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LUCA Ecaterina

**PULMONARY HYPERTENSION IN ELDERLY PATIENTS
WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

321.11 – GERONTOLOGY AND GERIATRICS

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Scientific adviser:

BODRUG Nicolae

Habilitated doctor of medical sciences, university professor _____

Members of the guidance committee:

CALANCEA Valentin,

Doctor of medical sciences, associate professor _____

ŞORIC Gabriela,

Doctor of medical sciences, associate professor _____

COŞCIUG Irina,

Doctor of medical sciences, associate professor _____

The public defense will take place on 13.12.2023 at 14:00, at the State University of Medicine and Pharmacy “Nicolae Testemitanu”, bd. Stephen the Great and Holy, 165, the office number 205, online: _____ in the meeting of the Committee for public defense of the doctoral thesis, approved by the decision of the Scientific Council of the Consortium of May 25, 2023 (minutes no. 6).

Componence of the Commission for public defense of the doctoral thesis:

Chairman:

MATCOVSCHI, Sergiu,

MD, PhD, professor _____

Members:

DUMITRAŞ, Tatiana,

PhD, associate professor _____

BODRUG, Nicolae

MD, PhD, professor _____

CUROCICHIN, Ghenadie,

MD, PhD, professor _____

CORLĂTEANU, Alexandru,

MD, PhD, professor _____

NEGARĂ, Anatolie,

PhD, associate professor _____

Official referents:

CALANCEA, Valentin,

Doctor of medical sciences, associate professor _____

PRADA, Gabriel-Ioan,

PhD, MD, professor, Bucureşti, România _____

STREBA, Costin Teodor,

PhD, MD, professor, Craiova, România _____

Author:

LUCA Ecaterina _____

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INTRODUCTION

The relevance and importance of the issue being investigated. According to the GOLD 2023 report, COPD remains a rising public health problem with a significant socio-economic burden. The condition is the 3th leading cause of death in the world, the 7th and 10th leading cause of disability in high- and low- or middle-income countries, respectively, and a leading worldwide cause of hospitalization [1].

According to the data of the National Agency for Public Health from Republic of Moldova the total incidence of chronic bronchitis and pulmonary emphysema in 2022 was 15.4 cases per 10.000 inhabitants. The prevalence of chronic bronchitis and pulmonary emphysema in 2022 constituted 159.3 cases per 10,000 inhabitants.

COPD mortality accounts for about 6% of all deaths worldwide. The disease has now become the third leading cause of death worldwide due to continued exposure to COPD risk factors and demographical ageing of the population. However, the impact of COPD on health can be underestimated, as about 50% of COPD mortality is caused by non-respiratory diseases, and COPD may increase the risk of death due to other comorbidities [1, 2].

COPD predominantly affects the elderly population [3, 4] with the disease being more serious, often unrecognized and untreated until it progresses to more severe symptoms [5, 6], is associated in average with 9 comorbidities, with higher mortality rates, with reduced response to therapeutic interventions and significant reduction in quality of life [5]. Acute exacerbations of COPD in the elderly are associated with accelerated progression of the disease, worsening and appearance of several symptoms, significant impairment of functional and cognitive performances, quality of sleep, life and prognosis [7, 8, 9]. Therefore, determining the peculiarities of the evolution of COPD in elderly patients is important for the early diagnosis of COPD, the implementation of effective interventions and for reducing the economic impact sustained by the public health system [10, 11].

Moreover, rational, generalizable and cost-effective strategies are needed to identify cardiovascular diseases, in particular PH and right heart failure, in the early stages of stable COPD and in the context of exacerbations, in order to reduce the impact of the disease in this group of patients [12].

According to the opinion of the scientists, despite of the advances in the perception of symptoms, evolution and management of diagnosis and therapy, over the past two decades there has been insufficient progress in early diagnosis of PH, especially in elderly patients. Timely and accurate diagnosis with the subsequent management of PH are very important because, despite of the therapeutical progress, the survival of this group of patients remains suboptimal [6, 12, 13].

Currently, the need to evaluate new biomarkers in COPD has been highlighted, but implementation in the clinical practice has largely been unsuccessful. The level of natriuretic peptides- NT-proBNP has been studied insufficiently in patients with heart-complicated lung diseases, especially in COPD associated with PH. Few studies have been dedicated to assessing NT-proBNP diagnostic and prognostic value in determining COPD severity, exacerbation risk

identifying of uncomplicated stable COPD, prognosis of the acute exacerbation installed and determining the possibility of development of secondary PH or pulmonary heart [12, 14]. At the same time, in the literature, data on natriuretic peptides in elderly patients are very rare, and their examination in patients with COPD in the Republic of Moldova is of the interest [15, 16].

Thus, based on the above, **the purpose of the research** is to highlight the clinical and paraclinical characteristics of elderly patients with chronic obstructive pulmonary disease and secondary pulmonary hypertension with the proposal of a diagnostic algorithm of it.

In order to achieve the goal, the following **general research objectives** were stipulated:

1. Clinical-paraclinical characterization of chronic obstructive pulmonary disease in elderly patients.
2. Clinical and paraclinical evaluation and characterization of pulmonary hypertension in elderly patients with chronic obstructive bronchopneumopathy.
3. Estimation of the impact of pulmonary hypertension secondary to chronic obstructive bronchopneumopathy on functional capacities of elderly patients.
4. The proposal of an algorithm for the diagnosis of chronic obstructive pulmonary disease with secondary pulmonary hypertension in elderly patients.

Scientific novelty of the obtained results. Based on a complex study, it was estimated: 1) the PH characteristics in elderly patients with COPD, highlighting the correlation of clinical, functional and paraclinical parameters; 2) the level of NT-proBNP values in acute exacerbation of COPD; 3) correlation of NT-proBNP value with PH degree in elderly COPD patients.

These results allowed the evaluation of clinical and paraclinical heterogeneity of COPD patients depending on the severity of COPD in the context of PH association or pulmonary cor. The paraclinic study proposes the diagnostic method for detecting secondary cardiovascular involvement of COPD.

Theoretical significance and applicative value of the study. The performed research helped to elucidate the clinical and paraclinical characteristics of COPD with secondary pulmonary hypertension in elderly patients and highlighted the differences compared to non-complicated patients. Moreover, the study allows to deepen the knowledge regarding the minimally invasive diagnostic method with the aim of implementing it in the practice of diagnostic and therapeutic management of the COPD patient. As a result, we will achieve a reduction in the incidence of serious forms of the disease, the frequency and number of exacerbations, their complications and severity, the rate of hospitalization and deaths in patients with COPD.

Approval of thesis results. The results of the study were presented and discussed in the following national and international scientific forums: Scientifico-practical Conference with international participation “Actualities in chronic obstructive pulmonary disease”, on 20 November, 2013, Chisinau, Republic of Moldova; Symposium “Centenary of Romanian Internal Medicine”, 25-26 October 2019, Cluj-Napoca, Romania; I National Congress of Geriatrics and Gerontology with international participation from the Republic of Moldova, September 23-24, 2021, Chisinau, Republic of Moldova; The 14th National Congress of Geriatrics and Gerontology with international participation “Multidimensional approach to active longevity”, October 20-23, 2022, Bucharest, Romania.

Keywords: Chronic obstructive pulmonary disease, elderly, dyspnea, comorbidities, acute exacerbation, pulmonary hypertension, lung heart, natriuretic peptides, spirometry, echocardiography.

1. PULMONARY HYPERTENSION IN ELDERLY PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Analysis of randomized clinical, case-control, retrospective and prospective observational studies has allowed the following main features of COPD in the elderly to be ascertained:

1. COPD is a complex and common condition in elderly patients, characterized by high rates of disturbing symptoms, significant risk of cognitive and functional decline, progression of the disease, frequent use of healthcare, extremely difficult treatment and increased mortality.
2. The elderly patients have an increased prevalence of COPD and a higher disease burden: significantly higher frequency, severity and impact of symptoms, lower exercise tolerance and lower daily activity capacities, higher incidence of acute severe exacerbations and higher prevalence of systemic comorbidities.
3. Acute exacerbations and comorbidities have a negative impact on elderly patients with COPD, manifested by increased rate and duration of hospitalization, increased rehospitalization and mortality rate.
4. Multidimensional assessment and multidisciplinary intervention, well known in respiratory assessment, should also be applied to the geriatric population.
5. PH is a serious complication in the progressively worsening natural history of COPD, with complex pathogenetic mechanisms, associated with acute exacerbation of COPD, reduced survival and significant socioeconomic impact on health resources.
6. The diagnosis of PH in COPD is difficult, especially in the mild form, and requires suspicion based on the clinical picture, objective examination, history of the disease and anamnesis, with review of a comprehensive set of scales, functional examinations and investigations that would confirm the criteria of pulmonary and secondary cardiovascular involvement.
7. Natriuretic peptide values are frequently elevated in patients with chronic obstructive pulmonary disease, reflecting the complex interrelated aspects of the cardiopulmonary continuum. Further increase in NP values during acute exacerbation of chronic obstructive pulmonary disease is, likely, a marker for both, acute stress and varying degrees of underlying cardiopulmonary disease.
8. The results of the studies suggest the role of PN as relevant diagnostic and prognostic biomarker, not only for patients with cardiovascular diseases, but also for patients with stable COPD or acute exacerbation associated with secondary pulmonary hypertension and pulmonary heart, allowing the selection of a subgroup of patients at higher risk, which requires increased attention and optimization of treatment.

2. MATERIAL AND METHODS OF STUDY

2.1. General feature of the research methodology

The study was carried out in the Department of Internal Medicine (Discipline of Geriatrics and Occupational Medicine) of the “Nicolae Testemitanu” State University of Medicine and Pharmacy and in the Public Medical-Sanitary Institution of Health Ministry Clinical Hospital from Republic of Moldova.

The study included 194 elderly patients (≥ 65 years), selected from no. 1, 2 Geriatrics Departments of the Public Medical-Sanitary Institution Ministry of Health Clinical Hospital. The general study group was divided into 2 sublots based on the presence of PH: first subplot – 97 patients with COPD without PH, second subplot– 97 patients with COPD and secondary PH.

Research design is presented through CONSORT diagram (Consolidated Standards of Reporting Trials) (figure 1).

In order to improve the accuracy of the research, we followed a number of inclusion criteria and exclusion criteria, thus ensuring a better delimiting of the study and centering on a specific representative group.

Study inclusion criteria:

1. Patients age ≥ 65 years.
2. Presence of COPD with various degrees of severity (mandatory presence of spirographic diagnostic criteria: $FEV1/FVC \leq 70\%$, negative postbronchodilatory test).
3. The presence of mental and physical capacities, which allows the understanding and compliance with the requirements of the study and the fulfillment of diagnostic methods: anamnestic data, objective data, questionnaire filling out, laboratory and instrumental investigation data.
4. Consent and signature of informed consent for the study inclusion.

Study exclusion criteria:

1. Serious concomitant pathologies that may cause myocardial remodeling or cardiovascular disorders of other nature than COPD (neoplasms, congenital and acquired cardiac abnormalities, cardiomyopathies, acute coronary syndrome, acute myocardial infarction, pulmonary artery thromboembolism, arterial hypertension third degree with the association of left heart failure, liver cirrhosis, portal hypertension, viral/bacterial pneumonia and tuberculosis).
2. Presence of diseases that change the level of NT-proBNP plasma: renal impairment (serum creatinine > 2.8 mg/dL), infectious diseases, malignancy, recent surgery, severe endocrine and hepatic dysfunction.
3. Severe degree of locomotor vulnerability.

4. Expressed disapproval for participation in the study.

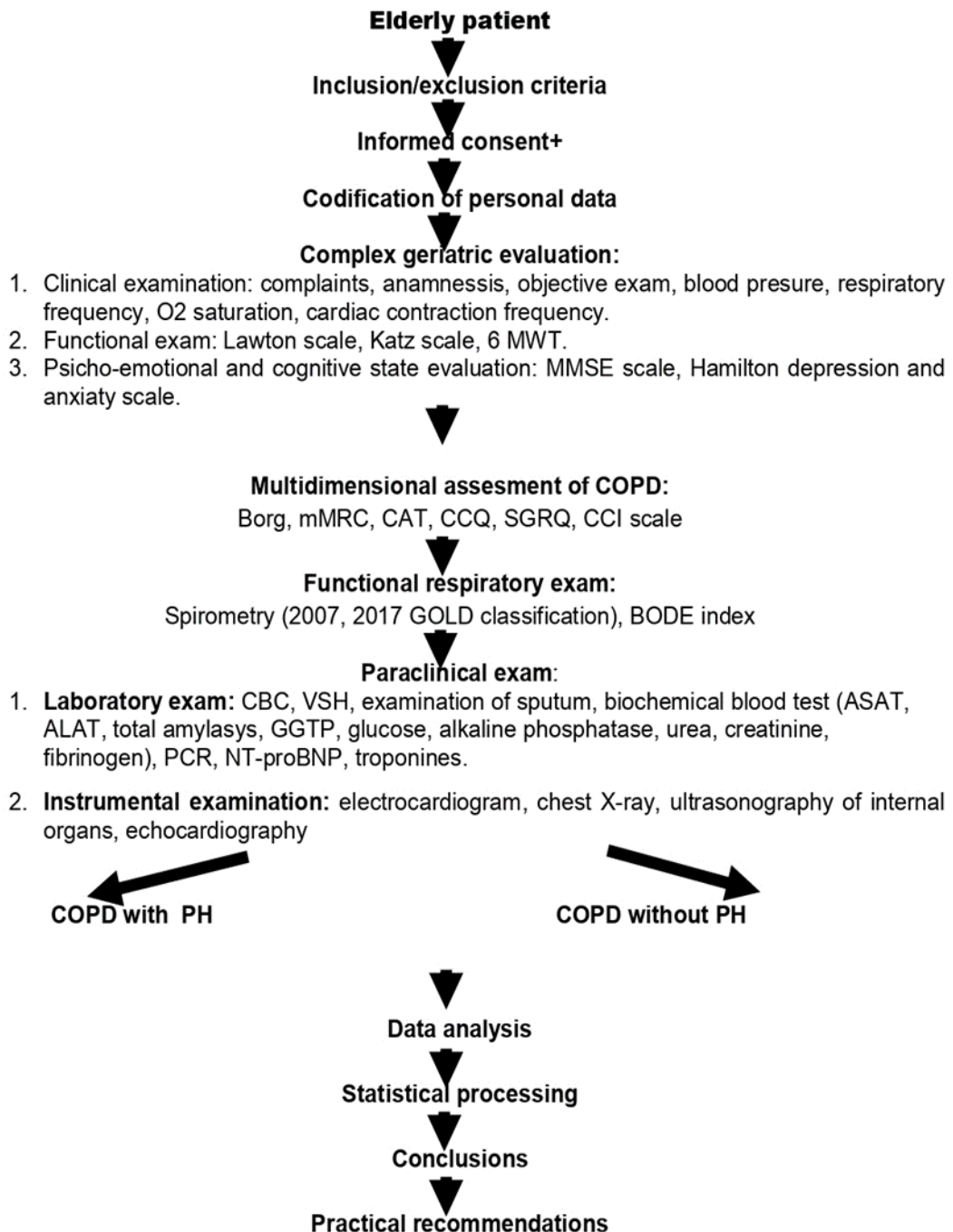


Figure 1. Study design CONSORT Diagramm of the patients flow.

2.2. Investigation methods and diagnostic criteria

All subjects underwent the following examinations:

1. Collection of clinical data: detailed characteristic of the acuses (duration, character and emphasis of cough, sputum production, dyspnoea), anamnesis history (rate of exacerbations, smoking history, occupational/household exposures, recurrent respiratory infections, socio-economical status) and personal pathological antecedents with the quantification of the comorbidities through Charlson Comorbidity Index.
2. General objective clinical examination, blood pressure, heart rate, respiratory rate and SaO₂.
3. Multidimensional approach to COPD using recommended questionnaires, proposed by GOLD: Borg scale, estimation of dyspnea degree (mMRC), evaluation of symptoms (CAT, CCQ), quantification of quality of life (SGRQ) and determination of prognosis (BODE index), that allow the characterisation and gradation of the acuses and impact of the respiratory disease.
4. Complex geriatric evaluation, performed through applying a set of specific assessment scales: Katz score – daily activities score, Lawton score – score of complex instrumental daily activities requiring the use of tools, MMSE test, Hamilton depression scale and Hamilton anxiety scale.
5. Conventional chest X-ray in post-anterior and lateral incidence
6. Biochemical methods: serum clinical-biochemical analyzes (blood count, C-reactive protein (mg/dL), fibrinogen (mg/dL), ALT (U/L), AST (U/L), total amylase (U/L), GGTP (U/L), glucose (mmol/L), alkaline phosphatase (U/L), urea (mmol/L), creatinine (mmol/L), troponine (mcg/L)), sputum examination, determination of NT-proBNP level in blood serum (pg/mL).
7. Pulmonary functional tests: spirometry – before and after bronchodilation and 6MWT.
8. Standard 12-lead electrocardiography.
9. Ultrasonography of internal organs for the assessment of the inferior cava vein and suprahepatic veins diameters and liver venous congestion signs.
10. Transthoracic echocardiography according to standard protocol for determining the size of the chambers of the heart and mPAP.

In COPD patients, exacerbations have been defined as acute worsening of existing respiratory symptoms, expressed by the presence for at least two consecutive days of increased intensity of at least two or even three "major" symptoms (dyspnea, purulent sputum, amount of sputum), a "major" symptom and a "minor" symptom (wheezing, sore throat, cough, nasal congestion and/or rhinorrhea) or the appearance of other new symptoms.

Transthoracic echocardiography with the pulsatile Doppler examination was used to measure systolic pressure in PA by evaluating blood systolic flow parameters in PA and in the right ventricle ejection tract using pre-installed cardiac measurement programs, module M. For mPAP measurement we used the following formula:

$$\text{mPAP} = 0,61 * \text{systolic pressure in PA} + 2 \text{ mm Hg}$$

mPAP value ≥ 25 mm Hg was considered as PH.

COPD patients received standard and follow-up care according to the national hospital and extra-hospital management protocols of this patient group. The information required for the study,

the results of clinical examinations and medical complications were collected from patients during clinical visits, according to the design of the study.

2.3. Methods of statistical processing of the results

The processing of primary data was carried out computerized with the help of statistical packets „*Statistical Package for the Social Science*” (SPSS), 16.0 version for Windows (SPSS Inc., Belmont, CA, USA, 2008) and *Microsoft Office Excel 2019* through standart methods variationally, correlative and discriminatory statistical analysis. To estimate the normality of the distribution of the quantitative variables values we used the Kolmogorov-Smirnov test. To estimate the significant differences between the averages of two groups, was used the t test (in the case of normal distribution of variable values) or the Mann-Whitney U test (in the case of asymmetric distribution of variable values) for independent samples. The data of contingency tables were analyzed using the variational statistics method (χ^2). In order to assess the intensity of the statistical links we used the correlation process. Statistically significant, we considered the differences with bilateral values $p < 0,05$.

3. CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN ELDERLY PATIENTS

3.1. Clinical and paraclinical features of chronic obstructive pulmonary disease in elderly patients

In the general study group, were selected 194 patients with acute COPD exacerbation aged 65-90 years (average age $71,84 \pm 0,4$ years; MD - 71,0, IIQ: 68,0-75,0), inclusive 135 (69,6%; 95% CI: 62,9-75,7) men and 59 (30,4%; 95% CI: 24,3-37,1) of women.

The complex geriatric evaluation revealed frequent complaints (cough – 100,0%, dyspnea – 100,0%, expectorations – 99,0%; 95% CI: 96,7-99,8, chest discomfort – 94,8%; 95% CI: 91,0-97,3, wheezing – 47,9%; 95% CI: 41,0-55,0, subfebrility – 15,5%; 95% CI: 10,9-21,0), risk factors (88,4%; 95% CI: 80,4-93,9 are smoking or smoked 10 or more packs of cigarettes per year), a significant number of comorbidities (on average $8,33 \pm 2,5$; Md - 8,0, IIQ: 6,0-10,0), abnormal mean Katz score values ($11,03 \pm 1,1$ points; Md - 11,0, IIQ: 10,0-12,0), Lawton score values ($13,44 \pm 2,2$ points; Md - 14,0, IIQ: 12,0-16,0), Hamilton anxiety score ($9,15 \pm 2,8$ points; Md - 10,0, IIQ: 7,0-11,0), Hamilton depression score ($6,51 \pm 3,1$ points; Md - 6,0, IIQ: 4,0-9,0) and MMSE score ($25,79 \pm 2,5$ points; Md - 26,0, IIQ: 24,0-28,0).

The multidimensional approach of acute exacerbation of COPD revealed pathological values of the questionnaires proposed by GOLD: Borg scale ($2,71 \pm 0,6$ points; Md - 3,0, IIQ: 2,0-3,0), CAT scale ($26,21 \pm 6,2$ points; Md - 26,0, IIQ: 22,75-32,0), total SGRQ score ($62,23 \pm 14,7$ points; Md - 61,78, IIQ: 50,5-73,8), total CCQ score ($3,52 \pm 0,9$ points; Md - 3,6, IIQ: 2,8-4,3), BODE index ($4,01 \pm 1,7$ points; Md - 4,0, IIQ: 3,0-5,0), dyspnea mMRC scale ($1,81 \pm 0,8$ points; Md - 2,0, IIQ: 1,0-2,0), CCI ($6,44 \pm 1,8$ points; Md - 6,0, IIQ: 5,0-7,0).

According to the GOLD (2007) classification, the study group was divided into patients with moderate COPD degree– 92 (47,4%; 95% CI: 40,5-54,4) of total cases, patients with severe COPD degree- 95 (49,0%; 95% CI: 42,0-56,0) of total cases and patients with very severe COPD degree 7 (3,6%; 95% CI: 1,6-7,0) of total cases. According to the GOLD (2017) classification, patients

with acute exacerbation of COPD in the general study group were allocated as follows: type B of COPD at 3 (1,5%; 95% CI: 0,4-4,1) patients, type C of COPD at 6 (3,1%; 95% CI: 1,3-6,3) patients and type D of COPD at 185 (95,4%; 95% CI: 91,7-97,7) patients.

The 6MWT evaluation revealed 2 (1,0%; 95% CI: 0,2-3,3) patients with very low effort tolerance, 94 (48,5%; 95% CI: 41,5-55,5) patients with low effort tolerance, 96 (49,5%; 95% CI: 42,5-56,5) of patients with moderate effort tolerance and 2 (1,0%; 95% CI: 0,2-3,3) patients with high effort tolerance.

Chronic respiratory failure 0 degree presented- 57 (29,4%; CI: 27,0-31,9) of patients, I degree presented- 126 (64,9%; 95% CI: 57,7-71,1) and the II degree presented- 11 (5,7%; 95% CI: 3,0-9,6) of patients.

Chest X-ray examination revealed susceptible signs for chronic bronchitis in 177 (91,2%; 95% CI: 86,6-94,6), susceptible signs for pulmonary emphysema in 40 (20,6%; 95% CI: 15,4-26,7) cases.

The transthoracic echocardiography determined hypertrophy signs of the right ventricle and pulmonary hypertension. The mean value of mPAP was $30,85 \pm 15,3$ mm Hg (Md – 24,5, IIQ: 19,0-34,0).

Mean values of NT-proBNP in the group was– $972,9 \pm 1052,1$ pg/mL (Md – 277,6, IIQ: 135,0-1929,7).

3.2. Clinical and paraclinical features of secondary pulmonary hypertension in chronic obstructive pulmonary disease in elderly patients

The study group included 97 patients with acute exacerbation of COPD and PH aged 65-90 years (average age $73,35 \pm 6,4$ years; Md – 72,0, IIQ: 68,0-78,0), including 65 (67,0%; 95% CI: 57,3-75,8) men and 32 (33,0%; 95% CI: 24,2-42,7) of women.

The complex geriatric evaluation revealed frequent, higher-intensity complaints (cough – 100,0%, dyspnoea – 100,0%, expectorations – 100,0%, chest discomfort – 97,9%; 95% CI: 93,6-99,6, wheezing – 79,4%; 95% CI: 70,3-86,2, subfebrility – 28,9%; 95% CI: 20,6-38,4), risk factors (90,7%; 95% CI: 79,4-96,8 are smoking or smoked or more packs of cigarettes per year), a significant number of comorbidities (on average $8,4 \pm 2,6$; Md – 8,0, IIQ: 6,0-10,0), abnormal mean Katz score values ($10,64 \pm 1,2$ points; Md – 11,0, IIQ: 10,0-12,0), Lawton score ($12,62 \pm 2,0$ points; Md – 12,0, IIQ: 11,0-14,0), Hamilton anxiety score ($9,90 \pm 2,3$ points; Md – 10,0, IIQ: 9,0-11,0), Hamilton depression score ($7,03 \pm 3,1$ points; Md – 7,0, IIQ: 4,5-10,0) and MMSE score ($25,14 \pm 2,4$ points; Md – 25,0, IIQ: 23,0-28,0).

The multidimensional approach of acute exacerbation of COPD with PH revealed pathological values of the questionnaires proposed by GOLD: Borg scale ($2,4 \pm 0,5$ points; Md – 2,0, IIQ: 2,0-3,0), CAT scale ($29,81 \pm 5,3$ points; Md – 31,0, IIQ: 27,0-34,0), total SGRQ score ($71,73 \pm 12,1$ points; Md – 72,8, IIQ: 64,58-78,92), total CCQ score ($4,08 \pm 0,8$ points; Md – 4,3, IIQ: 3,6-4,6), BODE index ($5,04 \pm 1,5$ points; Md – 5,0, IIQ: 4,0-6,0), dyspnoea mMRC scale ($2,35 \pm 0,6$ points; Md – 2,0, IIQ: 2,0-3,0), CCI ($6,56 \pm 1,8$ points; Md – 6,0, IIQ: 5,0-7,5).

According to the GOLD (2007) classification, the study group was divided into patients with moderate COPD degree– 11 (11,3%; 95% CI: 6,2-18,8) of cases, patients with severe COPD degree– 79 (81,4%; 95% CI: 72,8-88,2) of cases and patients with very severe COPD degree 7

(7,2%; 95% CI: 3,3-13,6) of cases. According to the GOLD (2017) classification, patients with acute exacerbation of COPD in the general study group were allocated as follows: type C of COPD at 1 (1,0%; 95% CI: 0,1-4,7) patients and type D of COPD at 96 (99,0%; 95% CI: 95,3-99,9) patients.

The 6MWT evaluation revealed 1 (1,0%; 95% CI: 0,1-4,7) patients with very low effort tolerance, 75 (77,3%; 95% CI: 68,3-84,8) patients with low effort tolerance, 21 (21,6%; 95% CI: 14,4-30,6) of patients with moderate effort tolerance.

Chronic respiratory failure 0 degree presented- 9 (9,3%; 95% CI: 4,7-16,2) of patients, I degree presented- 77 (79,4%; 95% CI: 73,3-84,6) and the II degree presented- 11 (11,3%; 95% CI: 7,5-16,4) of patients.

Chest X-ray examination revealed susceptible signs for chronic bronchitis in 96 (99,0%; 95% CI: 94,4-99,8), susceptible signs for pulmonary emphysema in 34 (35,1%; 95% CI: 26,3-45,0) cases.

The transthoracic echocardiography determined hypertrophy signs of the right ventricle and pulmonary hypertension. The mean value of mPAP was $42,44 \pm 14,0$ mm Hg (Md – 34,0, IIQ: 32,0-54,5).

Mean values of NT-proBNP in the group was– $1807,16 \pm 901,1$ pg/mL (Md – 1925,5, IIQ: 1122,45-2445,70).

3.3. Clinical and paraclinical features of chronic obstructive pulmonary disease without secondary pulmonary hypertension in elderly patients

The study group included 97 patients with acute COPD exacerbation without PH aged 65-86 years (average age $70,32 \pm 4,8$ years; Md – 70,0, IIQ: 67,0-72,0), inclusive 70 (72,2%; 95% CI: 62,7-80,3) men and 27 (27,8%; 95% CI: 19,7-37,3) of women.

The complex geriatric evaluation revealed statistically frequent, lower intensity complaints (cough – 100,0%, dyspnoea – 100,0%, expectorations – 97,9%, chest discomfort – 91,8%; 95% CI: 85,0-96,0), risk factors (86,0%; 95% CI: 73,5-94,0 among smokers, are smoking or smoked 10 or more packs of cigarettes per year), a significant number of comorbidities (on average $8,26 \pm 2,4$), abnormal mean Katz score values ($11,41 \pm 0,9$ points), Lawton score ($14,26 \pm 2,0$ points), Hamilton anxiety score ($8,4 \pm 3,1$ points), Hamilton depression score ($5,98 \pm 3,0$ points) and MMSE score ($26,43 \pm 2,4$ points).

The multidimensional approach of acute exacerbation of COPD without PH highlighted abnormal values of the questionnaires proposed by GOLD: Borg scale $3,02 \pm 0,5$ points (Md – 3,0, IIQ: 3,0-3,0), CAT scale – $22,61 \pm 4,8$ points (Md – 23,0, IIQ: 21,0-25,0), total SGRQ score – $52,73 \pm 10,2$ points (Md – 52,86, IIQ: 45,46-58,89), total CCQ score – $2,97 \pm 0,69$ points (Md – 3,0, IIQ: 2,45-3,50), BODE index – $2,97 \pm 1,15$ points (Md – 3,0, IIQ: 2,0-3,0), dyspnoea mMRC scale – $1,27 \pm 0,6$ points (Md – 1,0, IIQ: 1,0-2,0).

According to the GOLD (2007) classification, the study group was divided into patients with moderate COPD degree– 81 (83,5%; 95% CI: 75,2-89,9) of cases, patients with severe COPD

degree- 16 (16,5%; 95% CI: 10,1-24,8) of cases. Mild and very severe degree of COPD were not in the study group. According to the GOLD (2017) classification, patients with acute exacerbation of COPD in the non PH COPD group were allocated as follows: type B of COPD at 3 (3,1%; 95% CI: 0,9-8,0) patients, type C of COPD at 5 (5,2%; 95% CI: 2,0-10,9) patients and type D of COPD at 89 (91,8%; 95% CI: 85,0-96,0) patients.

The 6MWT evaluation revealed 1 (1,0%; 95% CI: 0,1-4,7) patients with very low effort tolerance, 19 (19,6%; 95% CI: 12,6-28,3) patients with low effort tolerance, 75 (77,3%; 95% CI: 68,3-84,8) of patients with moderate effort tolerance and 2 (2,1%; 95% CI: 0,4-6,4) patients with high effort tolerance

Chronic respiratory failure 0 degree presented- 48 (49,5%; CI: 42,5-56,5) of patients, I degree presented- 49 (50,5%; 95% CI: 43,5-57,5).

Chest X-ray examination revealed susceptible signs for chronic bronchitis in 81 (83,5%; 95% CI: 75,2-89,9), susceptible signs for pulmonary emphysema in 6 (6,2%; 95% CI: 2,6-12,3) cases.

The transthoracic echocardiography determined hypertrophy signs of the right ventricle. The mean value of mPAP was $19,26 \pm 1,7$ mm Hg (Md – 19,0, IIQ: 18,0-21,0).

Mean values of NT-proBNP in the group was – $138,65 \pm 81,8$ pg/mL (Md – 136,0, IIQ: 60,25-209,25).

4. PULMONARY HYPERTENSION IN ELDERLY PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

4.1. The impact of pulmonary hypertension secondary to chronic obstructive pulmonary disease in elderly patients

In the study groups, 97 patients with acute COPD and PH exacerbations aged 65-90 and 97 patients with acute COPD exacerbation without PH aged 65-86 were selected for inclusion. The study groups were similar depending on gender, living environment, social status, living conditions, risk factors (smoking and household pollution), number of comorbidities, general condition, duration of current hospitalization and number of hospitalizations in last year.

The mean age value was statistically significantly higher in the group of patients with acute COPD and PH exacerbations ($73,35 \pm 6,4$ years; MD – 72,0, IIQ: 68,0-78,0) compared to patients with acute COPD exacerbation without PH ($70,32 \pm 4,8$ years; MD – 70,0, IIQ: 67,0-72,0; $p < 0.01$). The complex clinical evaluation revealed in patients with acute exacerbation of COPD and PH compared to patients with acute exacerbation of COPD without HP, statistically significantly more frequent and more severe complaints, more frequent comorbidities, more serious medical examination abnormalities.

Although the mental state was clear in all patients from both groups of study, irritability and chronic insomnia were statistically significantly more common in patients with acute COPD and PH exacerbations, but short-term insomnia – statistically significantly more frequent in patients with acute COPD exacerbation without PH (figure 2).

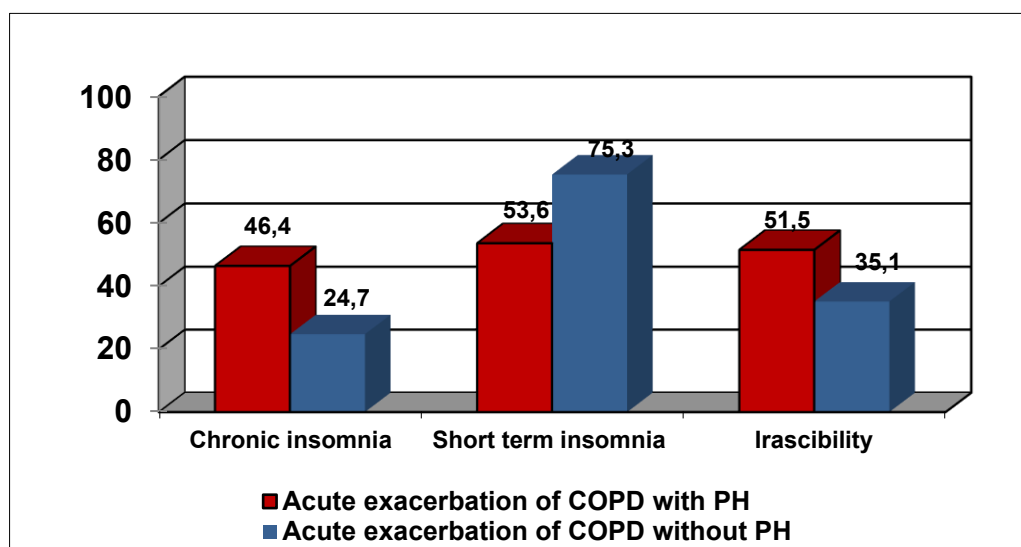


Figure 2. Statistically significant changes in mental health patients in study groups (%).

The geriatric evaluation according to the questionnaires reveals the negative impact of bronchial obstruction and PH on simple and complex daily activities, cognitive abilities and emotional state. Average Katz score values ($11,41 \pm 0,9$ points; Md – 12,0, IIQ: 11,0-12,0 and $10,64 \pm 1,2$ points; Md – 11,0, IIQ: 10,0-12,0, respectively; $p < 0,001$), Lawton score ($14,26 \pm 2,0$ points; Md – 15,0, IIQ: 12,0-16,0 and $12,62 \pm 2,0$ points; Md – 12,0, IIQ: 11,0-14,0, respectively; $p < 0,001$) and MMSE score ($26,43 \pm 2,4$ points; Md – 27,0, IIQ: 25,0-28,0 and $25,14 \pm 2,4$ points; Md – 25,0, IIQ: 23,0-28,0, respectively; $p < 0,001$) were statistically significantly higher in the group of patients with acute COPD exacerbation without PH, meanwhile the average values of Hamilton anxiety score ($9,90 \pm 2,3$ points; Md – 10,0, IIQ: 9,0-11,0 and $8,4 \pm 3,1$ points; Md – 9,0, IIQ: 6,0-11,0, respectively; $p < 0,001$) and Hamilton depression score ($7,03 \pm 3,1$ points; Md – 7,0, IIQ: 4,5-10,0 and $5,98 \pm 3,0$ points; Md – 6,0, IIQ: 4,0-8,0, respectively; $p < 0,05$) – were statistically significantly higher in the group of patients with acute COPD and PH exacerbations, fact that reflects the PH complicated COPD impact on emotional estate of the patient (figure 3).

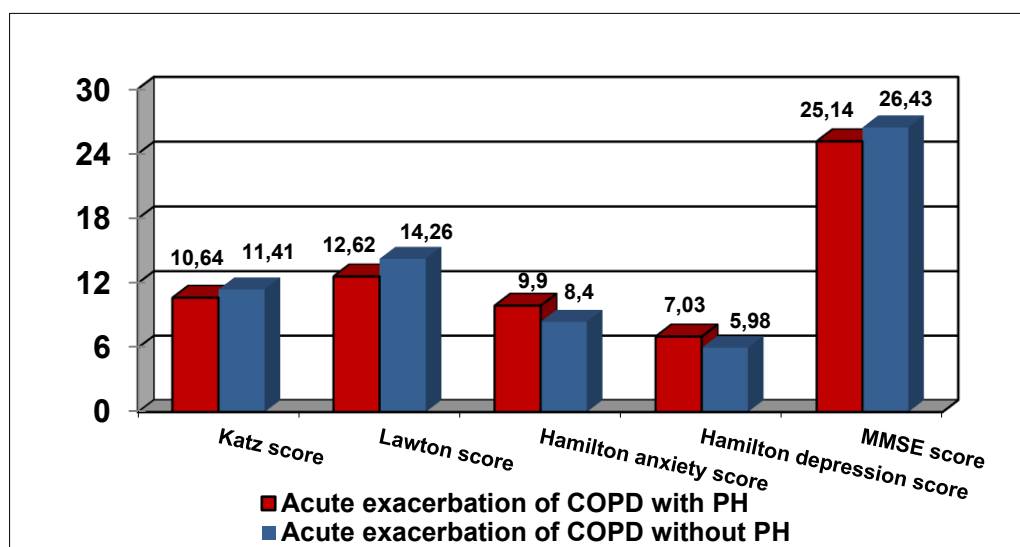


Figure 3. Complex geriatric evaluation in patients in study groups (points, mean values).

Although the evolution of COPD through exacerbation was observed in all patients in both study groups, the acute rare exacerbations of COPD (≤ 1) in the previous year, were statistically significantly more frequently mentioned by patients with acute COPD exacerbation without PH (58 – 59,8%; 95% CI: 49,9-69,1 and 13-13,4%; 95% CI: 7,7-21,2, respectively; $p < 0,001$), but frequent acute exacerbations of COPD (≥ 2) – statistically significantly more frequent in patients with acute exacerbations of COPD and PH (84-86,6%; 95% CI: 78,8-92,3 and 39-40,2%; 95% CI: 30,9-50,1, respectively; $p < 0,001$).

The functional clinical examination found moderate COPD (83.5%; 95% CI: 75,2-89,9 and 11,3%; 95% CI: 6,2-18,8, respectively; $p < 0,001$) statistically significantly more frequent in patients with acute COPD exacerbation without PH, but severe COPD (81,4%; 95% CI: 72,8-88,2 and 16,5%; 95% CI: 10,1-24,8, respectively; $p < 0,001$), very severe COPD (7,2%; 95% CI: 3,3-13,6 and 0% respectively; $p < 0,01$) and COPD type D (99,0%; 95% CI: 95,3-99,9 and 91,8%; 95% CI: 85,0-96,0, respectively; $p < 0,05$) – statistically significantly more frequent in patients with acute exacerbations COPD with PH (figure 4, 5).

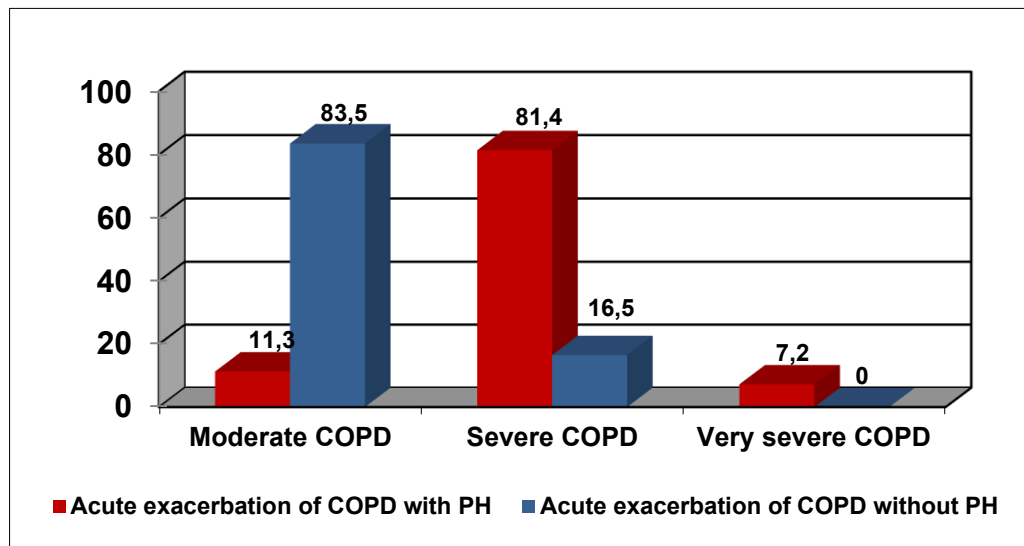


Figure 4. The severity degree of COPD according to the GOLD 2007 classification in patients from study groups (%).

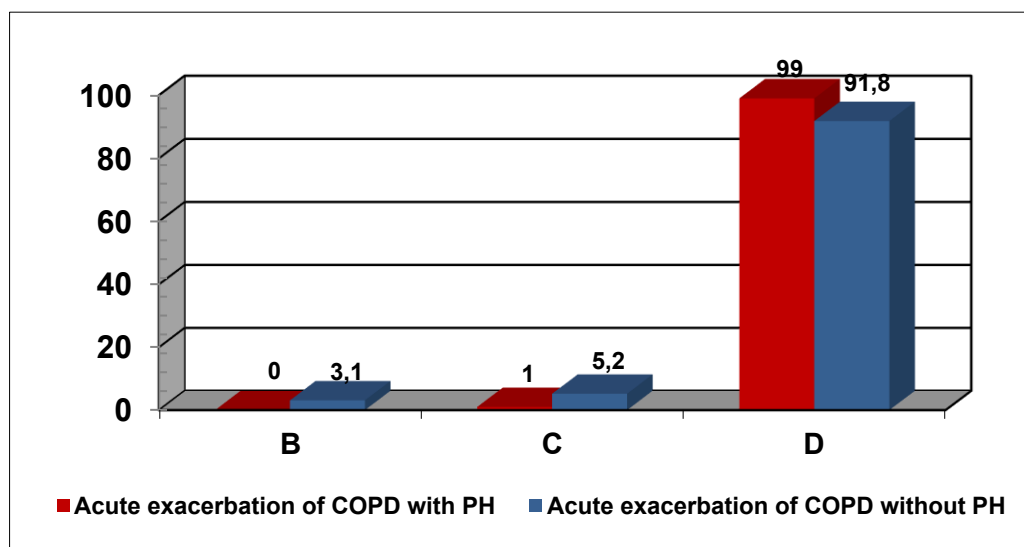


Figure 5. The severity degree of COPD according to the GOLD 2017 classification in patients in study groups (%).

The multidimensional approach of COPD, highlighted average values of the CAT scale ($29,81 \pm 5,3$ points; Md – 31,0, IIQ: 27,0-34,0 and $22,61 \pm 4,8$ points; Md – 23,0, IIQ: 21,0-25,0, respectively; $p < 0,001$), of total SGRQ score ($71,73 \pm 12,1$ points; Md – 72,8, IIQ: 64,58-78,92 and $52,73 \pm 10,2$ points; Md – 52,86, IIQ: 45,46-58,89, respectively; $p < 0,001$), of total CCQ score ($4,08 \pm 0,8$ points; Md – 4,3, IIQ: 3,6-4,6 and $2,97 \pm 0,7$ points; Md – 3,0, IIQ: 2,45-3,5, respectively; $p < 0,001$), of BODE index ($5,04 \pm 1,5$ points; Md – 5,0, IIQ: 4,0-6,0 and $2,97 \pm 1,2$ points; Md – 3,0, IIQ: 2,0-3,0, respectively; $p < 0,001$) and of dyspnea mMRC scale ($2,35 \pm 0,6$ points; Md – 2,0, IIQ: 2,0-3,0 and $1,27 \pm 0,6$ points; Md – 1,0, IIQ: 1,0-2,0, respectively; $p < 0,001$) statistically significantly higher in patients with acute exacerbation of COPD and PH, but mean value of Borg scale ($3,02 \pm 0,5$ points; Md – 3,0, IIQ: 3,0-3,0 and $2,4 \pm 0,5$ points; Md – 2,0, IIQ: 2,0-3,0,

respectively; $p<0,001$) – statistically significantly higher in the group of patients with acute COPD exacerbation without PH (figure 6).

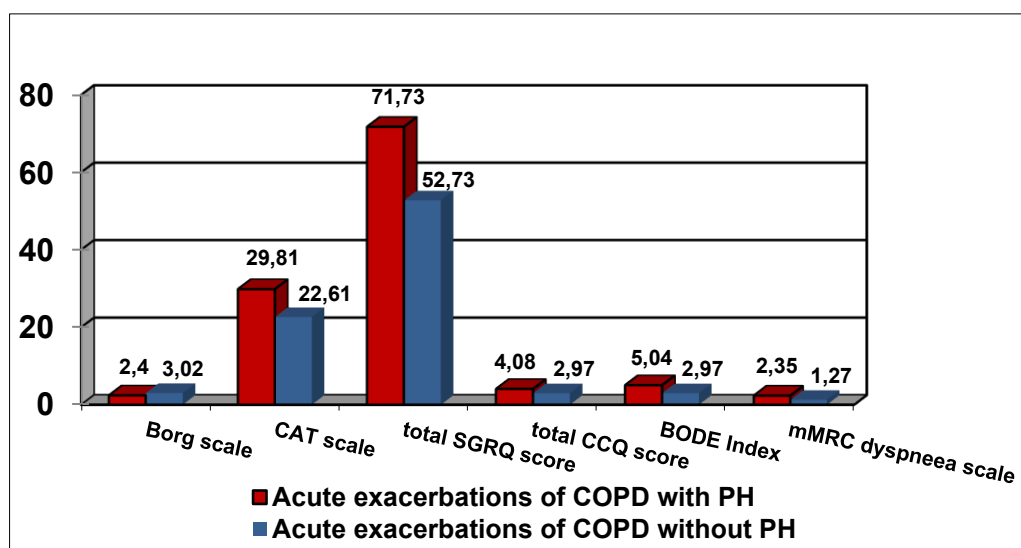


Figure 6. **Multidimensional assessment of acute exacerbation of COPD, in both groups of study using the questionnaires proposed by GOLD in elderly patients (points, averages).**

6MWT resulted in low effort tolerance (77,3%; 95% CI: 68,3-84,8 and 19,6%; 95% CI: 12,6-28,3, respectively; $p<0,001$) statistically significant more frequently in patients with acute exacerbations of COPD and PH, but moderate effort tolerance (77,3%; 95% CI: 68,3-84,8 and 21,6%; 95% CI: 14,4-30,6, respectively; $p<0,001$) – statistically significant more frequently in patients with acute exacerbations of COPD without PH.

Chronic respiratory failure zero showed statistically significantly more frequent patients with acute COPD exacerbation without PH (49,5 %; 95% CI: 39,7-59,3 and 9,3 %; 95% CI: 4,7-16,2, respectively; $p<0,001$), but first degree of chronic respiratory failure (79,4%; 95% CI: 70,3-86,2 and 50,5%; 95% CI: 43,5-57,5, respectively; $p<0,001$) and second degree of chronic respiratory failure (11,3%; 95% CI: 7,5-16,4 and 0% respectively; $p<0,05$) – statistically significantly more frequently in patients with acute COPD exacerbations and PH.

Evaluation of simple spirometry parameters found statistically significantly lower average values in patients with acute COPD exacerbations and PH compared to patients with acute COPD exacerbation without PH: FEV1 ($42,81\pm 7,6\%$; Md – 44,0, IIQ: 38,5-47,5 and $53,80\pm 6,1\%$; Md – 53,0, IIQ: 50,0-57,0, respectively; $p<0,001$), FVC ($59,31\pm 12,1\%$; Md – 59,0, IIQ: 51,0-69,0 and $65,05\pm 8,9\%$; Md – 63,0, IIQ: 59,0-69,5, respectively; $p<0,001$), FEV1/FVC ($56,17\pm 7,7\%$; Md – 57,5, IIQ: 49,50-61,95 and $63,53\pm 5,4\%$; Md – 65,0, IIQ: 60,30-68,25, respectively; $p<0,001$) and FEF 25-75% ($32,44\pm 11,2\%$; Md – 32,0, IIQ: 24,0-39,0 and $46,33\pm 9,4\%$; Md – 45,0, IIQ: 40,5-54,0, respectively; $p<0,001$).

The spirometry parameters after the bronchodilation test had the same tendency: FEV1 ($45,64\pm 7,7\%$; Md – 46,0, IIQ: 42,85-50,50 and $55,90\pm 6,0\%$; Md – 55,0, IIQ: 51,5-59,0, respectively; $p<0,001$), FVC ($62,03\pm 12,5\%$; Md – 61,0, IIQ: 52,75-69,70 and $67,02\pm 9,1\%$;

Md – 68,0, IIQ: 60,0-72,0, respectively; $p<0,01$), FEV1/FVC ($57,58\pm7,9\%$; Md – 58,0, IIQ: 52,45-64,0 and $64,03\pm4,8\%$; Md – 64,2, IIQ: 62,2-68,6, respectively; $p<0,001$) and FEF 25-75% ($35,54\pm10,2\%$; Md – 36,0, IIQ: 28,5-42,5 and $46,94\pm9,6\%$; Md – 48,0, IIQ: 42,0-51,0), respectively; $p<0,001$).

Therefore, the complex geriatric evaluation revealed in patients with acute exacerbation of COPD with PH compared to patients with acute COPD exacerbation without PH, statistically significantly more frequent more severe complaints, more frequent comorbidities, more severe indicators of objective clinical examination, worse results when assessing COPD severity using respiratory questionnaires, functional clinical examination, multidimensional approach and paraclinic examination of COPD (radiological, electrocardiographic, echocardiographic, laboratory, macroscopic and microscopic sputum and ultrasound of internal organs).

In the general group of patients with acute COPD exacerbation, the mean value of NT-proBNP was $972,91\pm75,5$ pg/ml. This parameter was statistically significantly higher in patients with acute COPD exacerbations and PH compared to patients with acute COPD exacerbation without PH ($1807,16\pm91,5$ pg/ml and $138,65\pm8,3$ pg/ml, respectively; $p<0,001$). Plasma value a NT-proBNP can be a useful prognostic marker of COPD progression and can help to identify cases of secondary PH in COPD patients.

The mean values of simple spirometry and after the bronchodilation test parameters were statistically significantly lower in patients with acute COPD exacerbations and PH compared to patients with acute COPD exacerbation without PH. Radiological, electrocardiographic, echocardiographic, laboratory, macroscopic and microscopic examinations of sputum and ultrasound of internal organs resulted in more frequent statistically significant negative results in patients with acute COPD exacerbations and PH compared to patients with acute COPD exacerbation without PH, this ensuring a more severe progression of COPD in the group of patients with PH.

5. DIAGNOSTIC ALGORITHM OF PULMONARY HYPERTENSION SECONDARY TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE

In the study we determined three major findings: the plasma levels of NT-proBNP in patients with acute exacerbation of COPD increased significantly simultaneously with the severity of the disease, with the severity of chronic respiratory failure and with the severity of secondary PH. Our results suggest that plasma NT-proBNP may be a useful prognostic marker of COPD progression. This factor may also help identify cases of secondary PH, screening patients at risk of death or at risk of developing symptomatic ventricular dysfunction at patients with acute exacerbation of COPD.

Based on international, national bibliographic and personal research data, we propose the application of spirometry in agreement with the clinical context, with the correlation of complex geriatric evaluation and multidimensional respiratory approach data with the severity of COPD, and introduction of natriuretic peptides evaluation in the algorithm of COPD with possible secondary PH diagnosing in older people, which would allow for earlier and safer diagnosis of COPD as well as the association of pulmonary hypertension to COPD in elderly patients (figure 7).

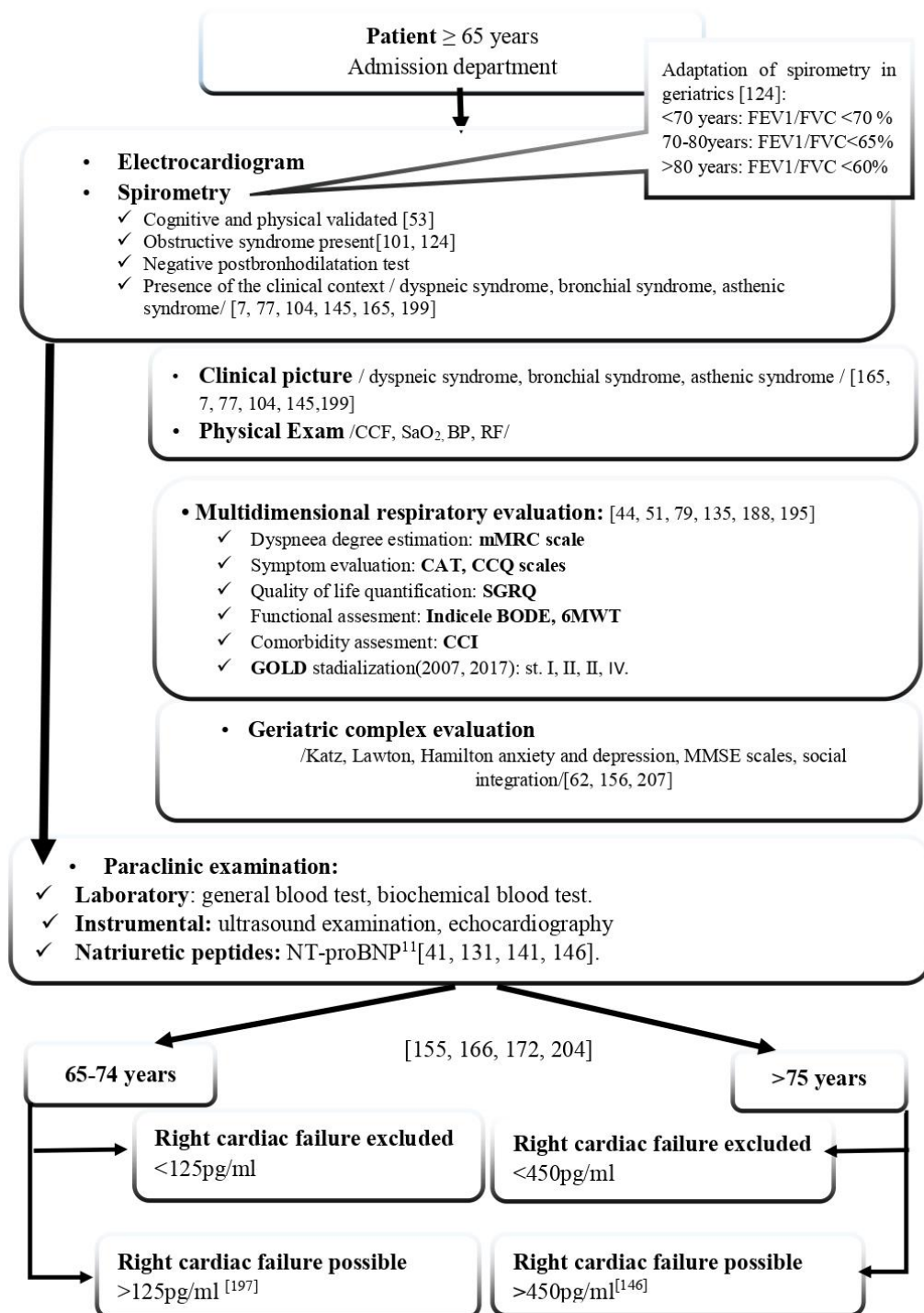


Figure 7. **Diagnostic algorithm for patients with COPD and secondary PH.**

GENERAL CONCLUSIONS

1. COPD is a serious disease with significant impact on elderly patient, aggravated by the pulmonary hypertension, with negative consequences on the quality of life, autonomy, general functioning and respiratory capacities, that requires the application of combined methods of diagnostic, laboratory and instrumental.
2. Complex evaluation of elderly patients with acute exacerbation of COPD revealed frequent complaints (cough, dyspnea, wheezing, chest discomfort), present risk factors (smoker or ex-smoker with 88.4% of smokers with > 10 packages/year, household pollution and long exposure to occupational harmful substances), high comorbidity index, with the burden of the disease objectified through the data obtained from the multidimensional approach of COPD, respiratory functional examination by spirometry and 6MWT, instrumental examination data (ECG: signs of right atrium hypertrophy at 18,0%; 95% CI: 13,1-23,9; deviation of the electrical axis of the heart to the right 42,8%; 95% CI: 32,9-52,4; right ventricle hypertrophy signs at 39,2%; 95% CI: 29,9-49,1; echocardiography mean value of mPAP $30,85 \pm 15,3$ mm Hg (MD – 24,5, IIQ: 19,0-34,0)) and laboratory data with mean NT-proBNP = $972,9 \pm 1052,1$ pg/ml (MD – 277,6, IIQ: 135,0-1929,7)).
3. Elderly patients with secondary to COPD pulmonary hypertension are characterized by frequent, more severe complaints and objective impairment data, frequent abnormal values of complex geriatric evaluation scores, more severe degree of bronchial obstruction, type D, with relevant impact on symptomatology, daily activity capacity, respiratory and general functional state, with the mean mPAP value of $42,44 \pm 14,0$ mm Hg (MD – 34,0, IIQ: 32,0-54,5), mostly moderate and severe degree of mPAP and high values of natriuretic peptides (NT-proBNP- $1807,16 \pm 901,1$ pg/ml; MD – 1925,5, IIQ: 1122,45-2445,70).
4. The development of secondary to COPD pulmonary hypertension in elderly patients occurs on the background of more serious respiratory impairment (reflected by the degree of more severe bronchial obstruction and abnormal values of multidimensional respiratory evaluation scales) and proves a negative impact, throughout the severity of the clinical picture (more frequent serious complaints, more severe indicators of objective clinical examination), more significant functional and psycho-emotional deterioration (more frequent impairment of the patient's autonomy, cognitive and psycho-emotional state, tolerance to effort according to 6MWT), more severe deviations detected at instrumental (ECG, EcoCG) and laboratory examination, with confirmation of the correlation NT-proBNP with the degree of respiratory failure, pulmonary hypertension and the presence of heart failure.
5. Based on international, national bibliographic and personal research data, we propose the algorithm for diagnosing COPD with possible secondary PH in elderly people, which would allow safer diagnosis of the severity of bronchial obstruction and association of pulmonary hypertension in elderly patients with COPD.

PRACTICAL RECOMMENDATIONS

1. Taking into account the high frequency of bronchopulmonary diseases in geriatric patients, it is recommended to perform the measurement of respiratory volumes in the form of spirometry in all patients admitted for stationary treatment with the integration of the results obtained according to the age groups and correlated with the clinical context.
2. For the purpose of managing elderly patients with COPD, it is necessary to correlate the autonomy, emotional and cognitive status data obtained through the complex geriatric evaluation (Katz score, Lawton score, MMSE test, Hamilton Depression scale and Hamilton anxiety scale) with the degree of complex estimated respiratory impairment (spirometry, functional examination and respiratory multidimensional assessment questionnaires).
3. Introduction of natriuretic peptide evaluation into the diagnostic protocol of elderly patients with COPD with possible secondary PH, which could confirm or exclude the diagnosis of right heart failure.

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INFORMATION REGARDING THE VALORIZATION OF RESEARCH RESULTS

LIST OF SCIENTIFIC PUBLICATIONS AND EVENTS at which the results of the researches for the doctoral thesis in medical sciences with the topic „*Pulmonary hypertension in elderly patients with chronic obstructive pulmonary disease*”, performed at Geriatrics and Occupational Medicine Discipline, Internal Medicine Department of mrs. **Luca Ecaterina**, „Nicolae Testemițanu” State University of Medicine and Pharmacy, were presented:

- **Articles in scientific journals abroad:**
- ✓ **articles in ISI, SCOPUS and other international databases***
- 1. **Luca E.**, Bodrug N. The frequency of pulmonary hypertension in chronic obstructive pulmonary disease of geriatric patients: a narrative literature review. In: *The Egyptian Journal of Internal Medicine*. 2022; 34 (1): 1-7, E-ISSN 2090-9098. two: 10.1186/s43162-022-00135-7.
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- **Publications in accredited national scientific journals:**
- ✓ **articles in category B magazines**
- 3. Bodrug N., **Luca E.**, Calancea V., Botezatu A., Tofan E. Particularitățile clinice ale bronhopneumopatiei obstructive cronice la vârstnici. În: *Buletinul Academiei de Științe a Moldovei. Științe Medicale*. 2021; 71 (3): 72-77. ISSN 1857-0011.

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LIST OF ABBREVIATIONS

BODE	-	Body mass index, Obstruction, Dyspnea, and Exercise
CBC	-	Blood cell counter
COPD	-	Chronic obstructive pulmonary disease
CAT	-	COPD Assessment Test
CCI	-	Charlson comorbidity index
CCQ	-	Clinical COPD Questionnaire
GOLD	-	Global Initiative for Chronic Obstructive Lung Disease
FVC	-	Forced vital capacity
PH	-	Pulmonary hypertension
6MWT	-	6 minute walking test
mMRC	-	modified Medical Research Council
MMSE	-	Mini mental state examination
NT-proBNP	-	Natriuretic peptide type B N-terminal fragment
PAP	-	Pressure in the pulmonar artery
mPAP	-	Medium Pressure in the pulmonar artery
SGRQ	-	St. George's Respiratory Questionnaire
FEV1	-	First second maximum forced expiratory volume

LUCA Ecaterina
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WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

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