. 127. – №. 1. – С. 94. e7-94. e23.
43) Stockley R. A. Biomarkers in chronic obstructive pulmonary disease: confusing or useful? //International journal of chronic obstructive pulmonary disease. – 2014. – Т. 9. – С. 163.
44) Tachkov K, Kamusheva M, Pencheva V, et al. Evaluation of the economic and social burden of chronic obstructive pulmonary disease (COPD) // Biotechnol Biotechnol Equip. -2017. -Т.31. – №. 4. -С. 855–861.
45) Tsoumakidou M., Tzanakis N., Siafakas N. M. Induced sputum in the investigation of airway inflammation of COPD //Respiratory medicine. – 2003. – Т. 97. – №. 8. – С. 863-871.
46) Tufvesson E., Ekberg M., Bjermer L. Inflammatory biomarkers in sputum predict COPD exacerbations //Lung. – 2013. – Т. 191. – №. 4. – С. 413-416.
47) Valvi D. et al. Fibrinogen, chronic obstructive pulmonary disease (COPD) and outcomes in two United States cohorts //International journal of chronic obstructive pulmonary disease. – 2012. – Т. 7. – С. 173.
48) Vestbo J. et al. Evaluation of COPD longitudinally to identify predictive surrogate end-points (ECLIPSE) //European Respiratory Journal. – 2008. – Т. 31. – №. 4. – С. 869-873.
49) Vestbo J. et al. Should we view chronic obstructive pulmonary disease differently after ECLIPSE?. A clinical perspective from the study team //American journal of respiratory and critical care medicine. – 2014. – Т. 189. – №. 9. – С. 1022-1030.
50) Wheaton A. G. et al. Employment and activity limitations among adults with chronic obstructive pulmonary disease—United States, 2013 //MMWR. Morbidity and mortality weekly report. – 2015. – Т. 64. – №. 11. – С. 289.
51) Wheaton A. G. et al. Pulmonary function, chronic respiratory symptoms, and health-related quality of life among adults in the United States–National Health and Nutrition Examination Survey 2007–2010 //BMC public health. – 2013. – Т. 13. – №. 1. – С. 1-9.
52) Woodcock J. Assessing the clinical utility of diagnostics used in drug therapy //Clinical Pharmacology & Therapeutics. – 2010. – Т. 88. – №. 6. – С. 765-773.
53) Zemans R. L. et al. Multiple biomarkers predict disease severity, progression and mortality in COPD //Respiratory research. – 2017. – Т. 18. – №. 1. – С. 1-10.
54) Zulueta J. J. et al. Emphysema scores predict death from COPD and lung cancer //Chest. – 2012. – Т. 141. – №. 5. – С. 1216-1223.