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# Factors of formation of small airways obstruction and lung hyperinflation in patients with combined pathology of asthma and chronic obstructive pulmonary disease

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**Abstract**
The most unfavorable variants of combined lung obstructive pathology are small airways obstruction and lung hyperinflation. The aim of this work was to study the factors of the formation of small airways obstruction and lung hyperinflation in patients with combined pathology of asthma and COPD. Severe violations of the lung function parameters in the form of small airways obstruction and pulmonary hyperinflation may exist simultaneously. The common factors of these complications are the elderly age of patients, bronchial obstruction, decreased exercise tolerance, severe dyspnea and high BODE index. The differences in risk factors are the dependence of small bronchial obstruction on the type of local bronchial inflammation and the disease from which the ACO debuted, while lungs hyperinflation depends on the factors of the general low health status and the decrease in the predicted life expectancy of the patients. Among the concomitant cardiovascular pathologies, arterial hypertension and the presence of left ventricular hypertrophy, along with obesity, have a greater effect on the obstruction of the distal respiratory tract, and ischemic heart disease - on lung hyperinflation. Pulmonary hypertension is a factor in the occurrence of both complications.

**Keywords:** Asthma-COPD overlap, small airways obstruction, lung hyperinflation

## Introduction
The combination of asthma and chronic obstructive pulmonary disease (asthma-COPD overlap (ACO)) in one patient is an actual problem in pulmonology [1]. An interesting question is the pathophysiology of violations of the lung function parameters in ACO patients, and the choice of adequate therapy for these patients. The most unfavorable variants of these disorders are small airways obstruction and lung hyperinflation [2].
Factors contributing to the formation of these states are numerous and go beyond purely pulmonary pathology. According to literature, it is known that increased airiness of lung tissue on the one hand is more common in patients with concomitant cardiovascular pathology. On the other hand, lung hyperinflation promotes hemodynamic disorders by breaking the venous return and reducing the right ventricle preload, and large intrathoracic pressure causes left ventricular dysfunction [3]. There is also evidence that the formation of lung emphysema is associated with the neutrophilic type of bronchial inflammation [4].
The aim of this work was to study the factors of the formation of small airways obstruction and lung hyperinflation in patients with combined pathology of asthma and COPD.

## Materials and Methods
The study included patients with ACO (n = 140) of an average age of 58.56 ± 0.81 years undergoing baseline therapy, but there were pronounced symptoms and impaired lung function. Diagnosis of ACO was exposed according to the criteria given in the main international guidelines for the management of asthma and COPD patients - GINA and GOLD [8, 9]. All patients had persistent, but variable symptoms characteristic of asthma and COPD, the state of patients was stable, no exacerbation 2 months before the study. The average forced expiratory volume for the first second (FEV1) of patients was (59.0 ± 1.4)% and the ratio of FEV1 to forced vital capacity (FVC) - FEV1 / FVC - (53.6 ± 0.8)%. In 91 patients, the disease debuted with asthma, in 49 other cases, a COPD was initially diagnosed.

Patients were on baseline asthma and COPD therapy according to the severity of the disease, all taking short-acting beta2 agonists (SABA) as needed, and drugs for disease control (inhaled corticosteroids (ICS), a combination of ICS/ long-acting beta agonists (LABA), Tiotropium bromide, or triple therapy - ICS/LABA/Tiotropium bromid).

All patients underwent: general clinical examination, body mass and height measurements, body mass index (BMI), office systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse blood pressure (PBP) measurements, spirometry, whole body plethysmography and impulse oscillometry ("Master Screen Pneumo Cardinal Health (Germany)), FeNO measurement, ambulatory blood pressure monitoring (EC-3H/ABP (Labtech, Hungary)), echocardiography (VIVID E9, General Electric), Charlson comorbidity index assessment, COPD symptoms evaluation (CAT), asthma symptoms assessment (ACQ7 Questionnaire), mMRC-scale dyspnea assessment, BODE Index measurement [7], cardiovascular risk measurement (SCORE scale), 6-minutes walking test in accordance with the standard protocol [8]. Blood analysis was also performed and the serum creatinine level was determined.

To assess the general probability of development of individual events under the influence of several risk factors, the Cochran-Mantel-Hensel criterion was used with the help of Review Manager software (RevMan 5.3) [9]. For the construction of a diagram illustrating the weight of the influence of the factors under study, the generator "DistillerSR Forest Plot Generator from Evidence Partners" [10] was used. In this case, the following reductions are applied: OR - odds ratio, LCL - lower confidence limit, UCL - upper confidence limit, WGHT - weight.

**Results and Discussion**

In studying the characteristics of the course of ACO with small airways obstruction, the criterion for distal respiratory tract obstruction was the parameter of impulse oscillometry R5-R20, which should not exceed 20% in healthy persons [11]. The OR of increasing the R5-R20 to 20% and more, as well as the weight of each individual factor was calculated (Figure 1).

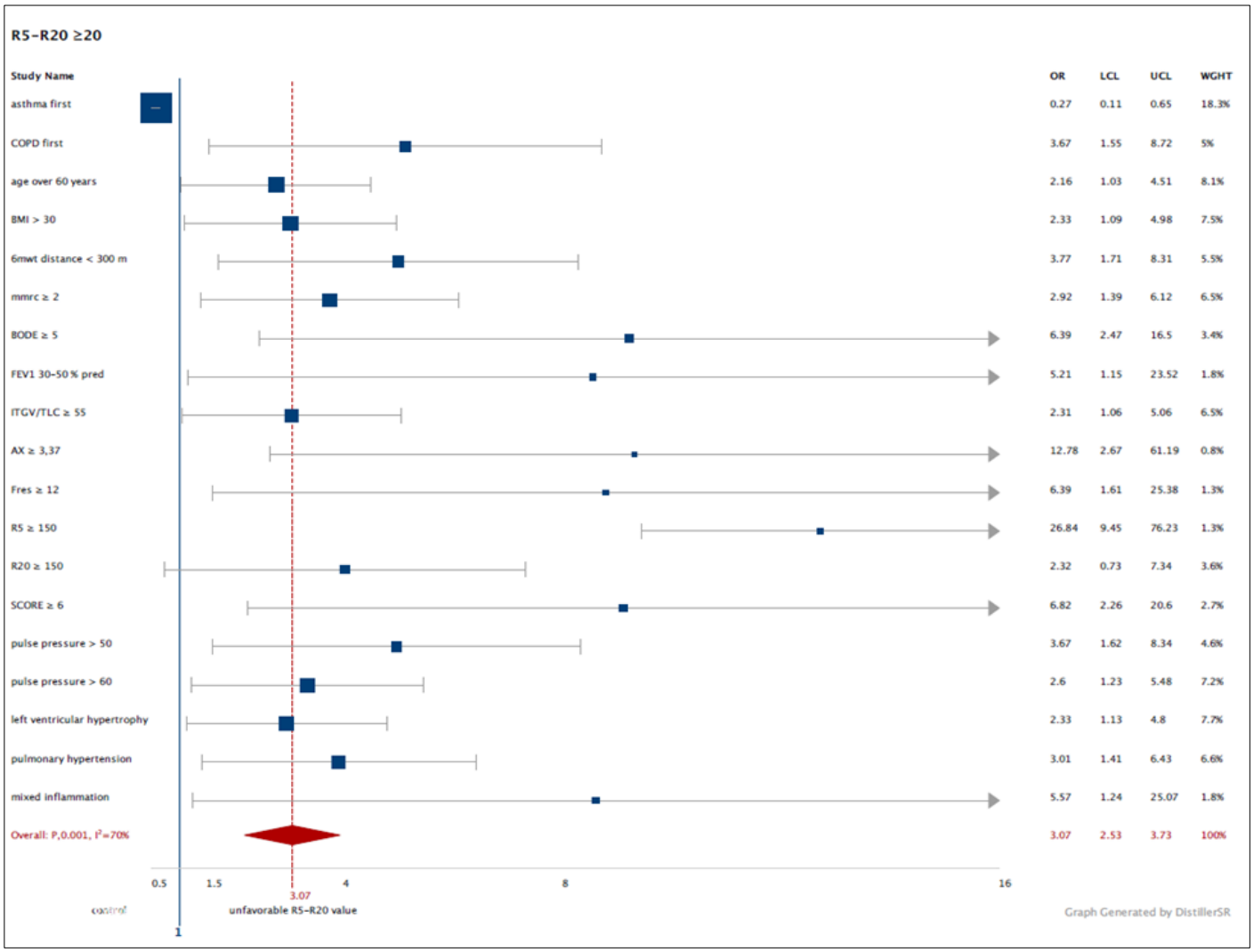


**Fig 1:** Risk factors of formation of small airways obstruction in patients with ACO

The results show that the risk of small airways obstruction reliably depends on the patient's primary pathology. In this case, patients with an initial diagnosis of asthma have statistically significant chances to be protected from this course (odds ratio = 0, 27; 95% confidence interval from 0, 11 to 0,65). Among other factors considered, the primary diagnosis of asthma is the most significant – 18, 3%. The onset of COPD on the contrary more than three times increases the risk of small bronchial obstruction (odds ratio = 3, 67; 95% confidence interval from 1, 55 to 8, 72).

Regardless of the initial diagnosis, the risk of distal bronchial obstruction is increased with age (2, 16 times in patients older than 60 years of age). Among other general-clinical signs, obesity leads to small airway obstruction with a weight of factor of 7,5%, reduced tolerance to physical activity (the distance passed in a 6-minute walking test less than 300 meters leads to the probability of distal airways obstruction in the ratio of 3,77 to 1).

The severity of the clinical course of the disease is also associated with the small airways obstruction, because with a dyspnea score of 2 and more (mMRC) it's risk increases in 2,92 times, and with a high BODE index (≥ 5 points) – 6,39 times. The total weight of these two parameters among other factors is 9,9%.

Functional markers of small bronchial obstruction are not only the decrease of FEV1 to the 30-50% (the risk of small airways obstruction in such conditions increases in 5, 21 times), but also the development of lung hyperinflation. With the increase of ITGV/TLC ratio up to 55% and more, the forecast for distal airway obstruction significantly decreases by 2, 3 times. The increase of the R5-R20 occurs simultaneously with other violations of the parameters of impulse oscillometry. The increase in the total resistance of the respiratory tract (R5 to 150% and above) and the resistance of the proximal airways (R20 to 150% and above), as well as an increase in AX above 3,37 and resonance frequency (Fres) above 12 Hz, increases the risk of distal obstruction at 26, 2, 12 and 6 times respectively.

Concomitant cardiovascular pathology is an unfavorable factor in the course of ACO. An increase of PBP over 50 or 60 mm Hg increases the risk of small bronchial obstruction of 3,62 and 2,6 times respectively. Left ventricular hypertrophy is associated with an increase in the incidence of small bronchial obstruction in 2, 33, pulmonary hypertension - is 3-fold, a high SCORE index of 6 and more points - in 6,82 times. The mixed (eosinophilic-neutrophilic) type of local inflammation increases the risk of small airways obstruction in 5, 55 times.

The factors of the development of lung hyperinflation in patients with ACO are clinical and functional features, as well as concomitant pathology (Figures 2 and 3).

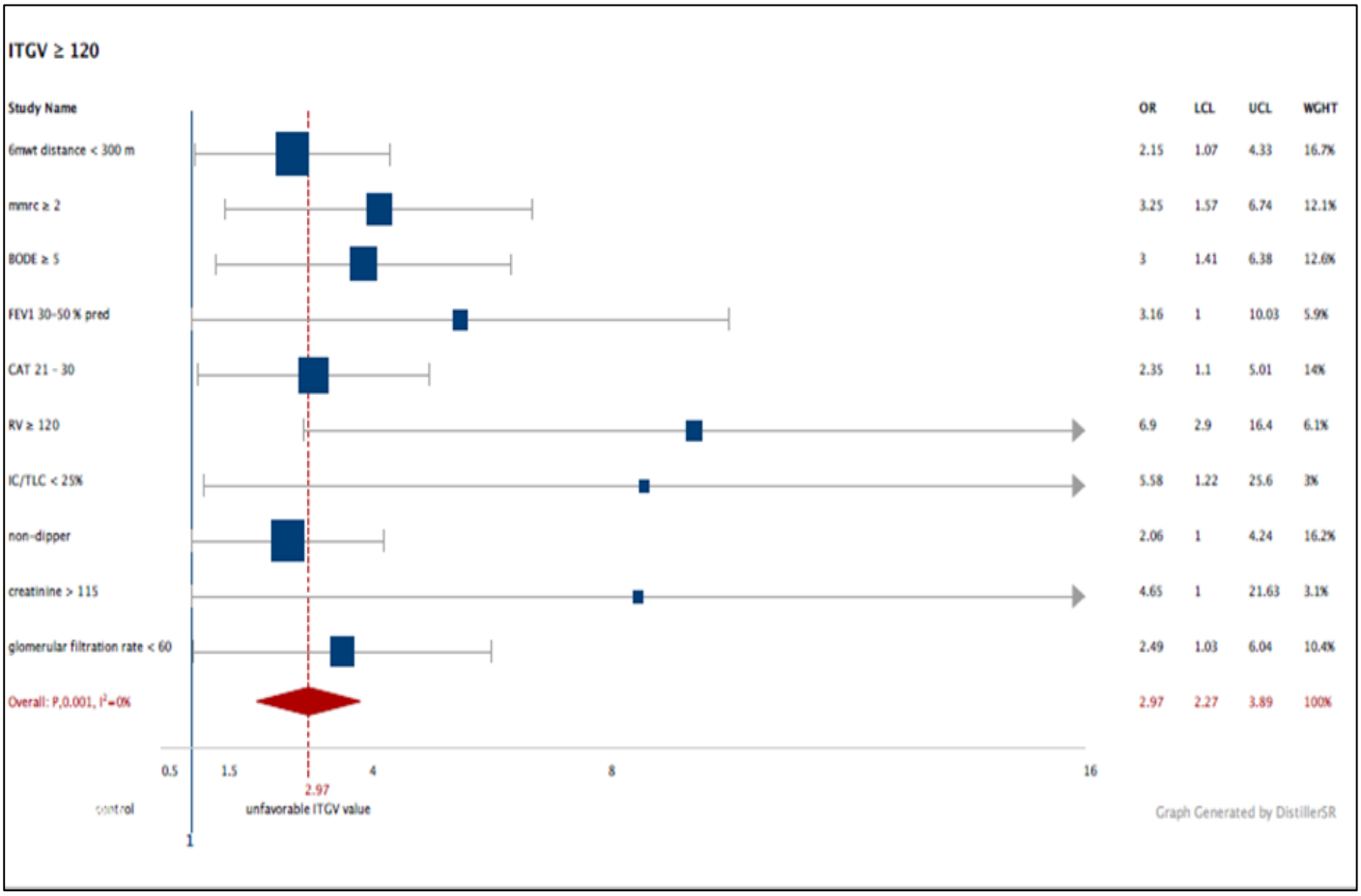


**Fig 2:** Risk factors for the formation of lungs hyperinflation in patients with ACO (increase of ITGV).

Like the small airways obstruction, lung hyperinflation is formed under the influence of age (every decade of life "adds" 16% to this risk), as well as with the more severe course of ACO. In an uncontrolled course of asthma (ACQ>1, 5), in COPD with severe symptoms (over 20 points of CAT test), dyspnea score of 2 and more (mMRC scale), a high BODE index of ≥ 5, and decreased exercise tolerance (distance less than 300 meters in a 6-minute walk), the incidence of hyperinflation increases from 2,15 to 15,74 times.

Functional factors in the formation of excessive airiness of the lungs are the decrease of FEV1 below 80% (especially within 30-50%), the decrease in inspiratory capacity in the structure of the total capacity of the lungs (IC/TLC up to 25% and lower) and air trapping (increase of residual volume (RV) to 120% and higher). The presence of small bronchial obstruction (an increase in R5-R20 according to impulse oscillometry) increases the risk of pulmonary hyperinflation by 2, 31 times. Thus, pulmonary hyperinflation can exist simultaneously with small airways obstruction.

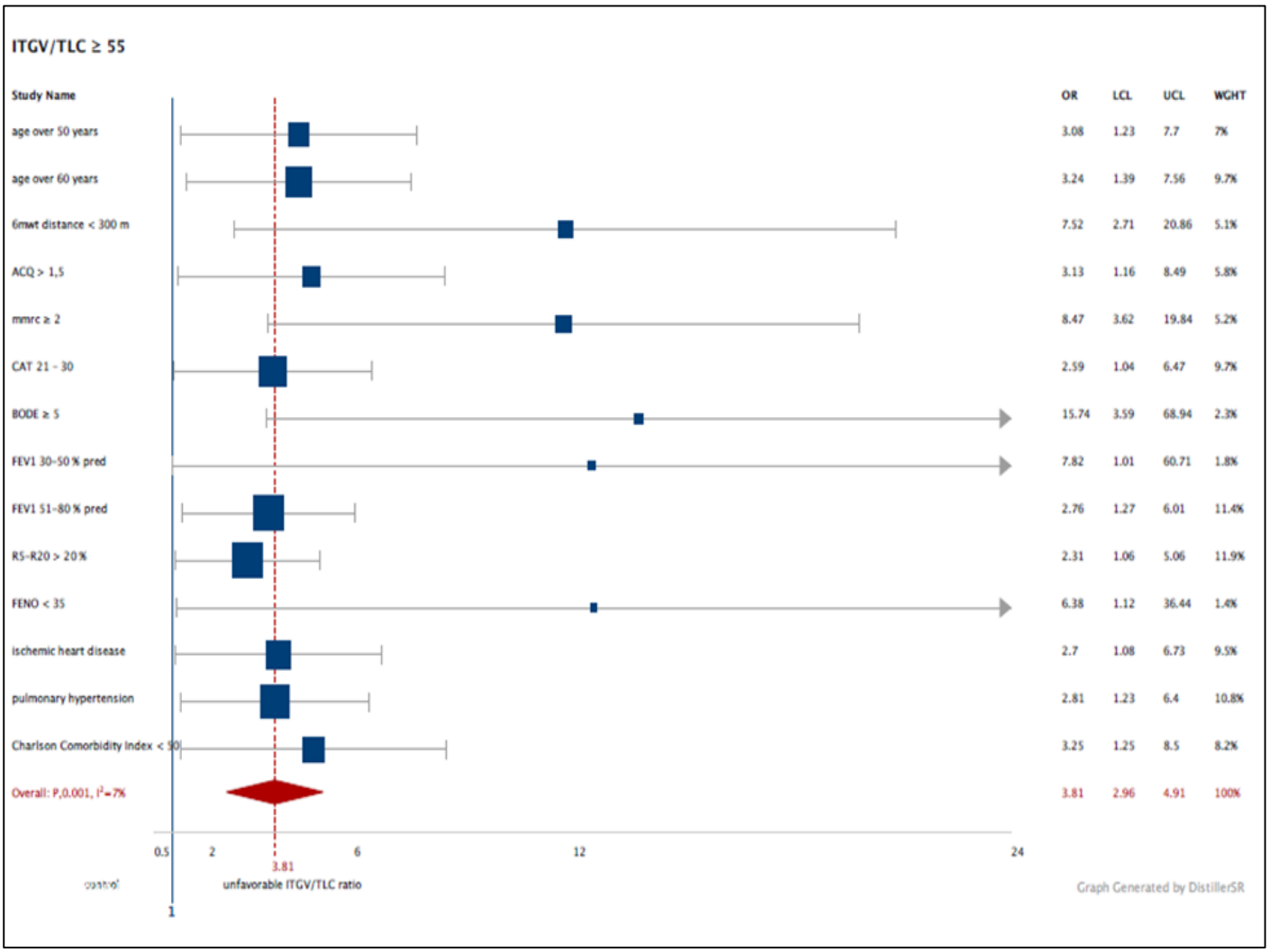


**Fig 3:** Risk Factors for the formation of lung hyperinflation in ACO patients (increase of ITGV/TLC)

The presence of concomitant cardiovascular disease and general low level of health is very relevant in ACO patients. Thus, 10 years life expectancy less than 50% (Charlson comorbidity index) increases the risk of pulmonary hyperinflation by 3, 25 times with the factor of 8,2%, concomitant ischemic heart disease – 2,7 times with a factor of 9,5% and pulmonary hypertension - in 2,81 times with a factor of 10,8%. The "non-dipping" status (ambulatory blood pressure monitoring) doubles the risk of lungs hyperinflation with a factor of 16, 2%.

Such indicators of a general low health status with a reduced life expectancy as an increase of serum creatinine level above 115 µmol/l and a decrease in glomerular filtration rate below 60 ml/min associated with an increased risk of lung hyperinflation in 4,65 and 2,49 times, with a total weight of two factors of 13,5%.

Thus, the assistance to ACO patients is not only in the pathogenetically justified purpose of anti-inflammatory and bronchodilator therapy, which will help prevent the formation of severe lung function disorders in the form of small airways obstruction and lung hyperinflation. Important is the question of timely detection and adequate treatment of concomitant pathology in this category of patients.

## Summary

Severe violations of the lung function parameters in the form of small airways obstruction and pulmonary hyperinflation may exist simultaneously. The common factors of these complications are the elderly age of patients, bronchial obstruction, especially FEV1 decrease below 50%, decreased exercise tolerance (distance in a 6-minute walking test less than 300 meters), severe dyspnea and high BODE index (≥ 5 points).

The differences in risk factors are the dependence of small bronchial obstruction on the type of local bronchial inflammation and the disease from which the ACO debuted, while lungs hyperinflation depends on the factors of the general low health status and the decrease in the predicted life expectancy of the patients.

Among the concomitant cardiovascular pathologies, arterial hypertension and the presence of left ventricular hypertrophy, along with obesity, have a greater effect on the obstruction of the distal respiratory tract, and ischemic heart disease - on lung hyperinflation. Pulmonary hypertension is a factor in the occurrence of both complications.

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