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CARDIOVASCULAR COMORBIDITIES IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN EXACERBATION

321.01 – INTERNAL BOLI (PULMONOLOGY)

Summary of doctoral thesis in medical sciences

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1. INTRODUCTION

The actuality and importance of the researched problem

Cardiovascular comorbidities (CVCs) in patients with chronic obstructive pulmonary disease (COPD) are important causes of morbidity and mortality, with a noticeable economic impact on public health systems. Currently, COPD is one of the top three causes of death in the world; in 2019, it caused 3.23 million deaths. Nearly 90% of deaths of COPD patients are attested in low- and middle-income people under 70. At the level of the person, the disease manifests itself through suffering, but also through substantial socio-economic costs, and at the macroeconomic level – through very high costs. In the EU, COPD is the leading cause of morbidity and mortality from respiratory disease, accounting for 8% of deaths of people affected by respiratory diseases [1, 2, 3]. In the Republic of Moldova, according to statistical data, in 2017, with J 44 code, 138.9 cases per 10,000 adult population were registered [4]. According to data published in recent years, the prevalence of cardiovascular disease (CVD) is obviously increased in patients with COPD: prevalence of heart failure – 4 times; prevalence of ischemic heart disease – 2 times; prevalence of myocardial infarction – 2.5 times; prevalence of peripheral arterial diseases and arrhythmias – 2.4 times; prevalence of strokes – by 1.4 [5].

Description of the situation in the field of research and identification of research problems

Cardiovascular disease, concomitant with COPD, is seen in the context of a "cardiopulmonary continuum". The mechanisms linking COPD and cardiovascular pathology are unclear. However, the presence of common risk factors and chronic systemic inflammation is considered one of the mechanisms. Systemic inflammation, present during exacerbation of COPD, provides a potential mechanism to explain the increased risk of associated cardiovascular events [6].

In the international context of continuous increase in the number of patients with chronic respiratory diseases and CVD, a study assessing the incidence of these diseases among the population of the Republic of Moldova is of real use for the purpose of guiding public health policies and dimensioning the necessary effort at the level of the health system in the management of these diseases. They are not rigorous CVC identification and management systems in COPD, validated for widespread use. Methods to quantify the weight of CVC should be part of a multidimensional assessment of the severity of COPD, as CVC can have varying complexity and impact across the population by age, gender, ethnicity and etiology; they need to be adapted, adjusted, used correctly in the stratification of the risk of death, appropriate diagnosis.

Thus, it is necessary to conduct a complex population study, accompanied by some applicative value assessments in several approaches of COPD: GOLD classification, groups A, B, C, D, multidimensional indices at group level, in order to develop new diagnostic strategies, prognosis for CVC and to develop validated models for estimating the impact of CVC in the evolution of COPD.

The purpose of the study: Evaluation of cardiovascular comorbidities in patients with chronic obstructive pulmonary disease, in exacerbation, and development, improvement of the Algorithm for early diagnosis of the risk of cardiovascular complications in patients with COPD. To achieve this goal, we have set ourselves the following **objectives**:

1. To study the relevant clinical and paraclinical parameters in stratification of patients with COPD in exacerbation.

2. To identificate the risk respiratory and cardiovascular factors, depending on the stratification of patients with COPD in exacerbation.
3. To evaluate the frequency of cardiovascular comorbidities and their association with clinical variants of COPD in personalized evaluation of patients.
4. To examine the impact of cardiovascular comorbidities on mortality and readmission rates, up to 1 year after discharge, and create a „Predictive model in the probability of survival of patients with COPD associated with CVC".
5. To elaborate an „Algorithm for early diagnosis of major cardiovascular events in patients with COPD associated with CVC", with the establishment of prognostic risk factors, as well as with the establishment of spheres of major impact of cardiovascular comorbidities on the patient with COPD.

General research methodology. The paper represents a complex multicenter research and contains a prospective observational study, with the evaluation of clinical-evolutionary characteristics and the establishment of the pattern of patients with COPD, associated with cardiovascular comorbidities. The study is a result of scientific collaboration with the participation of three medical centers from the Republic of Moldova (Pulmonology Clinic of IMSP SCM "Sfânta Treime", IMSP Clinic of the Institute of Phthisiopneumology "Chiril Draganiuc" and IMSP Institute of Cardiology). The investigated sample included 426 patients with COPD, associated or not associated with cardiovascular comorbidities, enrolled in the order of admission, based on informed consent, based on a structured, specially developed clinical questionnaire. The study was approved by the Research Ethics Committee of the State University of Medicine and Pharmacy "Nicolae Testemitanu", Chisinau, Republic of Moldova (approval number 17/12 of11.12.2015) and was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. All patients were followed similarly until the end of the study. The evaluation criteria were not changed during the research.

Scientific novelty and originality of the research. Based on a complex prospective observational case-control study, the rate of cardiovascular comorbidities and their association to clinical and functional parameters, groups B, C, D of patients with COPD was estimated. Common risk factors and pathogenetic mechanisms for COPD and cardiovascular pathology, clinical, laboratory heterogeneity and clinical variants of cardiovascular comorbidities in patients with COPD were evaluated. Charlson and CODEX scores, predictive indices of mortality, rehospitalizations and cardiovascular comorbidities, were evaluated 12 months after discharge of patients, after exacerbation of COPD. The univariate analysis, calculating the relative risk of patients with COPD, revealed the presence of predictive indices of death, which were the basis for predicting the risk of developing major cardiovascular events in the „Algorithm for early diagnosis of major cardiovascular events in patients with COPD associated with CVC". Multivariate logistic regression of physiological parameters allowed to create the „Predictive model in the probability of survival of patients with COPD associated with CVC".

The important scientific problem solved in the thesis consists in the scientific substantiation of the evaluation of clinical, paraclinical parameters with the identification of respiratory and cardiovascular risk factors, cardiovascular comorbidities for stratification of patients with COPD, which led to the elaboration of the „Algorithm for early diagnosis of major cardiovascular events in patients with COPD associated with CVC", with the establishment of several prognostic variables and of major impact spheres of cardiovascular comorbidities on the

patient with COPD and the creation of the „Predictive model in the probability of survival of patients with COPD associated with CVC“ through multivariate logistic regression of physiological parameters. The data obtained in the study form the basis for measures to improve and optimize the evaluation of patients with COPD associated with CVC.

The theoretical significance of the research. The obtained results were implemented in developing the concept about the role of cardiovascular comorbidities in the evolution of COPD, by elucidating risk factors, respiratory and cardiovascular, cardiovascular comorbidities and clinical, paraclinical parameters, relevant in stratification of patients with COPD, exacerbation, in assessing the level of quality of life. The rate of cardiovascular comorbidities and their association with clinical variants of COPD was estimated for personalized evaluation of patients and determination of the impact of cardiovascular comorbidities on mortality and readmission rate, up to 1 year, after discharge. The correlation of markers of cardiopulmonary involvement and mortality level at 1 year was estimated. Through univariate analysis and relative risk calculation in patients with COPD, predictive indices of death were detected, which formed the basis for predicting the risk of developing major cardiovascular events in the „Algorithm for early diagnosis of major cardiovascular events in patients with COPD associated with CVC“, and by multivariate logistic regression of physiological parameters, The „Predictive model in the probability of survival of patients with COPD associated with CVC“, was created.

Applicative value of the topic. Study results offer new diagnostic and prognostic options in COPD and cardiovascular comorbidities. Important criteria for assessing the risk of developing cardiovascular comorbidities in patients with COPD have been strengthened. A set of recommendations has been developed to optimize the management of patients with COPD, associated with CVC , in order to improve the quality of life of patients by modulating the risk factors involved, nominated in the „Algorithm for early diagnosis of major cardiovascular events in patients with COPD associated with CVC“. The „Predictive model in the probability of survival of patients with COPD associated with CVC“ was created, with the establishment of risk factors (with prognostic value), as well as with the establishment of spheres of major impact on patients.

Approval of results. The results of the thesis were presented and debated at: The 55th Congress of the Romanian Society of Cardiology, Sinaia, Romania, 2016; The 58th Congress of the Romanian Society of Cardiology, Sinaia, Romania, 2019; The 59th Congress of the Romanian Society of Cardiology, Sinaia, Romania, 2020; Nanotechnologies and Biomedical Engineering. Edition 5, Chisinau, Pontos, November 3-5, 2021; International Congress at the University "Apollonia", Iasi, 2-5 March 2017, 1-4 March 2018, 28 February, 3 March 2019; Scientific conference "Inspire knowledge in COPD", Institute of Phthisiopneumology "Chiril Draganiuc", Chişinău, 15 November 2016; Scientific conference in marking World COPD Day, entitled "Many aspects of COPD", Chisinau, November 15, 2017; Scientific conference "News in phthisiopulmonology", Chisinau, September 15, 2017; Scientific conference "Never too early, never too late", Institute of Phthisiopneumology "Chiril Draganiuc", Chisinau, November 21, 2018; The V National Congress of Phthisiopulmonology, with international participation "News in etiology, pathogenesis, prophylaxis, diagnosis and treatment of tuberculosis and nonspecific pulmonary diseases", Institute of Phthisiopneumology "Chiril Draganiuc", Chisinau, October 2, 2019; annual scientific conferences, dedicated to the days of the State University of Medicine and Pharmacy "Nicolae Testemitanu", Chisinau, October 19, 2016, October 19, 2017, October

18, 2018, October 17, 2019; VI National Congress of Obstetrics and Gynecology, with international participation, Chisinau, September 13-15, 2018; MedEspera International Medical Congress for Students and Young Doctors, Chisinau 24-26 September 2020; Congress dedicated to the 75th anniversary of the foundation of Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, 21-23 October 2020; Conference "Research in biomedicine and health: quality, excellence and performance", Chisinau, October 20-22, 2021.

Publications on the topic of the thesis. The scientific results presented in this paper have been published in 25 scientific publications of which: 2 articles in ISI journals, SCOPUS and other international databases, 7 articles in scientific journals, 16 theses in the proceedings of national and international scientific conferences.

Volume and structure of the thesis. The thesis is exposed on 127 pages and includes annotation (in Romanian, Russian, English), list of abbreviations, list of figures, list of tables, introduction, 4 chapters, synthesis of obtained results, general conclusions and practical recommendations, bibliography from 208 sources, 47 tables, 21 figures, a patent, an innovator certificate, an implementing act, information on the exploitation of research results and declaration of accountability.

Keywords: cardiovascular comorbidities, chronic obstructive pulmonary disease.

2. RESEARCH METHODOLOGY

2.1. Research material and methods. In this study were included 426 patients, hospitalized with exacerbation of COPD in the Pulmonology Clinic of Municipal hospital "Holy Trinity", Clinic of the Institute of Phthisiopneumology "Chiril Draganiuc" and in Institute of Cardiology, during 2015-2019. The patients represented a comparable socio-economic and ethnic structure. Patients were enrolled in the study on the order of admission and based on informed consent. The informed written consent was obtained from each patient at the time of admission and was approved by the Research Ethics Committee of State University of Medicine and Pharmacy "Nicolae Testemitanu", approval number 17/12 of 11.12.2015. The study was conducted in accordance with ethical guidelines specified in the 1975 Declaration of Helsinki.

The clinical diagnosis of COPD was suspected in patients with persistent respiratory symptoms and airflow limitation caused by abnormalities detected in the airways and/or alveoli, and was confirmed by the VEMS/FVC ratio <70% postbronchodilator [1]. Patients involved in the study were evaluated according to national protocol [7], according to GOLD recommendations [8], 2016. The initial classification of COPD, based on GOLD, was based solely on the reduction of VEMS, a decisive feature in limiting airflow. COPD staging was performed based on lung function test results obtained during the period without exacerbation. The combined assessment of COPD assumed dyspnoea severity (mMRC score) as predictive of mortality, associated with VEMS, CAT score, and COPD exacerbations, arranged in a multidimensional grading system [9].

2.2. Study design

Type of study: descriptive, prospective study. Patient monitoring for 12 months.

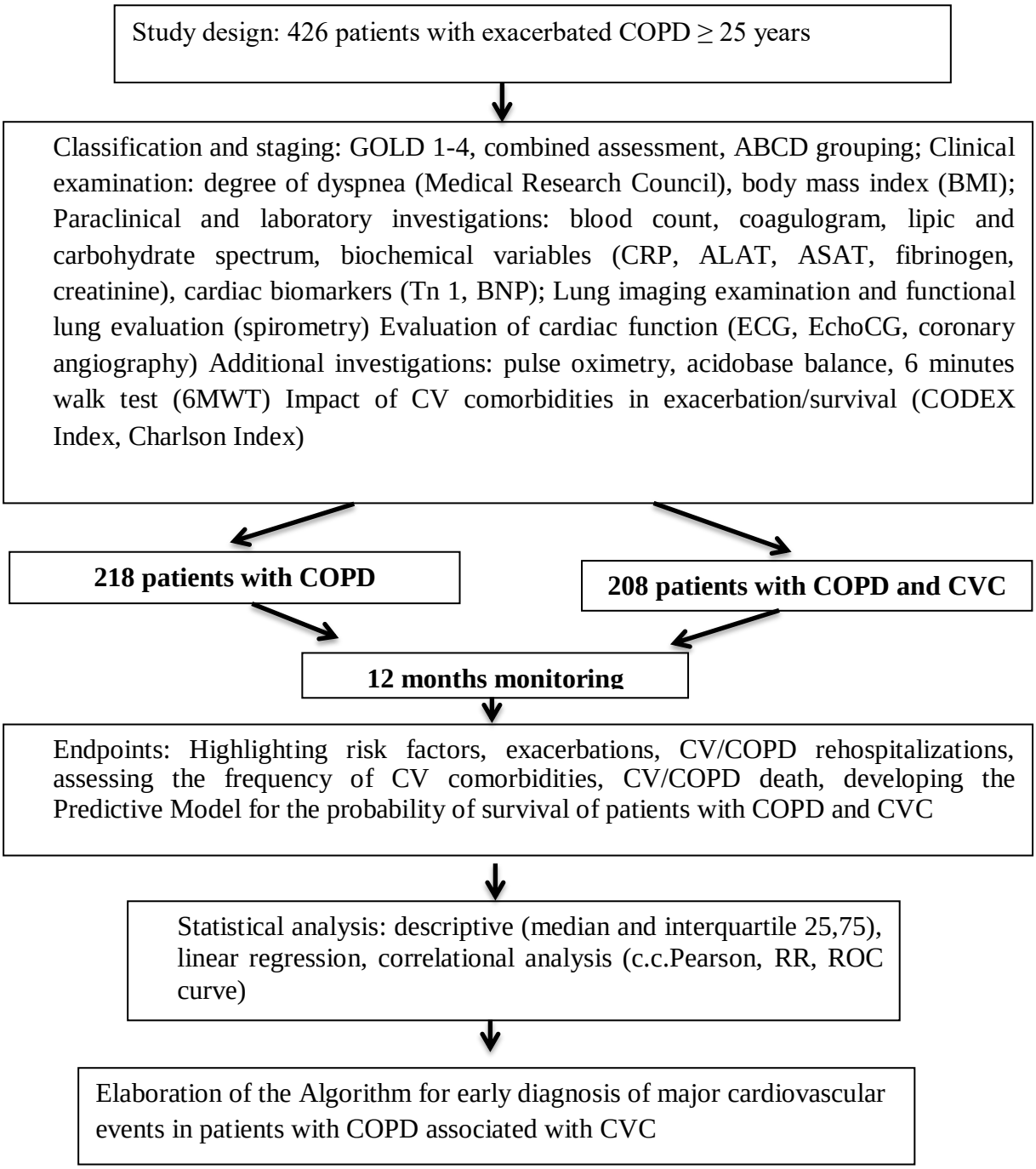

Figure 2.1. Study design.

2.3. Investigation methods

Data collection was carried out in 2 stages: prospective study and retrospective analysis of data from patient observation records and repeated remote examination of patients included in the study. The prospective study and retrospective analysis of the data from the patients' observation records were carried out unannounced, with the extraction of anamnestic, clinical data, disease evolution data and the results of the examinations performed. Patients in the COPD and CVC study group (n=208) and COPD control patients without CVC (n=218) were examined in accordance with the requirements and recommendations of the European Society of Cardiology and the National Clinical Protocols: *COPD, Stable angina, Acute myocardial infarction, Hypertension and Heart failure*, standard protocol, which included demographic questioning,

anamnestic, clinical, regarding the evolution of the disease and the results of the performed examinations [7, 10].

The details of the intervention included: personal and demographic data (name, age, gender, address, telephone); characteristic of bronchoobstructive syndrome, angina, which determined recent hospitalization, how to seek medical assistance, duration from onset of pain to address; highlighting cardiovascular risk factors (smoking, exsmokers, passive smokers, contact with dusts, chemicals, but also with smoke resulting from biomass, wood heating, hypertension, diabetes, obesity, dyslipidemia, etc.); evaluation of bronchoobstructive syndrome, hemodynamic data at hospitalization: respiratory rate, frequency of heart contractions, blood pressure, manifestations of heart failure; in the study of systemic inflammation, highly sensitive C-reactive protein (CRP), hemoglobin, leukocytes and eosinophils, platelets, fibrinogen, neutrophil/leukocyte ratio; cardiac biomarkers: cerebral natriuretic peptide (BNP), troponin I, creatine kinase-MB; results of biochemical analyzes: urea, creatinine, lipidogram, blood glucose, prothrombin index, etc.); lung function tests (spirometry): COPD was diagnosed on the basis of the postbronchodilation test, according to GOLD guidelines, after confirmation of persistent airway obstruction and after excluding asthma; pulse oximetry and arterial gas analysis; standard posteroanterior chest X-rays were performed and evaluated in the presence or absence of congestion and other conditions that belonged to the inclusion criteria; peculiarities of instrumental examinations: electrocardiogram (ECG); echocardiogram (EchoCG); 6 minutes effort test; angiocoronary angiography; highlighting the clinical variant of COPD: GOLD I-IV, ABCD grouping (categories), focus on the clinical variant of evolution of hypertension, acute myocardial infarction with Q wave or non-Q, unstable angina pectoris, acute/chronic respiratory failure, chronic/acute heart failure; consideration of the duration of hospitalization; Questionnaires: CAT, modified Medical Research Council (mMRC); calculation of risk scores according to Charlson and CODEX methods.

Remote repeated examination of patients under study. At this stage, patients were actively contacted (by phone) and were invited for repeated examination in the municipal hospital "Holy Trinity". The examination program included: telephone discussion with patients who gave up repeated examination in order to identify their clinical condition, exercise tolerance, remedies they administer, causes of refusal to participate in the study; examination of survivors, one year after discharge, according to the following plan: personal and demographic data; specifying the data of COPD exacerbations and highlighting the peculiarities of CVC evolution during the reference period, identifying cases of acute heart failure, number of repeated hospitalizations due to exacerbation of pulmonary/cardiovascular pathology.

The endpoints were: Highlighting relevant clinical and paraclinical risk factors, parameters, and clinical features in stratification of patients with COPD, exacerbation; assessing the prevalence of cardiovascular comorbidities and their association with clinical variants of COPD in personalized patient assessment; Cardiovascular, respiratory and total mortality; hospitalization in exacerbation of COPD, ARF (acute respiratory failure); primary cardiac hospitalization (AHF – acute heart failure).

2.4. Mathematical-statistical processing methods. The obtained data were processed computerized, applying the set of statistical programs SPSS 23.0. The normality of the distribution of quantitative traits was assessed by the Kolmogorov–Smirnov method. The results of the characteristics, distributed within the limits of the norm, were presented as mean values

(M) and the standard deviation of mean arithmetical (m). The comparison of average values, at the level of these parameters, in two independent groups, was performed using the unpaired t-Student test and, in two dependent groups – the paired t-Student test. The signs, which did not comply with the law of distribution within the norm, were presented as median and interquartile interval (Mn, Q25-Q75). The analysis of Boxplot and Whisker allowed graphical representation of the distribution of maximum – minimum values, of the Median and percentiles – 25, 75. In order to highlight predictive factors, HR determination with linear regression method was used. The efficiency of the models was measured using the ROC curve.

3. CHAPTER SUMMARY

3.1. General characteristic of patients included in the study 426 patients with COPD were investigated, of whom men predominated (n – 268; 62.91%), compared to women (n – 158; 37.09%, p<0.0001). Analyzing the average age of patients, we found that this parameter varied between 25 and 82 years, the average value of patients in the total Group was 64.48± 0.9 years, men being younger than women (63.18 ± 0.3 vs 66.73± 0.9 years, p<0.05).

Depending on the design of the study, the total Group was divided into: Group I – 218 (51.90%) patients with COPD and Group II – 208 (48.82%) patients with COPD, with cardiovascular comorbidities of coronary origin (CVC). The prospective study of demographic data revealed the following results: at the level of the average age of patients, differences between Group I and Group II (64.26 ± 0.3, 64.98± 0.9, years > 0.05) were not attested. The analysis, depending on sex, of patients in the studied groups reveals an identical M:F ratio (p>0.05).

3.2. Explorations of pulmonary ventilation Mean external respiratory function indices in patients with COPD (as a percentage of normal) suggested altered external respiratory function and severity in bronchial obstruction. The disturbance of bronchial permeability was confirmed by diminishing pulmonary dynamic constants: VEMS – in patients in Group I and those in Group II.

Table 3.1. Pulmonary ventilation indices according to the degree of bronchial patency disorder in patients with COPD

Clues	Group I	Group II	Standard deviation	CI 95%	p G1-G2
VEMS1	63.09	43.45	21.19	10.18-28.61	<0.0001
CV	64.08	59.09	29.26	4.21- 14.09	=0.0290
Tiffeneau *Index*	69.01	56.83	16.18	3.00-21.09	= 0.0093

Note: VEMS1– maximum expiratory volume 1 second; CV – vital capacity.

Explorations of pulmonary ventilation confirmed the expressed presence of bronchoobstructive syndrome in all patients (Table 3.1) in both men and women, with moderate and severe degrees of bronchial permeability disorder.

3.3. Highlighting clinical features for stratification of patients with COPD

The predominant proportion of patients in the total Group, classified according to clinical features, was represented by B category, as opposed to C or D categories– 172 (40.40%) vs 144 (33.80%) vs 110 (25.80%), respectively. Patients with C and D categories prevailed – 254 (59.60%, p<0.001). The same trend was estimated in patients in Groups I and II of comparison: patients in B category predominated, compared to other – C, D categories.

Table 3.2. Stratification of patients with COPD, according to clinical features

Category	Features	Spirometry classification	Exacerbations	mMRC score	CAT score	n (%)
B	Low risk, varied symptomatology	GOLD 1-2 260 (61.00%)	≤1	≥2	≥10	172 (40.40%)
C	High risk, reduced symptomatology	GOLD 3 122 (28.70%)	≥2	0-1	<10	144 (33.80%)
D	High risk, multiple symptomatology	GOLD 4 44 (10.3%)	≥2	≥2	≥10	110 (25.80%)

The rate of exacerbations (Table 3.3) was calculated based on the number of exacerbations per year, i.e. 2 ≤ exacerbations per year and 3 ≥ exacerbations per year.

Table 3.3. Exacerbation rate per year in patients with COPD

Rate of exacerbations /year	Group I, n(%)	Group II, n(%)	CI 95%	P G_1-G_2
≤ 2	83 (38.07%)	47 (22.59%)	6.75- 23.85	= 0.0005
≥ *3*	135 (61.93%)	161 (73.85%)	3.04 - 20.51	= 0.0086

The rate of exacerbations per year ≥ 3 in patients in Group II was higher than in Group I – 161 (73.85%) vs 135 cases (61.93%; respectively, 95% CI: 3.04-20.5; p = 0.0086). Patients in Group I prevailed over those in Group II, with a rate of exacerbations per year of ≤ 2: 83 (38.07%) vs 47 cases (22.59%, respectively, 95% CI: 6.75-23.85; p=0.0005). The seasonality of exacerbations was mainly autumn-winter: 214 (50.23%) cases; spring – 178 (41.78%) cases; and summer – 34 (7.98%) cases.

3.4. Assessment of the rate of general comorbidities Analyzing the data of general comorbidities (Table 3.4), the presence of the following diseases was identified: obesity – in 104 (24,41%) patients; diabetes mellitus – in 92 (21.59%) patients; pathology of the nervous system (encephalopathy, depression, dementia) – in 91 (21.36%) patients; dyslipidemia – to 97 (22.76%); pathology of the digestive apparatus (digestive ulcer, chronic hepatitis) – in 52 (12.21%). No significant difference was observed in sex and age levels (p>0.05).

Table 3.4. General comorbidity rate in patients with COPD

Comorbidity	Group I, n(%)	Group II, n(%)	pG2-G1
Diabetes mellitus	44 (20.18 %)	48 (23.07 %)	>0.05
Obesity	57 (26.15 %)	47 (22.59 %)	>0.05
Dyslipidemia	43 (19.60%)	54 (25.80 %)	<0.05
Pathology of the nervous system	47 (21.56%)	44 (21.15 %)	>0.05
Pathology of the digestive system	32 (14.68 %)	20 (9.62 %)	>0.05

3.5. Highlighting relevant laboratory parameters and clinical features in stratification of patients with COPD in exacerbation

The results of the laboratory investigation did not reveal statistical differences regarding the level of hemoglobin in patients from the compared groups: Group I vs Group II, both at the median estimate (135.00 vs 135.00 g/l, respectively, and at the 75th percentile level (150.00 vs 146.00 g/l, respectively) and at 25th percentile level (120.00 vs 124.00 g/l, respectively).

Table 3. 5. Laboratory markers in patients with COPD

Clues	Group I	Group II	Standard deviation	CI 95%	pG II -G I
Erythrocytes,10^{12}/L	4.64	4.52	0.67	0.01 - 0.24	= 0.0653
Hb, g/l	135.17	133,42	23.20	1.07 - 4.57	=0.1906
Leukocytes,×10^{9}/L	11.17	10.55	4.88	0.30 - 1.54	=0.1906
Neutrophils,%	64.6	96.6	5.85	2.08 - 4.31	<0.0001
RNL	1.03	0,97	2.54	2.75-4.00	<0.0001
ESR, mm/hr	18.05	23.72	15.59	2.91-8.42	<0.0001
Eosinophils, %	2.01	1.59	1.12	0.20 - 0.63	<0.0001

Note: Hb – hemoglobin; RNL – neutrophil/leukocyte ratio; ESR – erythrocyte sedimentation rate.

The data of the blood count investigation did not reveal statistical differences regarding the number of leukocytes in peripheral blood (Figure 3.1), in the patients in the comparated groups: Group I vs Group II, both at the estimation of the median (10.60 vs 10.10, respectively), at the level of the 75th percentile (12.60 vs 12.60 x109/l, respectively) and at the level of the 25th percentile (7.90 vs 7.00, respectively). Leukocytosis was registered in most patients (85.34%), without statistical difference, in both comparison groups (10.55 vs 11.17 x10^{9}/l, 95% CI 0.30-1.54, p=0.1906, respectively), but the level of non-segmented, with deviation of the leukocyte formula to the left, was higher in people in Group II (96.6 vs 64.6 %, p<0,0001).

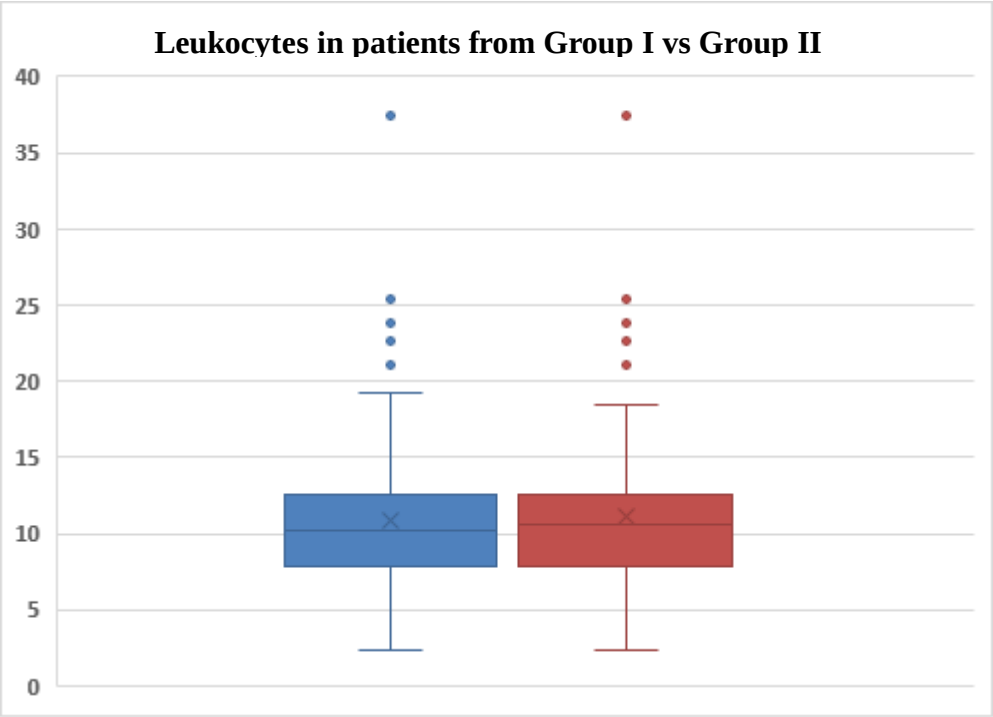

Figure 3.1. Box & whisker analysis of the number of leukocytes in peripheral blood in patients with COPD.

The mean neutrophil/leukocyte (RNL) ratio levels in all COPD patients (Figure 3.2) were 0.74, significantly higher in Group I patients compared to Group II patients (1.03 vs 0.97, 95% CI 2.75-4.00, p<0.0001, respectively).

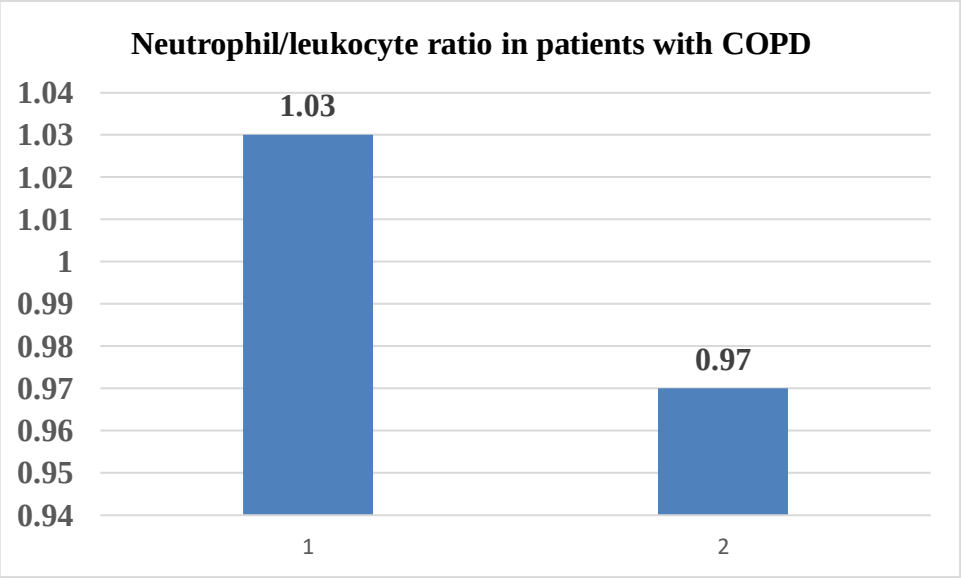

Figure 3.2. Neutrophil/leukocyte ratio in patients with COPD.

3.6. Highlighting relevant biochemical parameters and clinical features in stratification of patients with COPD, in exacerbation

Average PCR levels in the blood of Group I patients compared to Group II were significantly higher (9,00 vs 3.92 mg/L, CI 95% 4.45-5.70, p <0.001, respectively).

The investigation data, at fibrinogen variable level, were comparable in patients from the study groups: Group I and Group II, both in estimating the median (3.30 vs 3.70 g/L, respectively) and the 75th percentile (4.40 vs 4.60 g/L, respectively) and the 25th percentile (2.80 vs 2.80 g/L, respectively). The median fibrinogen was 3.50± 1.24 g/L and mean values in patients in these groups were comparable (pL1-L2>0.05). The data of the investigation, at the level of prothrombin variable, were comparable in patients from the investigated groups: Group I and Group II, both in estimating the median (88.00 vs 88.00%, respectively) and the 75th percentile (97.00 vs 100.00%, respectively) and the 25th percentile (80.00 vs 78.50%, respectively).

3.7. Study of cardiac biomarkers and clinical features for stratification of patients with COPD in exacerbation

Investigation of cardiac biomarkers (Table 3.6) and clinical features for stratification of patients with exacerbated COPD was a primary focus in our study. Cardiac biomarkers, natriuretic peptide (BNP) and troponin I (Tn I), were detected by electrochemiluminescence method.

Table 3.6. Cardiac biomarkers in patients with COPD

Clues		Group	
		I	II
BNP, pg/ml	Mediate	20.78	1054.30
	Median	12.47	773.43
	Standard deviation	23.29	963.85
	Minimum	7.8	26.40
	Maximum	115.30	5936.30
	The 25th percentiles	9.87	386.67
	The 75th percentiles	15.07	1520.64
Troponin I, ng/ml	Mediate	0.52	1.06
	Median	0.41	0.59
	Standard deviation	0.46	1.13
	Minimum	0.10	0.10
	Maximum	3.50	5.65
	The 25th percentiles	0.36	0.30
	The 75th percentiles	0.50	1.25

The increase in cardiac troponin I (Tn I), in the total group, (0.79±0.60 ng/ml) was observed in 92 (21.59%) patients. There were differences in Tn I level between Group II, compared to Group I -1.06±0.60 vs 0.52±0.60 ng/ml, 95% CI: 0.46-0.61, respectively, $p<0.0001$. The investigation data, at the level of Tn I variable, were statistically higher when comparing patients in Group II compared to those in Group I, both in estimating the median (0.59 vs 0.41 ng/ml, respectively) and the 75th percentile (1.25 vs 0.50 ng/ml, respectively) and the 25th percentile (0.30 vs 0.36 ng/ml, respectively). The distribution of patients with COPD in the total Group, according to cardiac Tn I values, found the following: the limits of the mean Tn I value, from 0.06 to 1.1 ng/ml, were recorded in 164 (38.5%) patients; 1.2 to 2.2 ng/ml – in 16 (3.80%) patients; 2.3 to 3.3 ng/ml – in 13 (3.10%) patients; from 3.4 to 4.4 ng/ml – in 6 (1.40%) patients; All differences – $p<0.0001$, from 4.5 to 6 ng/ml – in 2 (0.5%) patients and ≥7 – in only one patient.

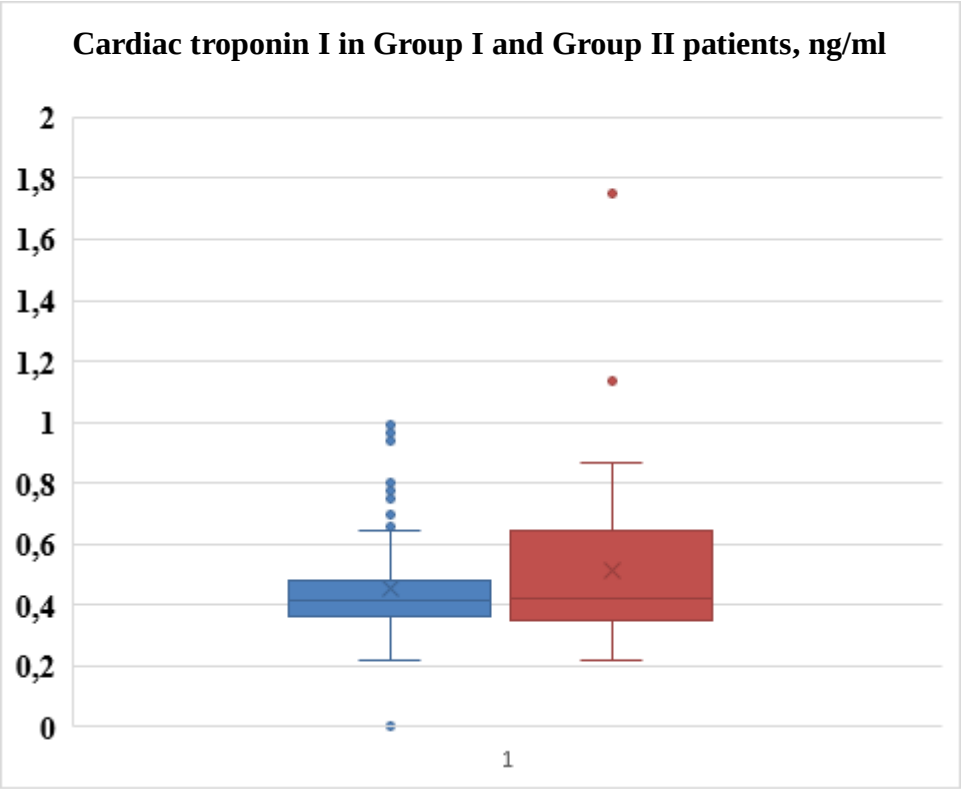

Figure 3.3. Cardiac troponin I in Group I and Group II patients.

Box & whisker analysis (Figure 3.3.) on Tn I in Groups I and II confirmed a statistical difference between these comparison groups. The median TnI was 0.94±0.44 ng/ml in patients in the total Group. On the Box and Whisker chart, the summarization by the 5 values of the TnI distribution is graphically reflected: minimum value – 0.22 ng/ml; first quartile (or lower quartile) – 0.36 ng/ml; second quartile – 0.48 ng/ml and third quartile – 0.69 ng/ml.

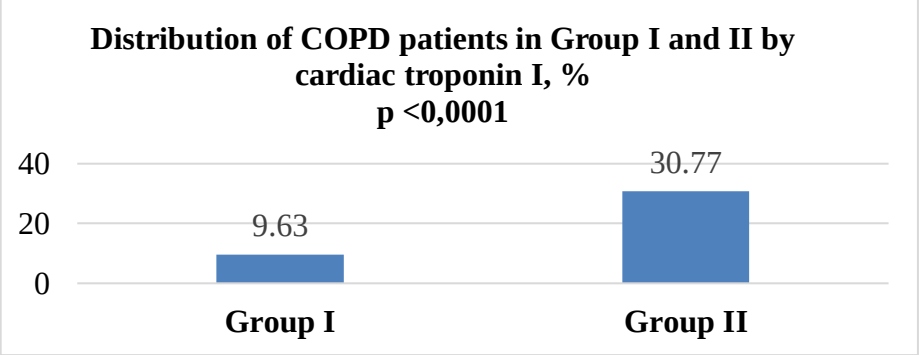

Figure 3.4. Distribution of COPD patients in Groups I and II by cardiac troponin I.

The distribution of patients with COPD, from Groups I and II, according to the value of cardiac troponin I revealed that more patients in Group II, compared to those in Group I, had this positive biomarker – 21 (9.63%) cases; respectively, 95% CI: 13.65 - 28.47, p< 0.0001 (Figure 3.4).

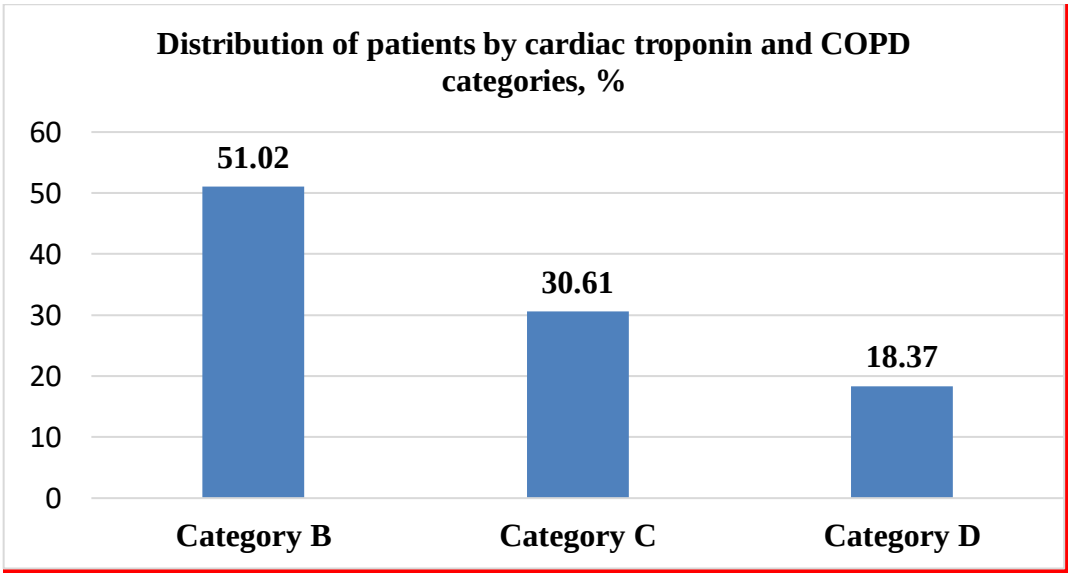

Figure 3.5. Distribution of patients by cardiac troponin I and COPD categories.

The distribution of COPD patients in the total Group, according to cardiac troponin I (Tn I) and categories B, C, D (Figure 3.5) showed the following: category D COPD patients were Tn I positive more frequently than category B and category C COPD patients – 28 (60.86%) cases vs 32 (38.55%) cases, 95% CI: 4.32- 38.34, pB-D = 0.0154 and - 28 (60.86%) vs 20 (39.21%), 95% CI: 1.76- 39.27, pC-D = 0.0341. Cardiac troponin I positivity was attested in all categories (B, C, D), and the distribution of COPD patients in Group II according to these groups did not vary significantly ($p>0.05$).

The results of the investigation, at BNP variable level, were statistically distinct in comparing patients in Group I vs patients in Group II, both at the median estimate (12.47 vs 773.43 pg/ml, respectively), at the 75th percentile level (15.07 vs 1520.64 pg/ml, respectively) and at the 25th percentile level (9.87 vs 386.67 pg/ml, respectively). The concentration of BNP increased to 98 (23.00%) patients in the total Group. The average value was 631.05±110.4 pg/ml, and the median - 853.23±69.43 pg/ml. It was revealed that more patients in Group II, compared to those in Group I, had increased serum BNP – 86 (41.35%) cases vs 12 (5.50%) cases, respectively; 95% CI: 28.30-43.02; $p<0.0001$. The distribution of COPD patients in Group II by increased BNP and sex highlighted the following: men had increased BNP more frequently, compared to women – 54 (12.68%) cases vs 33 (7.74%) cases; 95% CI: 11.50-12.61; $p = 0.0120$. There was a significant correlation between serum BNP concentration and patients' age ($p=0.01$).

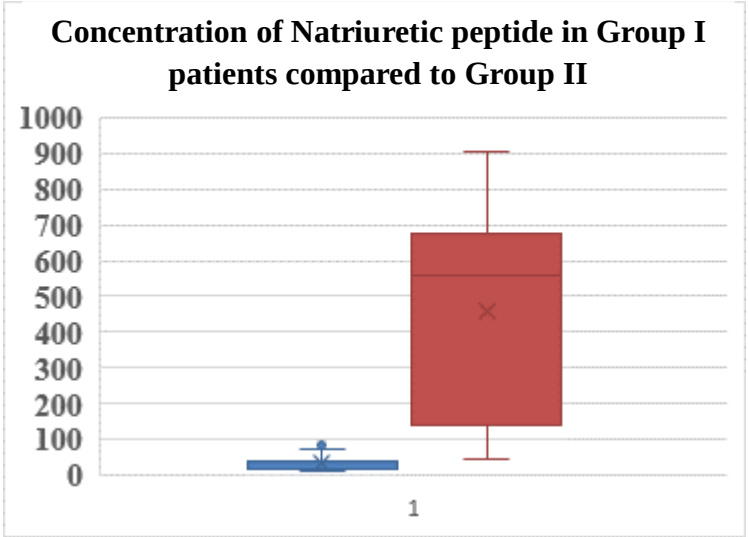

Figure 3.6. Box & whisker analysis of Natriuretic peptide in Group I patients compared to Group II.

It was determined the statistical difference between the average value of BNP, in patients in Group II, compared to those in Group I – 1054.30±110.40 vs 207.8±110.4 pg/ml, 95% CI: 831.73-861.26, pL1-L2<0.0001, also confirmed by Box & Whisker analysis. On the Boxplot chart (Figure 3.6) is graphically reflected the summarization by the 5 values of the BNP distribution: minimum value – of 46.24; first quartile (or lower quartile) – 137.84; median – 556.96; third quartile (or upper quartile) – 678.19; and the maximum value – 904.58 pg/ml. There was a significant correlation between serum BNP concentration and hypoxaemia, and peak 75th percentile BNP was detected in patients with hypoxaemia (SpO2 <90%). The distribution of COPD patients in the total Group according to BNP values showed: one (0.5%) patient had a value up to 35.0 pg/ml; range of 35.1-100.0 pm/ml was recorded in 10 (4.8%) patients; range of 100.1-300.0 pg/ml – to 9 (4.3%); range of 300.1-500.0 ng/ml – to 4 (1.9%); range of 500.1-1000.0 pg/ml – in 26 (12.4%) patients, range of 1000.1-1500.0 pg/ml – in 15 (7.2%) patients, and in 22 (10.5%) patients values of >1500.10 pg/ml.

Table 3.7. Distribution of COPD patients in Group II by BNP

BNP	Category B	Category C	Category D	CI 95%	p
N (%)	35 (50.00%)	18 (25.71%)	16 (22.86%)	8.22-38.68 11.23-41.22 11.30-16.86	pB-C = 0.0032 pB-D = 0.0009 pC-D = 0.6952

The distribution of COPD patients in Group II, according to BNP and categories B, C, D, revealed the predominance of patients in category B versus categorys C and D – 35 (50.00%) vs 18 (25.71%) vs 16 (22.86%) patients; pB-C = 0.0032 (Table 3.7).

The estimation of the ROC curves for Tn I and BNP (Figure 3.7), in patients in the total Group, showed that the BNP value is above the main diagonal and has an area of 0.867, better performance than Tn I, which has an area of 0.468 with a worse performance than BNP.

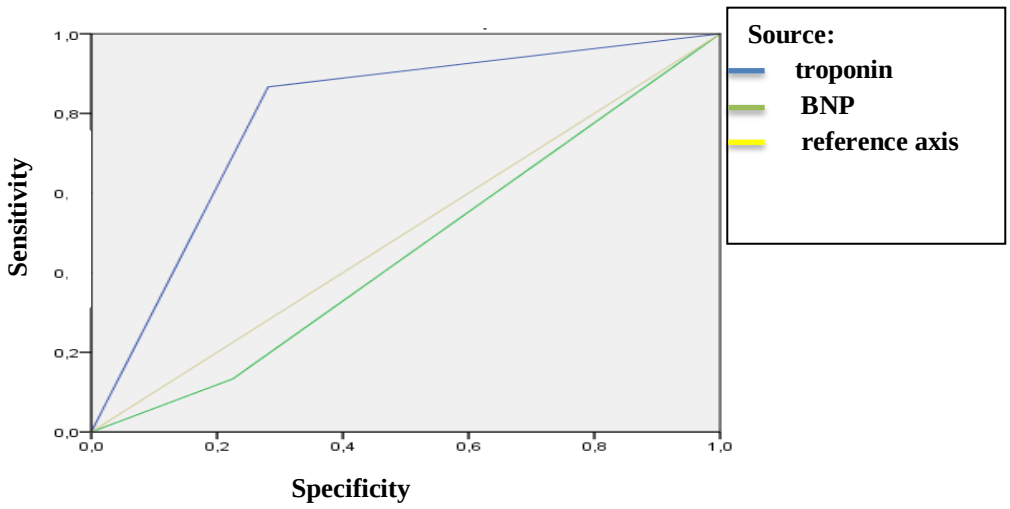

Figure 3.7. ROC curves for TnI and BNP in patients in the total Group.

Areas under the TBR curves for TnI and BNP in patients in the total Group demonstrated higher BNP compared to Tn I (0.867 vs 0.468, respectively).

3.8. Odds ratio of cardiovascular risk factors

Analyzing the Odds Report (RS) observed: of the cardiopulmonary risk factors studied, all RS values were greater than 1 and confidence interval with values close to RS, calculated; therefore, we can confirm that there is a positive association between risk factors, such as: smoking, obesity, diabetes, dyslipidemia and the presence of CVC in patients with COPD (Figure3.12).

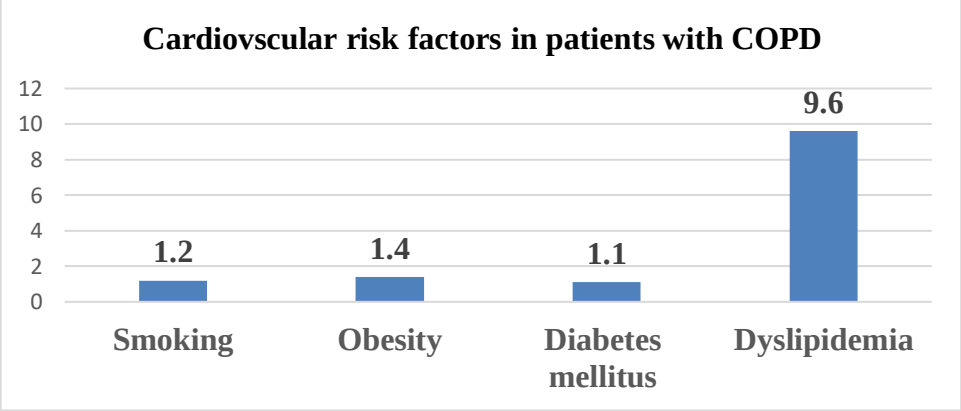

Figure 3.8. Odds ratio of risk factors in patients with COPD

3.9. Evaluation of associations of cardiovascular comorbidities with clinical variants of COPD

In 208 (48.82%) patients with COPD, the course was accompanied by ischaemic heart disease (IHD), of these, 159 (76.44%) had typical stable exercise angina, 49 (23.56%) – old myocardial infarction, and 40 (19.23%) underwent myocardiac revascularization. The mean duration of COPD, in the presence of IPC, was statistically significant (p = 0.023) longer than in patients not diagnosed with CVC and in 13.5% of patients, IHD preceded the onset of COPD.

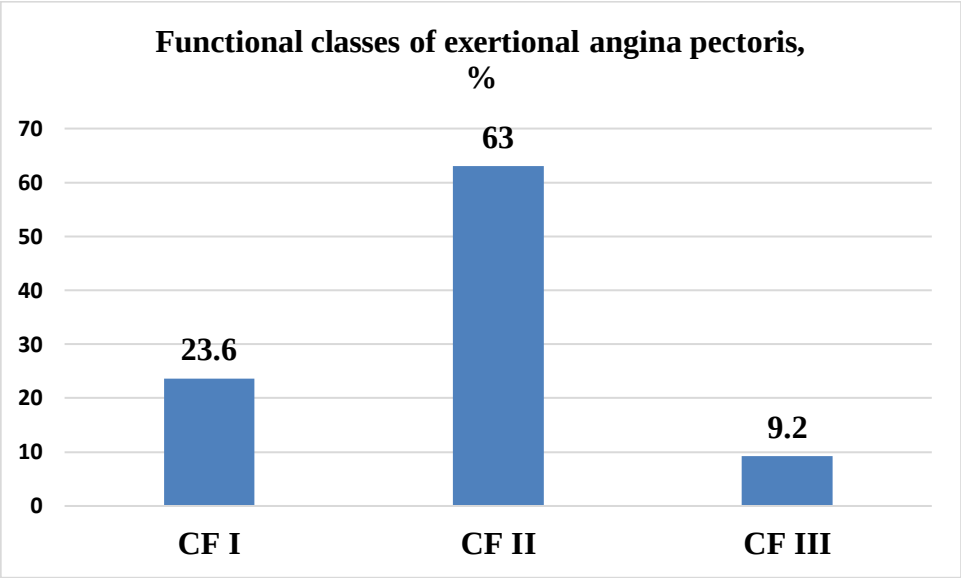

Figure 3.9. Distribution of patients with COPD and CPI, according to functional classes of exercise angina. Note: CF – functional class.

The distribution of patients with COPD and ICC, according to functional classes (CF) of exertional angina pectoris (Figure 3.9), revealed that: 9 (4.3%) patients had symptoms of CF I; 131 (63.0%) patients – CF II and 19 (9.2%) patients – CF III (pLT-L2<0.0001). The clinical pattern of COPD was accompanied by atypical angina pectoris and shortness of breath, manifestations of transient myocardial ischemia. Investigating the cardiovascular system, a tachycardia was attested up to 110±5.8 beats / minute in 181 (42.5%) patients, accentuated noise II on the pulmonary artery - in 43 (20.67%) patients. Arterial hypertension was experienced by 208 (100.0%) patients from Group II, which constitutes 48.82% of the entire cohort researched. The average systolic blood pressure was at the level of 132.64±13.45 mmHg, and the average diastolic – at the level of 94.54±8.49 mmHg. Analysis of the data obtained (Figure 3.10) showed that in patients with COPD, both men and women experience a high degree of hypertension.

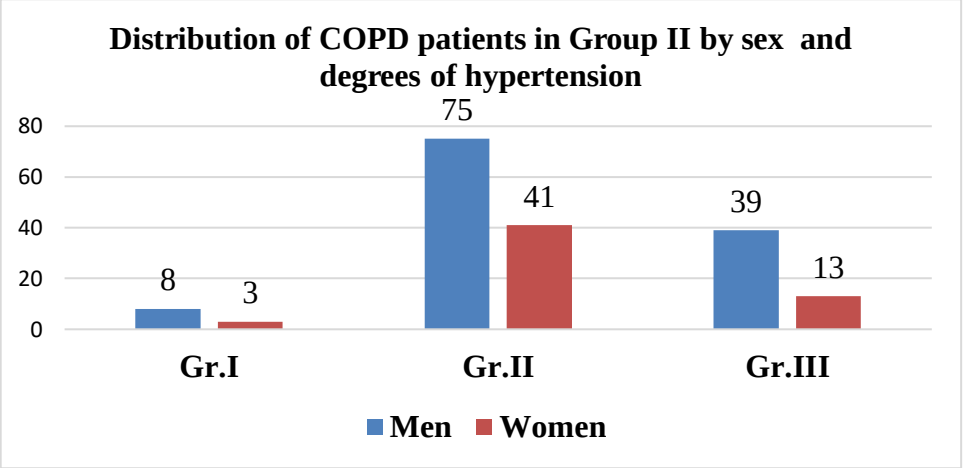

Figure 3.10. Distribution of COPD patients in Group II by sex and degrees of hypertension.

Cardiovascular manifestations in patients with COPD and CVC were also found by ECG changes: various rhythm disturbances, intraventricular conduction disorders, predominantly, incomplete blockages of right Hiss ram, signs of left ventricular hypertrophy and disorders of repolarization processes. ECG characteristics (Table 3.8), at pulmonary heart level, in patients with COPD, were manifested by the presence of the QRS AEC SIQIII axis in 36 (8.5%) patients, with no differences per groups (p=0.0588). Pulmonary P aspect (increased P-wave amplitude in D2, D3, AVF, R/S amplitude in V1 >1) was recorded in 251 (58.92%) people, and complete right ram blockage of the Hiss beam was attested in 36 (8.45%) cases. The deviation of the electrical axis of the heart to the left was determined more frequently in patients in Group II, compared to those in Group I – 53 (25.5%) vs 36 (16.5%), 95% CI: 1.2636% to 16.6745, p=0.0225. The deviation of the electrical axis of the heart to the right was recorded more frequently in patients in Group I, compared to those in Group II – 68 (31.2%) vs 61 (19.3%), 95% CI: 3.64-19.91, p = 0.0048. The frequency of the vertical electrical axis did not differ significantly in patients in the comparison groups.

Table 3.8. Distribution of patients with COPD, with ECG changes

ECG	Group I	Group II	CI 95%	p pGII-GI
AEC SIQIII	13 (5.96%)	23 (11.06%)	0.24-10.65	= 0.0588
Horizontal	72 (33.00%)	50 (24.0%)	7.01-10.98	< 0.0001
Vertically	29 (13.3%)	21 (10.1%)	3.00-9.36-	= 0.3056
Left	36 (16.5%)	53 (25.5%)	1.26-16.67	= 0.0225
Right	68 (31.2%)	61 (19.3%)	3.64-19.91	= 0.0048
Pulmonary P	128 (58.71%)	123 (59.13%)	8.86-9.67	= 0.9299
Right bundle branch block of Hiss	13 (3.06%)	23 (5.39%)	1.64-6.59	= 0.2312
S/ventricular tachycardia	24 (11.0%)	27 (13.0%)	0.56-3.43	= 0.0063
Ventricular extrasystole	18 (13.2%)	44 (21.1%)	5.75-10.04	<0.0001
S/ventricular extrasystole	30 (13.8%)	59 (28.4%)	6.88- 22.18	= 0.0002
Atrial Fibrillation	23 (11.1%)	41 (18.8%)	5.55-9.84	<0.0001

Note: AEC – electrical axis of the heart, s/ventricular-supraventricular.

In patients with COPD accompanied by CVC, the number of supraventricular extrasystoles per day was statistically significantly higher than in individuals with isolated COPD – 59 (28.4%) vs 30 (13.8%), 95% CI: 6.88-22.18, p = 0.0002. The number of ventricular extrasystoles per day in patients with COPD accompanied by CVC was statistically significant (p

<0.001) higher than in people with isolated COPD – 44(21.1%) vs 18 (13.2%), CI 95%: 5.75-10.04, p<0.0001. Supraventricular tachycardia was recorded in 51 (12.0%) patients, more frequently in Group II, compared to patients in Group I – 27 (13.0%) vs 24 (11.0%), 95% CI: 0.56-3.43, p=0.0063. Atrial fibrillation (AF) was statistically significantly more common in patients with COPD, associated with CVC, as opposed to patients with isolated COPD – 41 (18.8%) vs 23 (11.1%), 95% CI: 5.55-9.84, p< 0.0001 [192]. The frequency of paroxysmal AF, in our study, was associated with COPD severity degrees: in patients with mild COPD, paroxysmal AF manifested itself only in 10.0% of cases, and in patients with COPD moderate and severe degrees – in 24.6% of cases (p = 0.07).

3.10. Echocardiographic indices in patients with COPD

Echocardiographic sizes were statistically significantly distinct (p<0.001) in the COPD group accompanied by CVC compared to patients with isolated COPD (Table 3.9).

Table 3.9. Echocardiographic indices in COPD patients in Group I and Group II

Echocardiography	Group I	Group II	CI 95%	pG1-G2
LVDD (mm)	51.19±9.11	54.57±9.11	1.64-5.11	<0.0001
LVSD (mm)	40.13±18.82	48.65±18.82	2.10-4.93	<0.0001
LVEF (%)	52.65±11.36	45.75±11.36	4.73-9.06	<0.0001
IVS (mm)	11.28±2.40	12.20±2.40	1.37-0.46	<0.05
LA Diameter (mm)	38.35±23.00	44.08±23.00	1.34-10.11	<0.010
PFAT (ms)	86.48±2.96	89.56 ± 1.36	2.63-3.52	<0.05
PASP (mmHg)	42.50±8.75	46.73±1.23	3.02-5.43	<0.0001
RV (mm)	44.88±6.48	45.38±6.86	0.77-1.77	= 0.439
RA (mm)	46.52±4.37	48.63±6.87	1.02-3.20	<0.05

Note: LVDD - left ventricular telediastolic diameter, LVSD - left ventricular telesystolic diameter, LVEF - left ventricular ejection fraction, IVS - interventricular septum, LA - anteroposterior diameter of left atrium, PFAT - pulmonary flow acceleration time, PASP pulmonary artery systolic pressure, RV- right ventricular size, RA - right atrium size.

The frequency of recording right ventricular diastolic (RV) dysfunction in patients with COPD in combination with CVC was statistically significantly higher than in patients with isolated COPD. Statistically higher significant indices were: left atrium size (LA) (44.08±23.00 vs 38.35±23.00mm, 95% CI: 1.34-10.11, p<0.01, respectively); LVDD (54.57±9.11 vs 51.19±9.11mm, 95% CI: 1.64-5.11, p<0.001); LVSD (48.65±18.82 vs 40.13±18.82mm, 95% CI: 2.10-4.93, p<0.0001).

The differences in the distribution of left ventricular remodeling types between the groups of patients with isolated COPD and patients with COPD accompanied by CVC were statistically significant: interventricular septum (12.20±2.40 vs 11.28±2.40mm, 95% CI: 0.46-1.37, p<0.05) in patients with COPD in combination with CVC compared to patients with isolated COPD (Table 3.9). Concomitantly with the progression of bronchial obstruction, increased systolic pressure of the pulmonary artery; thus, the mean values of systolic pressure of the pulmonary artery in patients with severe bronchial obstruction in Group II exceeded 46.73±1.23 mm analogous values, in patients with moderate bronchial obstruction in Group I – 42.50±8.75 mm. Systolic pulmonary artery pressure in patients with CVC was significantly higher than in patients with isolated COPD (46.73±1.23 vs 42.50±8.75 mmHg, p<0.001). The increase in pulmonary artery systolic pressure was accompanied by increased pulmonary flow acceleration time (PFAT). The TAFP index was statistically significantly higher (89.56 ± 1.36 vs 86.48±2.96

ms, 95% CI: 2.63-3.52, p <0.05) than in patients with isolated COPD. The size of RA in the COPD group associated with CVC was statistically significantly higher (48.63±6.87 vs 46.52±4.37mm, 95% CI: 1.02-3.20, p = <0.05, respectively) than in patients with isolated COPD.

3.11. Distribution of patients with COPD, according to functional classes in chronic heart failure, according to NYHA classification

Analyzing the distribution of patients with COPD, according to functional classes (FC) in chronic heart failure (CHF), according to NYHA classification, statistical differences were revealed between study groups (Table 3.10).

Table 3.10. Distribution of patients with COPD by functional classes in chronic heart failure according to NYHA classification

CHF NYHA	Group I	Group II	CI 95%	p
NYHA I	27 (12.4%)	25 (12.0%)	0.53-1.33	= 0.4026
NYHA II	107 (49.1%)	125 (60.1%)	6.25-15.74	<0.0001
NYHA III	32 (14,.%)	49 (23.1%)	1.06-2.93	<0.0001

Note: CHF- chronic heart failure, NYHA- New York Heart Association.

The distribution of patients with COPD, according to CHF functional classes, according to NYHA classification attested the presence of CHF in 365 (85.68%) patients, I FC NYHA– in 52 (12.2%) patients, II FC NYHA– in 232 (54.5%) patients, III FC NYHA – in 81 (19.1%) patients. The distribution of patients with COPD, according to the functional classes of CHF, demonstrated that, in the comparison groups, patients in Group II, with II FC NYHA predominated compared to those in Group I – 125 (60.1%) vs 107 (49.1%), 95% CI: 6.25-15.74; p<0.0001. The number of patients with COPD and FC III NYHA was higher in Group II than in Group I – 30 (14.4%) vs 27 (12.4%), 95% CI: 1.06-2.93, respectively; p< 0.0001.

3.12. Changes in coronary blood flow in patients with COPD

The characteristics of coronary bed lesion were assessed using angiocoronary angiography, to which 40 patients were subjected. Statistical analysis in this subgroup, at the level of the three main coronary arteries (anterior descending, circumflex, right coronary) and at the level of the left trunk of the coronary artery, revealed the presence of hemodynamically significant stenosis (≥50%), with involvement of 1, 2 or 3 arteries, in patients in Group II. Coronary angiographic data in patients in the group of subjects with COPD, accompanied by CVC, revealed atherosclerotic lesions of the coronary bed in 40 (19.23%) patients, with COPD, category B, compared to COPD patients, category C and, significantly higher, than COPD patients, category D – 17 (42.50%) vs 17 (42.50%) vs 4 (10.00%), 95% CI: 13.36- 48.95, respectively; p = 0.0010. There was a predominance of patients with COPD, severe categories, C and D, unlike the group that included the COPD, moderately severe B category – 17 (42.50%) vs 21(52.50%), respectively; p<0.001.

Monitoring patients with COPD and CVC during the hospital period detected 15 patients who developed acute coronary syndrome (ACS). In patients with ACS, in combination with COPD, features of the clinical picture of ACS, high frequency of atypical forms of myocardial infarction (asthmatic and asymptomatic) were more often revealed. The given peculiarity of the

clinical picture of SCA created prerequisites for establishing an incorrect diagnosis and, consequently, late recognition of myocardial infarction.

3.13. Examining the impact of cardiovascular comorbidities on mortality and readmission rates up to 1 year after discharge

During monitoring, 276 (64.80%) participants had repeated hospitalizations, 171 (65.6%) subjects from Group I and 180 (63.9%) subjects from Group II; equivalent statistical number (CI 95%: 7.31-10.70, p = 0.7138).

Table 3.11. General characteristic of surviving COPD patients compared to deceased COPD patients

Clues	Survivors, n=402	Deceased, n=24	CI 95%	P_{S-D}
Men	250 (62.18%)	20 (83.33%)	1.41-32.24	= 0.0369
Women	152 (37.81%)	4 (16.66%)	1.41-32.24	= 0.0369
B:F ratio	1.64:1	5:1		
Average age, years	64.719	62.875	15.10-22.16	= 0.8546
Standard deviation	12.41	12.28		
Median	66.00	63.00	13.91-23.31	= 0.7637

Note: S – Survivors; D – The deceased.

Under monitoring, 24 (5.63%) patients died (mean age 62.88±12.28 years, Mn- 63.00); of these, the number of men was 5 times higher than the number of women – 20 (83.33%) vs 4 (16.66%); p <0,001 (Table 3.11). The distribution of patients with COPD, survivors, compared to COPD patients, deceased, according to the background did not reveal significant differences between study groups, but the distribution according to the activity environment highlighted the predominance of chronic incapacity for work, in patients with COPD, deceased, as opposed to survivors: 7 (31.81%) vs 40 (10.07%), respectively, CI 95%: 6.40-41.89; p= 0.0011.

The distribution of patients with COPD, survivors, compared to patients with COPD, deceased 355 (89.87%) vs 23 (95.83%), respectively, depending on the presence of dyspnea revealed no significant differences between study groups (p=0.3405). The distribution of patients with COPD, survivors, compared to patients with COPD, deceased 186 (47.38%) vs 13 (56.52%), respectively, depending on the presence of smoking revealed differences between study groups (95% CI: 10.80- 27.33, p = 0.0845), although according to the Smoker Index there were no differences (31.64±13.50 vs 38.31±15.73, respectively; p= 0.4968).

Table 3.12. Stratification of surviving COPD patients compared to deceased COPD patients according to GOLD classification

GOLD	Survivors, n=402	Deceased, n=24	CI 95%	p
II	253 (62,94%)	7 (29,17 %)	13.19-48.74	= 0.0010
III	67 (16,66%)	9 (37,50 %)	3.63- 40.43	= 0.0115
IV	36 (8,95%)	8 (33,33 %)	8.44-44.16	= 0.0002

Stratification of surviving COPD patients compared to deceased COPD patients (Table 3.12) according to GOLD classification established that death was associated with stages III, IV GOLD (2016), multiple symptoms and a high risk of frequent exacerbations – 8 (33.33%) vs 36 (8.95%) survivors, 95% CI: 8.44-44.16, p = 0.0002. Deceased COPD patients had a higher CAT score compared to COPD patients, survivors – 21.20 vs 14.21, 95% CI: 9.53 – 4.44; p<0.0001, but score not confirmed by median estimate (18.50 vs 15.00, 95% CI: 7.87-23.16; p= 0.6431.

Table 3.13. Stratification of surviving COPD patients compared to deceased COPD patients by clinical features

Category	Survivors, n=402	Deceased, n=24	CI 95%	p
B	165 (41.04%)	7 (29.16%)	-8.66-26.93	= 0.2498
C	144 (35.82 %)	0 (0 %)	20.48-39.78	= 0.0004
D	93 (23.13 %)	17 (70.83 %)	26.52-61.98	<0.0001

The majority of deceased COPD patients by clinical features accounted for COPD category D compared to surviving COPD patients – 17 (70.83 %) vs 93 (23.13%), CI 95%: 26.52-61.98; p<0.0001 (Table 3.13). Deceased COPD patients were more frequently obese compared to surviving COPD patients. There were statistically truthful differences in the distribution of deceased COPD patients according to BMI >30 – 8 (33.33%) vs 71 (17.66%), CI 95%: 0.20-35.92; p = 0.0553, and in the BMI<25 category, surviving COPD patients predominated, compared to deceased COPD patients – 181 (45.02%) vs 6 (25%), CI 95%: 0.44-33.90; p= 0.0552.

VEMS in deceased COPD patients compared to COPD patients survivors were less – 44.87±21.44 vs 69.21±21.44, 95C% I: 4.58- 42.63; p = 0.0133, respectively; also Tiffeneau Index – 50.69 vs 69.95, 95% CI: 0.20-38.40; p<0.0001, respectively (Table 3.14).

Table 3.14. Ventilation indices in surviving COPD patients compared to deceased COPD patients

Clues	Survivors, n=402	Deceased, n=24	Standard deviation	CI 95%	p
VEMS	69.21	44.87	21.44	4.58- 42.63	= 0.0133
CV	68.25	68.66	29.67	15.98-20.05	= 0.9666
Tiffeneau Index	69.95	50.69	7.77	0.20-38.40	= 0.0480

Patients with COPD, deceased had more frequent SpO2 <90%, compared to patients with COPD, survivors – 8 (38.09%) vs 43 (13.39%), 95% CI: 7.82-44.68; p = 0.0009, respectively.

Table 3.15. Distribution of surviving COPD patients compared to deceased COPD patients according to the presence of non-cardiac comorbidities

Comorbidity	Survivors, n=402	Deceased, n=24	CI 95%	p
Diabetes mellitus	86 (21.39%)	7 (29.16 %)	7.10- 28.11	= 0.3713
Obesity	90 (22.38%)	14 (58.33%)	15.97-53.56	= 0.0001
Dyslipidemia	93 (23.13%)	4 (16.66%)	-13.09-17.36	= 0.4633
Pathology of the nervous system	78 (19.40 %)	13 (54.16%)	14.72- 52.57	= 0.0001
Pathology of the digestive system	39 (9.70%)	14 (58.33 %)	28.55-65.74	< 0.0001

The presence of non-cardiac comorbidities (Table 3.15) was significantly superior in deceased COPD patients. More than half of the deceased patients had obesity – 14 (58.33%) vs 90 (22.38%), survivors, (p=0.0001).

Table 3.16. Distribution of surviving COPD patients compared to deceased COPD patients according to the presence of functional class of ischemic heart disease

FC	Survivors, n=402	Deceased, n=24	CI 95%	p
I FC	234 (58.20%)	19(79.16%)	0.76-33.53	= 0.0425
II FC	27 (6.71%)	1(4.16%)	7.02-13.65	= 0.6246
III FC	5(1.23%)	0	2.85-12.58	= 0.5852

Note: FC – functional class.

The distribution of patients with COPD, deceased, compared to patients with COPD, survivors (Table 3.16), according to the presence of ischemic heart disease (IHD) showed statistically reliable data of the presence of IHD of I FC – in 19 (79.16%) vs 234 (58.20%), respectively, 95% CI: 0.76-33.53; p=0.0425, as well as II-III FC – in 27 (6.71%) vs 1(4.16%) patients, respectively, CI 95%: 7.02-13.65; p= 0.6246.

The distribution of patients with COPD, deceased, compared to patients with COPD, survivors, according to the presence of heart failure (CHF), according to the NYHA classification and functional classes (FC), revealed statistically reliable data of the presence of CHF NYHA I FC – in 6 (25.00%) vs 46 (11.44%) patients, respectively; p=0.0489, and NYHA II-III were equivalent in comparison groups – in 16 (66.67%) vs 281 (69.90%) patiens, respectively; p = 0.7383. During follow-up, a total of 13 (54.16%) patients died from acute heart failure, and 11 (45.84%) – from acute respiratory failure, with a true statistical difference in the cause of death (p<0,001).

3.14. Predictive factors in cardiovascular death in patients with COPD accompanied by CVC

The calculation of the relative predictive risk of death (Figure 3.11) in patients with COPD revealed the presence of the following indices: male gender (RR- 2.1), with COPD, category D (RR- 1.82) and disability (RR- 1.34), VEMS1 (RR- 1.37), reduced Tiffeneau index (RR- 1.47), SpO2<90% (RR- 3.11), CODEX score (RR- 1.64), obesity (RR- 2.60), CRP (RR- 2.20) and NLR (RR- 1.39), troponin I (RR-1.52) and BNP (RR- 2.20).

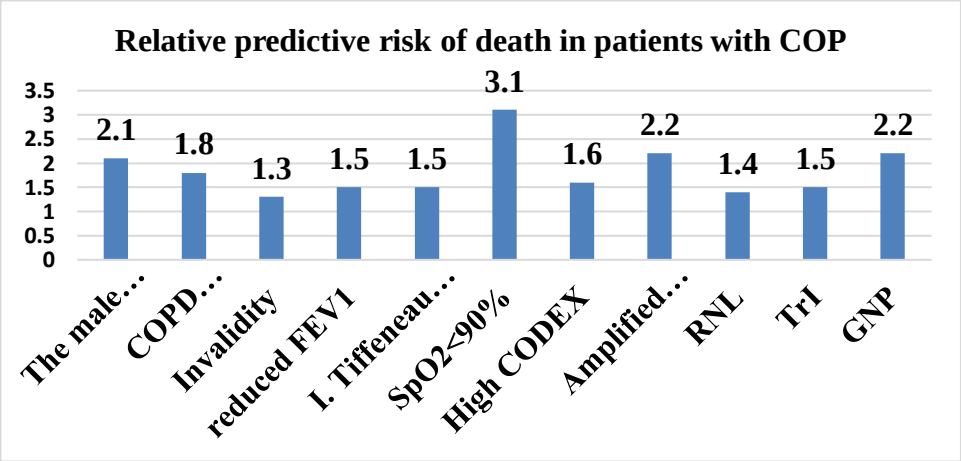

Figure 3.11. Relative predictive risk of death in patients with COPD.

The development of the predictive model in determining the probability of death in patients with COPD, accompanied by CVC, depending on the parameters and indices examined in our study included: increased BNP value, reduced VEMS1 and increased CODEX score, indices estimated by *Multifactor Logistic Regression* of SPPS 23 calculation system.

Table 3.17. Variables in the equation, estimated by Multifactor Logistic Regression

			χ2	df	Signif.
Pas 0	Variables	BNP	0.511	1	0.045
		VEMS	18.780	1	0.000
		COPD	12.043	1	0.001
		CODEX	14.012	1	0.000
	General Statistics		24.684	4	0.000

Note: df – degrees of freedom; Signif. – statistical significance.

The null hypothesis (potential predictors are unable to predict the outcome better than the constant) was rejected (omnibus test of model coefficients ($\chi2 = 24.623$, df = 4, $p < 0.001$) (Table 3.17).

Further analysis showed the following features of the developed model: the determination indicator, Nagelkerke R Square, showed the value of 0.183 (18.3%), which means that 18.3% of the variant of the variable of interest (patient death) was explained/covered by the proposed model. The calibration indicator (Hosmer-Lemeshow test) demonstrated an insignificant value, $\chi2 = 5.505$, df = 8, $p = 0.702$, the results being faithful in the sense of predicting the results obtained by the prediction score obtained.

Table 3.18. Variables in the predictive model of probability of death in patients with COPD associated with CVC

		B	SE	Wald	Sig.	Exp (B)	95% CI Exp (B)	
							Min.	Max.
	BNP	0.559	0.742	0.566	0.052	1.748	0.408	7.487
	COPD	-0.368	0.649	0.323	0.570	0.692	0.194	2.467
	CODEX	0.474	0.279	2.895	0.059	1.607	0.930	2.776
	Constant	-4.210	1.537	7.507	0.006	0.015		

Note: Constant – value of the equation constant; B – coefficients B, SE – standard errors; Wald – Wald statistics; Sig. – statistical significance; Exp (B) – odds ratio (OR), 95% CI for EXP (B); CI – confidence interval for odds ratio Variables: BNP, COPD, CODEX.

The model included the constant (B = 4.210), BNP (pg/l) (B = 0.559), COPD (B = -0.368), CODEX (B = 0.474), with logical signs ahead of the coefficients (Table 3.18). Taking into account the mentioned coefficients, the elaborated model has the following mathematical expression (Formula1):

$$p = \frac{1}{1+e^{-(4.210) +(0.559)* \text{BNP (pg/l)}+ (-0.368)* \text{BPOC} + (0.474) * \text{CODEX}}}$$

Where, p – probability of death; e (exponential) – constant equal to 4.210.

Finally, the parameters in the developed model had the following effects. For patients with an increased BNP, the risk of death was estimated 1.7-fold (OR = 1.748 (95% CI 0.408 - 7.487) and with an increased CODEX score - 1.6-fold (OR = 1.607 (95% CI - 2.776) higher, compared

to an undetected individual. As an indicator of discrimination, the area under the ROC curve was used, which, in the predictive model, was 0.778, with a confidence interval of 95% (0.699 and 0.917) and a significant difference from the value of 0.5 (p = 0.001) (Figure 3.12.).

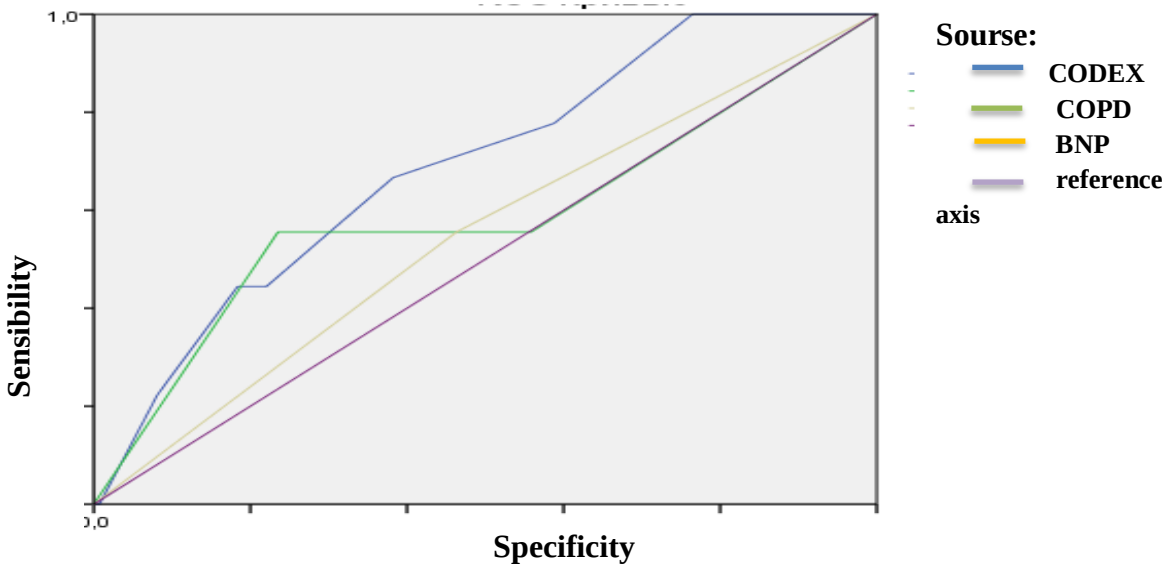

Figure 3.12. ROC curve in predictive model of probability of death in patients with COPD, associated with CVC, depending on BNP, VEMS and CODEX.

In this research, a predictive model of 12-month probability survival in COPD patients associated with CVC was proposed based on BNP, VEMS and CODEX score.

3.15. Elaboration of the Algorithm for early diagnosis of major cardiovascular events in patients with COPD, associated with CVC

The elaboration of the „Algorithm for early diagnosis of major cardiovascular events in patients with COPD associated with CVC", is an imperative necessity in order to optimize the timely and differential diagnosis, in the situation where both pathologies coexist: CVC and exacerbation of COPD. Therapeutic management should be carried out depending on the diagnosis associated with acute clinical decompensation. Treatment of such patients can be quite a challenging act, in particular, in the exacerbation of the disease. Although the reason for decompensation may be cardiovascular and respiratory in nature, we propose that both conditions be addressed simultaneously, due to constant interaction and bidirectional impact.

The „Algorithm for early diagnosis of major cardiovascular events in patients with COPD associated with CVC" includes complex assessment in steps (Figure 4.4): revised combined assessment of GOLD COPD and Categories A, B, C, D; pulse oximetry; Examination of acid-base and electrolyte balance; 6-minute walking test; Charlson comorbidity index; CODEX Index; Serum biomarkers: NLR, CRP, TrI, BNP; ECG examination; Echocardiographic examination; Coronary angiographic evaluation.

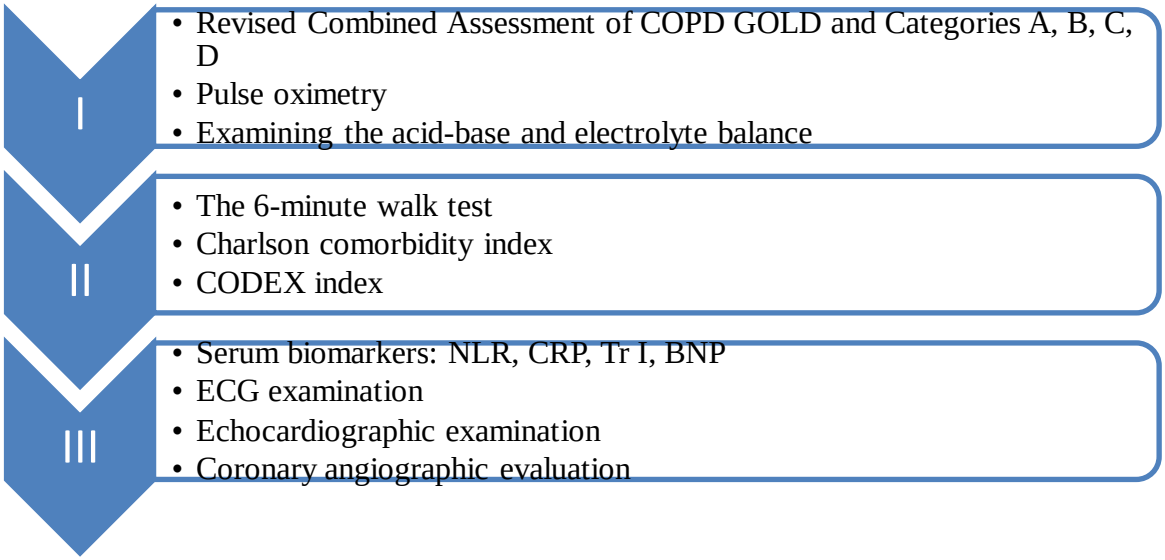

Figure 3.14. Algorithm for early diagnosis of major cardiovascular events in patients with COPD, associated with CVC.

The results of this study indicate that the algorithm is effective in detecting and predicting the risk of death in COPD patients through a rapid, inexpensive and non-invasive approach. The algorithm is variable-based, with significant predictive performance ($p<0.001$) better compared to that achieved by each significant variable alone. The algorithm described in this study provides a new way to combine and rank well-known prognostic criteria (GOLD 2015, 2023), but also the CODEX Index, cardiac biomarkers, ECG and EchoCG to identify CVC in patients with COPD in the clinic. The algorithm could also be particularly useful in primary care, as GPs have constant and confidential relationships with patients, with the ability to intercept COPD patients at risk of developing CVC early on, and not included in primary prevention. The algorithm could help better manage patients with COPD versus treatment options, designed not only to prevent cardiovascular risk, but also to identify patients with COPD, at risk of developing ACS and who are eligible for coronary arteriography, facilitating diagnostic and management processes.

GENERAL CONCLUSIONS

1. The overall picture per COPD patients included in the research, in terms of personal characteristics, highlighted the presence of obstructive syndrome pattern, whose appanage was the acute aggravation of symptoms, especially respiratory ones: dyspnoea after mMRC and the rate of exacerbations per year ≥ 3 were higher in patients with COPD, associated with CVC ($p=0.0086$). Analyzing cardiovascular risk factors in COPD patients included in this study, was estimated Odds Ratio values with pertinent evidence of positive association between risk factors such as: smoking (1.08), obesity (1.46), DM (1.08), dyslipidemia (9.5741) and CVC presence.

2. The evaluation, at the level of associations of cardiovascular comorbidities with clinical variants of COPD, revealed that, in 48.82% of patients with COPD, the evolution was combined with CVC , hypertension being attested in all patients; of these: 76.44% had typical stable angina of CF II effort, 23.56% – old myocardial infarction; 85.68% – CHF, more commonly II FC NYHA, and 19.23% of patients underwent myocardial revascularization. The clinical pattern of COPD, associated with CVC, was accompanied by atypical angina pectoris and shortness of breath, manifestations of transient myocardial ischemia. In patients with COPD associated with CVC, atrial fibrillation was recorded in 15.0% of cases, supraventricular tachycardia – in 12.0% of cases, extrasystoles, supraventricular and ventricular – in 28.4% of cases.

3. The combination of COPD and CVC increases systemic inflammation with significant activation of proinflammatory markers (CRP, NLR, fibrinogen) and cardiac biomarkers (TrI, BNP); associated with hypoxaemia with a higher incidence of acute cardiovascular failure in these patients. The structural and functional changes of the heart, in the combined pathology, are mainly directed towards pathological cardiac remodeling with left ventricle hypertrophy, increase in left ventricle diastolic diameter, right ventricle and right atria correlated with hemodynamic indices and serum biomarkers. The results of the correlation analysis between VEMS, blood gas composition and right and left heart hemodynamic parameters in COPD patients in combination with CVC indicate that there is a relationship between the degree of bronchial obstruction and changes in the hemodynamics of the right and left ventricles.

4. High frequency of COPD coursework, combined with cardiovascular comorbidity, is associated with a poor prognosis. During the follow-up, 64.80% of participants had repeated hospitalizations from both categories, and 5.63% of patients died, of which 54.16% died imminently from acute heart failure, and 45.84% patients – due to acute respiratory failure ($p<0.001$), more common in men, 5 times more frequently than in women ($p <0.001$). The pattern of deceased patients was associated with stages III, IV GOLD (2015), with a varied symptomatology and with a high risk of frequent exacerbations – belonging to the COPD D category, SpO2 <90%, reduced value of VEMS1 and low Tiffeneau Index, high CODEX score and presence of non-cardiac and cardiovascular comorbidities: presence of ischemic heart disease with II-III funcion classes of angina pectoris, III grade of arterial hypertension, chronic heart failure II-III NYHA funcion classes. A strong association of COPD exacerbation with acute cardiovascular events was noted in patients with severe airflow limitation in the first 30 days after the episode of COPD exacerbation.

5. The univariate analysis, calculating the relative risk of patients with COPD, revealed the impact of the following predictive indices of death: male gender (RR- 2.1), with COPD type D (RR- 1.82), and disability (RR- 1.34), VEMS1 (RR- 1.37), Low Tiffeneau Index (RR- 1.47), SpO2<90% (RR- 3.11), obesity (RR- 2.60), CRP (RR- 2.20) and NLR (RR- 1.39), troponin (RR- 1.52) and BNP (RR- 2.20), which formed the basis for the development of the "*Algorithm for Early Diagnosis of Major Cardiovascular Events in Patients with CVC-associated COPD"*. Multivariate logistic regression of these physiological parameters allowed to develop a „Predictive model in the probability of survival of patients with COPD associated with CVC".

PRACTICAL RECOMMENDATIONS

1. At the level of emergency care, internists and pulmonologists, it is recommended to positively identify acute coronary events, in exacerbation of COPD; these, diagnosed in time, can reduce mortality and morbidity rates).

2. In patient groups, with a high frequency of pathway associated with cardiovascular pathology (categories B and D), it is recommended to include the "*Algorithm for Early Diagnosis of Major Cardiovascular Events in Patients with CVC-associated COPD"*, with ECG monitoring perspective and echocardiographic monitoring.

3. At the level of primary care, internists and pulmonologists, to optimize the management of patients with COPD, it is necessary to take into account both the severity of dyspnea and the frequency of exacerbations, but the combination with cardiovascular pathology.

4. To determine the risk of an adverse course of COPD, it is recommended to use the „Predictive model in the probability of survival of patients with COPD associated with CVC", in early diagnosis of major cardiovascular events and in prescribing optimal appropriate treatment.

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INFORMATION REGARDING THE VALUATION OF RESEARCH RESULTS

LIST OF SCIENTIFIC PUBLICATIONS AND EVENTS
at which the research results for the doctoral thesis in medical sciences were presented with the theme "Cardiovascular comorbidities in patients with chronic obstructive pulmonary disease", carried out within the Department of Internal Medicine: Discipline of clinical syntheses,
of Popa Ana, State University of Medicine and Pharmacy "Nicolae Testemițanu" from the Republic of Moldova

SCIENTIFIC WORKS

- **Articles in scientific journals abroad::**

  ✓ **articles in ISI, SCOPUS and other international databases***

  1. **Popa A.,** Caproș N., Dumitraș T. Non-invasive Monitoring of Pulse Rate and Desaturation Events with Oximeter in COPD Patients with Cardiovascular Comorbidities. In: 5th International Conference on Nanotechnologies and Biomedical Engineering. ICNBME 2021, *IFMBE Proceedings 87*. Chişinău. 2021, pp. 743-749. **(IF:0,38).** ISBN 978-9975-72-592-7
  2. **Попа А.,** Капрош Н., Савка М. Половые различия в функции легких при хронической обструктивной болезни легких. In: *Туберкульоз, легеневі хвороби, ВІЛ-інфекція*, № 3 (42), 2020, p57-61. ISSN 2220-5071 (Print), ISSN 2522-1094(Online)

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Annex 1. **Innovator's certificate "Algorithm for the evaluation of cardiovascular comorbidities in patients with chronic obstructive pulmonary disease"**

Republica Moldova
Ministerul Sănătăţii

CERTIFICAT DE INOVATOR

Nr. 5970

Pentru inovaţia cu titlul

ALGORITMUL DE EVALUARE A COMORBIDITĂȚILOR CARDIOVASCULARE LA PACIENȚII CU BRONHOPNEUMOPATIE OBSTRUCTIVĂ CRONICĂ

Inovaţia a fost înregistrată pe data de
la Universitatea de Stat de Medicină şi Farmacie
"Nicolae Testemiţanu"

Se recunoaşte calitatea de autor(i)

POPA Ana

Data eliberării 03 Ianuarie 2023

L.Ş.

(Semnătura autorizată)

Annex 2. **Patent of invention**

MD 1363 Y 2019.08.31

REPUBLICA MOLDOVA

(19) Agenţia de Stat pentru Proprietatea Intelectuală

(11) 1363 (13) Y

(51) Int.Cl: ***A61M 11/06*** **(2006.01)**

A61M 15/00 (2006.01)

(12) BREVET DE INVENŢIEDE SCURTĂ DURATĂ

În termen de 6 luni de la data publicării menţiunii privind hotărârea de acordare a brevetului de invenţie de scurtă durată, orice persoană poate face opoziţie la acordarea brevetului	
(21) Nr. depozit: s 2018 0102 **(22) Data depozit:** 2018.11.08	**(45) Data publicării hotărârii de acordare a brevetului:** 2019.08.31, BOPI nr. 8/2019

(71) Solicitant: ARABADJI Vasilii, MD

(72) Inventatori: ARABADJI Vasilii, MD; CAPROŞ Natalia, MD; POPA Ana, MD; MATCOVSCHI Sergiu, MD; LUPAN Mihail, MD; DOGOT Marta, MD

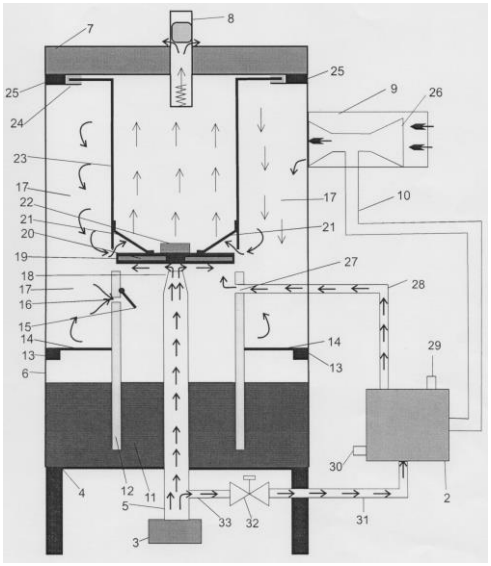
(73) Titular: ARABADJI Vasilii, MD

(54) Nebulizator

(57) Rezumat:

Invenţia se referă la medicină, în special la nebulizatoare pentru generarea soluţiilor medicinale.

Nebulizatorul conţine un corp exterior (1), în interiorul căruia pe un locaş (4) este amplasat un corp interior (6) pentru soluţia medicinală (11). În partea superioară a corpului (6) este instalat un cilindru superior (23), iar în partea inferioară a lui, prin suporturi (13) cu fixatori (14), este instalat un cilindru inferior (12). Totodată, in centrul corpului (6) şi cilindrului inferior (12), coaxial acestora, este amplasată o conductă de aer (5) cu o pompă (3), capătul căreia este dotată cu o duză (18), instalată perpendicular faţă de un reflector (19). Pe suprafaţa de lucru a reflectorului (19) este instalat un încălzitor termoelectric (20).



MD 1363 Y 2019.08.31

Annex 3. **Certificate of completion of the training course "Spirometry. Methods of recording and interpreting the spirogram"**

Ministerul Sănătății al Republicii Moldova
IP Universitatea de Stat de Medicină și Farmacie „Nicolae Testemițanu”
Centrul Universitar de Simulare în Instruirea Medicală

CUSIM

CERTIFICAT DE ABSOLVIRE

Dna Popa Ana,

a absolvit cursul de instruire prin simulare:

Spirografia. Metode de înregistrare și interpretare a spirogramei,

desfășurat în cadrul
Centrului Universitar de Simulare în Instruirea Medicală,
la data 17 martie 2017.

Sesiunea de instruire a fost creditată cu
4 (patru) credite EMC

Director CUSIM, **Andrei ROMANCENCO**

Seria **SIM** Cod **XVII** Nr. **00030** din **17 martie 2017**

***Annex 4*. Certificate of completion of the international pre-conference course**

UNIVERSITATEA DE MEDICINĂ ŞI FARMACIE
„GRIGORE T. POPA" IAŞI

Colegiul Medicilor Iaşi
Coordonator Comisia Profesional Ştiinţifică şi de Învăţământ
Vicepreşedinte
Prof. Dr. Florin Mitu

CERTIFICAT DE ABSOLVIRE

D-l / D-na Dr.

Ana POPA

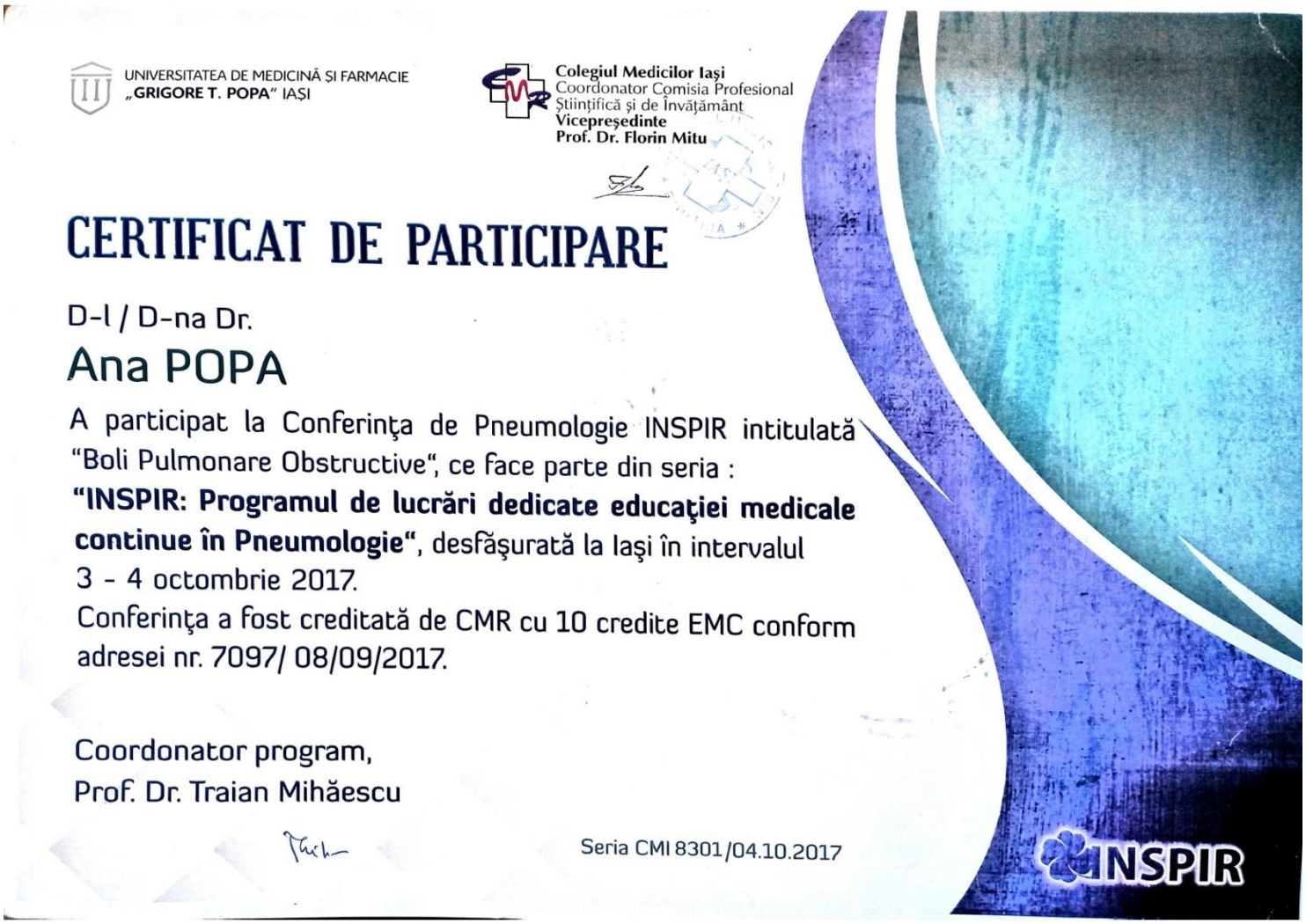
A absolvit cursul preconferinţă de formare continuă : **"Știința îmbunătățirii sistemului sanitar: o privire în abordarea viitoare a managementului sanitar"**, promovând evaluarea finală organizată. Cursul face parte din seria: **„INSPIR : Programul de lucrări dedicate educaţiei medicale continue în Pneumologie"**, şi s-a desfăşurat la Iaşi la data de 2 octombrie 2017.
Cursul a fost creditat de CMR cu 6 credite EMC conform adresei nr. 7097/ 08/09/2017.

Coordonator program,
Prof. Dr. Traian Mihăescu

Seria CMI 8146 /02.10.2017

INSPIR

Annex 5. **Certificat de participare la Conferința international**



UNIVERSITATEA DE MEDICINĂ ŞI FARMACIE
„GRIGORE T. POPA" IAŞI

Colegiul Medicilor Iaşi
Coordonator Comisia Profesional
Ştiinţifică şi de Învăţământ
Vicepreşedinte
Prof. Dr. Florin Mitu

CERTIFICAT DE PARTICIPARE

D-l / D-na Dr.

Ana POPA

A participat la Conferinţa de Pneumologie INSPIR intitulată "Boli Pulmonare Obstructive", ce face parte din seria : **"INSPIR: Programul de lucrări dedicate educaţiei medicale continue în Pneumologie"**, desfăşurată la Iaşi în intervalul 3 - 4 octombrie 2017.
Conferinţa a fost creditată de CMR cu 10 credite EMC conform adresei nr. 7097/ 08/09/2017.

Coordonator program,
Prof. Dr. Traian Mihăescu

Seria CMI 8301/04.10.2017

INSPIR

Annex 6. Certificat de implementare a inovației

Instituție Publica
USMF „Nicolae Testemițanu" din Republica Moldova
Institutul Național de Cercetare în Medicină și Sănătate

Pag. 5 / 5

APROB
Prorector pentru activitate de cercetare,
USMF „Nicolae Testemițanu" din RM
academician al AȘM,
prof. univ., dr. hab. șt. med.
Stanislav GROPPA
februarie 2023

ACTUL nr..1...
DE IMPLEMENTARE A INOVAȚIEI
(în procesul științifico–practic)

1. **Denumirea ofertei pentru implementare: ALGORITMUL DE EVALUARE A COMORBIDITĂȚILOR CARDIOVASCULARE LA PACIENȚII CU BRONHOPNEUMOPATIE OBSTRUCTIVĂ CRONICĂ**
2. **Autori:** POPA Ana, medic, doctorandă.
3. **Numărul inovației:** ***nr. 5970 din 03 ianuarie 2023***
4. **Unde și când a fost implementată:** Propunerea a fost utilizată în studiul: „ Comorbidități cardiovasculare la pacienții cu bronhopneumopatie obstructivă cronică", realizat la Disciplina de sinteze clinice, Departamentul Medicina Internă în secția „Pulmonologie", IMSP Spitalul Clinic Municipal „Sfânta Treime", în perioada anilor 2015-2023 aa.
5. **Eficacitatea implementării**: constă în depistarea eficientă a pacienților cu BPOC și CCV salvați cu includerea evaluării funcției cardiovasculare în timpul optimal pentru revascularizare coronariană și prevenția insuficienței cardiace acute.
6. **Rezultatele:** A fost obținut algoritmul de evaluare a comorbidităților cardiovasculare la pacienții cu bronhopneumopatie obstructivă cronică.
7. **Obiecții**: Valoarea aplicativă a algoritmului este justificată de evaluarea funcției cardiovasculare ce permite managementul terapeutic optim condus în ferestre importante de timp în scopul prevenirii complicațiilor. Metoda este adresată medicilor pulmonologi, internişti şi se utilizează în practică în IMSP Spitalul Clinic Municipal „Sfânta Treime".

Prezenta inovație este implementată conform descrierii în cerere.

Director IMSP SCM „Sfânta Treime
Dr. șt. med., conf. cercet. _____ **Oleg CRUDU**

Șef Departament Cercetare,
dr. hab. șt. med., conf. univ. _____ **Elena RAEVSCHI**

5