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Yuriy Ivanovich Feschenko
National Institute of Physiology and Pulmonology Named After F.G. Lanovskyi NAMS of Ukraine

Liudmyla Aleksandrovna Iashyna
National Institute of Physiology and Pulmonology Named After F.G. Lanovskyi NAMS of Ukraine

Ksenia Vladimirovna Nazarenko
National Institute of Physiology and Pulmonology Named After F.G. Lanovskyi NAMS of Ukraine

Svetlana Genrichovna Opimakh
National Institute of Physiology and Pulmonology Named After F.G. Lanovskyi NAMS of Ukraine

Correspondence
Ksenia Vladimirovna Nazarenko
National Institute of Physiology and Pulmonology Named After F.G. Lanovskyi NAMS of Ukraine

Risk factors of unfavorable life expectancy prognosis in patients with a combined pathology of asthma and chronic obstructive pulmonary disease

Yuriy Ivanovich Feschenko, Liudmyla Aleksandrovna Iashyna, Ksenia Vladimirovna Nazarenko and Svetlana Genrichovna Opimakh

Abstract
For a combined pathology of asthma and chronic obstructive pulmonary disease (asthma-COPD overlap - ACO), a higher frequency of exacerbations and their severe course, accelerated pulmonary function decline, a decrease in the quality of life of patients, a high incidence of comorbid diseases, and other negative effects are characteristic. The aim of this work was to study the risk factors of an unfavorable prognosis for the duration of life in patients with asthma-COPD overlap. Risk factors that reduce the life expectancy of patients with ACO are the elderly age, the onset of COPD, the more severe clinical course (mMRC, CAT and BODE scales), decreased physical endurance, severe bronchial obstruction, pulmonary hyperinflation, systemic and eosinophilic inflammation, and the most important factors of low survival are concomitant cardiovascular disease and diabetes mellitus. The practical value of the data obtained is the widespread use of available disease assessment tools (mMRC, CAT and BODE), the appointment of adequate bronchodilator and anti-inflammatory therapy for ACO, and the mandatory detection and treatment of concomitant diseases.

Keywords: Asthma-COPD overlap, prognosis, comorbidity

Introduction
For a combined pathology of asthma and chronic obstructive pulmonary disease (asthma-COPD overlap - ACO), a higher frequency of exacerbations and their severe course, accelerated pulmonary function decline, a decrease in the quality of life of patients, a high incidence of comorbid diseases, and other negative effects [1, 2] are characteristic.
The presence of several chronic diseases in one patient is associated with a decrease in the quality of life, disorders in the psycho-emotional sphere, longer hospitalizations, an increase in the incidence of complications and high mortality, as well as an increased resources of the health care system [3, 4]. In general clinical practice, comorbid conditions should be taken into account when choosing an algorithm for diagnostics and treatment of a particular disease.
The phenotyping, the allocation of separate groups of patients with similar characteristics within the framework of a heterogeneous population with lung obstructive pathology, is aimed at the rational use of diagnostic tools and optimization of the results of treatment, based on a differentiated approach to its conduction [5].
When identifying and validating the phenotypes of asthma, COPD, ACO, an important task is to select and characterize clinically and prognostically significant disease outcomes with an assessment of the risk factors for their achievement [6]. Identification and assessment of the impact of individual factors in the development of adverse effects in lung obstructive diseases may be useful in substantiating and conducting a differentiated approach to the evaluation, prevention and treatment of ACO with a better prediction of efficacy and safety. The research strategy for determining the risk factors for an adverse prognosis for life expectancy in patients with ACO is based on the use of a number of validated indices that have proven their intended use in patients with COPD and asthma.
To estimate the long-term mortality prognosis M.E. Charlson proposed an easy-to-use calculation tool - Charlson Comorbidity Index. When it is calculated, the points corresponding to the attendant disease are summed together, and one point is added for every 10 years of human life when the patient is over 40 years old [7]. According to the calculation of the comorbidity index, we can conclude about the predicted survival rate of patients for the next 10 years.

The aim of this work was to study the risk factors of an unfavorable prognosis for the duration of life in patients with asthma-COPD overlap.

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, office systolic blood pressure, diastolic blood pressure, pulse blood pressure measurement, spirometry and bodyplethismography (Master Screen Pneumo, Cardinal Health, Germany)), ambulatory blood pressure monitoring (EC-3H / ABP (Labtech, Hungary)), echocardiography (VIVID E9, General Electric), Charlson Comorbidity Index, COPD Evaluation (CAT test), mMRC Dyspnea Scale, BODE Index calculation [10], six-minute walking test according to a standard protocol [11].

Blood biochemistry and general blood analysis were performed in the clinical and biochemical laboratory of the SO National institute of phthysiology and pulmonology. The levels of glucose, creatinine were determined. The glomerular filtration rate was calculated by the CKD-EPI formula [12]. Also, the levels of highly specific C-reactive protein and NT-pro BNP were 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) [13]. 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" [14] 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

Among the adverse effects of any pathological condition, the most dramatic is the premature death of the patient. In the study of factors in which the prognosis of 10-year survival in the patients we surveyed does not reach 50%, the following is established (Fig. 1).

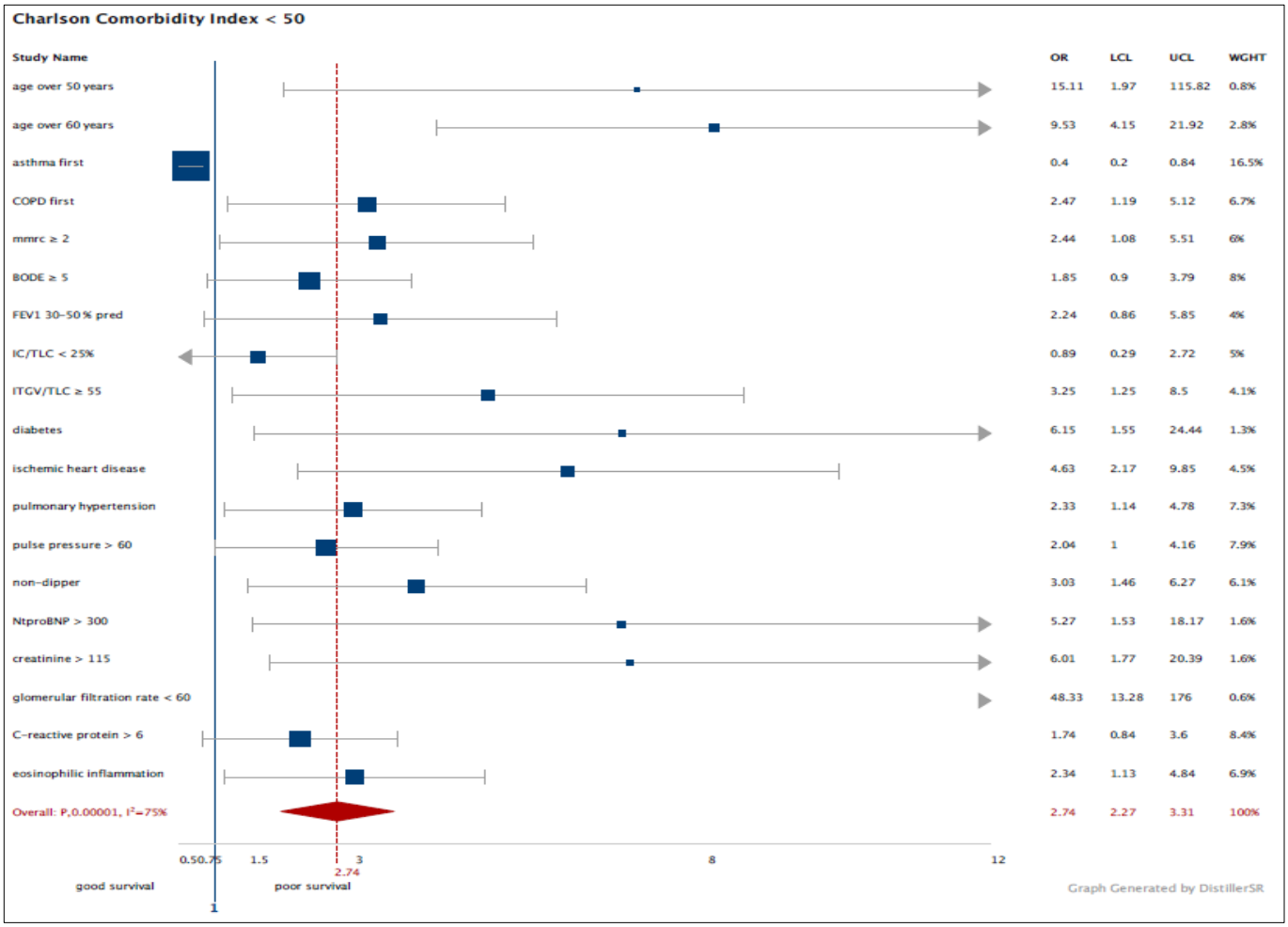

Fig 1: Risk factors for low survival of patients with ACO.

Anamnestic data show that, with age, life expectancy naturally worsens. In our group of patients with ACO, the risk of low survival occurs after 50 years of life, but the weight of this factor among others is only 0.8%, so there are no grounds for pessimistic attitude to treatment of older patients. Interestingly, patients with a primary diagnosis of asthma have a statistically significantly higher survival prediction (odds ratio = 0.4; confidence interval from 0.2 to 0.84). In this case, among the other factors considered, the primary diagnosis of asthma is the most significant - 16.5%. On the contrary, the onset of COPD is a significant risk factor for premature death of patients, which in our opinion can be explained by the lack of adequate treatment for this category of patients at the onset of the disease.

The severity of the clinical course of the disease also has a negative impact on the life prognosis of patients, since with a degree of dyspnea of 2 and above scores on the mMRC scale, the risk of low life expectancy is increased by 2,4 times, and in the high BODE index ≥ 5 points – 1,8 times, the total weight of these two parameters among other factors is 16%. Functional markers of low life expectancy are not so much the fall of FEV1, but the development of lungs hyperinflation. After all, with the growth of intrathoracic gas volume/ total lung capacity ratio (ITGV/TLC) up to 55% and more, life expectancy has deteriorated significantly more than three times. The weight of functional disorders is 13,1% among other factors.

At the same time, the most important risks factors of death in patients with ACO remain beyond the attention of pulmonologists. Focusing on the restoration and maintenance of the proper lung function should not distract from the actual threats that are among the concomitant pathology in this category of patients. The presence of diabetes increases the risk of low life expectancy by 6 times, ischemic heart disease – 4,6 fold, pulmonary hypertension – in 2,3 times. An increase in pulse pressure of more than 60 mm Hg increases this risk by 2 times, and the presence of a daily profile of blood pressure with a low decrease in blood pressure at night ("non-dipper") – in 3 times. The laboratory mortality-related data, also demonstrated its negative effects in our study: the level of NT-proBNP> 300 pg/ml increases the risk of mortality by more than 5-fold, the creatinine level > 115 - 6-fold, and the drop in glomerular filtration rate (GFR) below 60 ml/min/1,73 m2 - 48 times. The listed concomitant pathology options together account for 31% among other causes of low survival.

The state of systemic inflammation with an increase in C-reactive protein>6 mg/l has a relative weight of 8,4% among other studied risk factors and a 74% increase in the risk of low life expectancy. Eosinophilic inflammation increases this risk by 2, 3 times with a factor of almost 7%.

Charlson comorbidity index, of course, is not the only tool for estimating the life expectancy. Thus, it was found that a decrease in the inspiratory capacity/total lung capacity (IC/TLC) ratio below 25% is considered a risk factor for the death in COPD patients [15]. We separated the most important factors that influence the unfavorable redistribution of the total lung capacity with a decrease in inspiratory capacity in the ACO patients (Fig. 2).

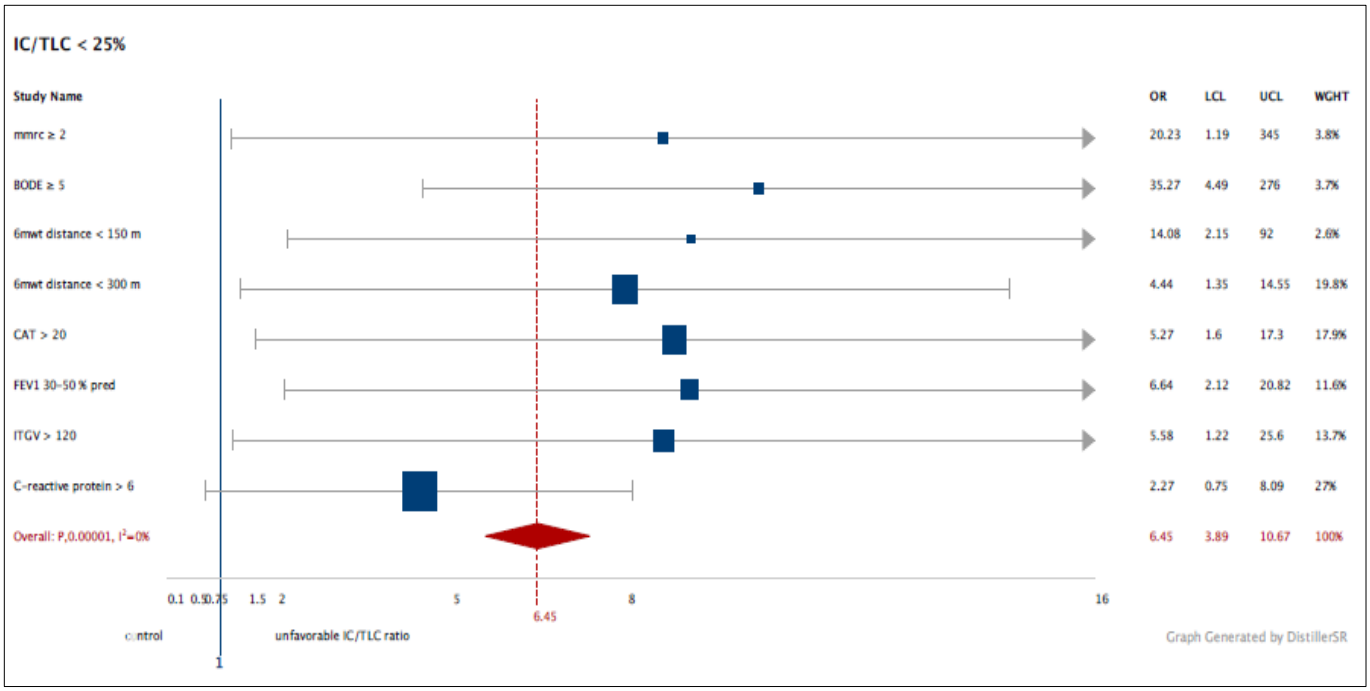

Fig 2: Factors of risk of unfavorable redistribution of total lung capacity with decreased inspiratory capacity.

The development of this complication contributes to systemic inflammation (the weight of the factor C-reactive protein> 6 among others is 27%) and severe bronchial obstruction with hyperinflation of the lungs (FEV1 30-50% and ITGV> 120% together have a weight of 25.3%). Other risk factors for decreasing of IC / TLC below 25% with a total weight of 47.7% are purely clinical, which can be recognized at the level of primary medical care. This is a reduction in the distance in the 6-minute walking test less than 300 or 150 meters, a dyspnea score of 2 or higher (mMRC), a CAT-test score of over 20 points, and a high BODE score of ≥ 5 points.

Conclusions

Risk factors that reduce the life expectancy of patients with ACO are the elderly age, the onset of COPD, the more severe clinical course (mMRC, CAT and BODE scales), decreased

physical endurance, severe bronchial obstruction, pulmonary hyperinflation, systemic and eosinophilic inflammation, and the most important factors of low survival are concomitant cardiovascular disease and diabetes mellitus.

The practical value of the data obtained is the widespread use of available disease assessment tools (mMRC, CAT and BODE), the appointment of adequate bronchodilator and anti-inflammatory therapy for ACO, and the mandatory detection and treatment of concomitant diseases.

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