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COMMUNITY-ACQUIRED PNEUMONIA IN PATIENTS WITH CHRONIC HEART FAILURE

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INTRODUCTION

Relevance and importance of the addressed issue

Community-acquired pneumonia (CAP) is an acute inflammation of the lung tissue of infectious etiology, acquired outside the hospital, and is a global public health problem. Despite advances in the diagnosis and treatment of community-acquired pneumonia, mortality from severe pneumonia, including during the COVID-19 pandemic, remains high. Studies over the past 5 years have shown that the mortality rate from community-acquired pneumonia is approximately 1-5% in outpatients, more than 10% in patients hospitalized in general wards, and 30-65% in patients admitted to the intensive care unit [1, 2, 3].

The progression of community-acquired pneumonia is influenced by the presence of comorbidities, among which chronic heart failure (CHF) is of significant importance. Chronic heart failure is a clinical syndrome caused by a structural and/or functional abnormality of the heart, resulting in increased intracardiac pressures and/or inadequate cardiac output at rest and/or during exertion [4]. Although the incidence of CHF has stabilized in high-income countries over the past decade, its prevalence remains high, driven by an aging population, increased risk factors, and the effectiveness of new therapies. It is estimated that globally, approximately 64.3 million people suffer from heart failure. In developed countries, the prevalence of heart failure is generally estimated at 1-2% of the general adult population. The incidence of heart failure in European countries and the United States varies from 1 to 9 cases per 1,000 population per year [5, 6].

Establishing a diagnosis of CAP in patients with CHF is difficult due to a number of clinical similarities between these two nosological entities, as well as the less pronounced clinical manifestations of pneumonia (insidious onset, absence of the typical pulmonary condensation syndrome, weaker inflammatory response syndrome) in patients with heart failure, due to the fact that most of these patients are elderly [7, 8]. Only a few studies have addressed the issue of community-acquired pneumonia in patients with chronic heart failure, with the incidence of this association ranging from 29 to 39 cases per 1,000 population per year [9].

Another aspect is that the coexistence of CAP and CHF worsens the progression of both pathologies and increases the risk of severe pneumonia and mortality. Therefore, in the management of CAP against a background of pre-existing CHF, early identification of patients at high risk of mortality is essential. The widespread use of CAP severity scores, such as CURB-65, DS-CRB-65, and PSI/PORT, has greatly contributed to the stratification of the risk of severe progression and mortality, but these scores have not been evaluated in patients with pneumonia and pre-existing CHF [10, 11].

Recently, some biomarkers have been evaluated that could help assess the severity of CAP, such as inflammatory markers, heart failure markers, and oxidative stress

markers. Biomarkers can facilitate clinical decisions to guide antimicrobial treatment, predict prognosis in CAP, and provide additional information about disease severity and the distinction between bacterial and viral etiology of CAP [12, 13].

Over the last decade, scientific literature has shown increased interest in the role of oxidative stress in the pathogenesis and evolution of various pathologies, including community-acquired pneumonia. Oxidative stress, defined as the imbalance between the production of reactive oxygen species and the ability of endogenous antioxidant mechanisms to neutralize them, leads to structural and functional damage to cellular components, with an impact on the intensification of the inflammatory process and damage to the lung parenchyma. Clinical studies have demonstrated significantly increased levels of oxidative stress markers in patients with community-acquired pneumonia and chronic heart failure compared to a control group of healthy subjects [14, 15, 16]. The impact of oxidative stress on the evolution of community-acquired pneumonia in patients with chronic heart failure remains to be studied [17, 18, 19].

At the same time, the correlation between CAP evolution, oxidative stress, systemic inflammatory response syndrome, left ventricular ejection fraction, and functional class of heart failure in patients with CHF has not yet been fully studied. Therefore, our study focuses on evaluating oxidative stress parameters and correlating them with several clinical and paraclinical parameters in patients hospitalized with CAP and concomitant CHF.

Thus, **the aim of this study** is to highlight the clinical, paraclinical, and oxidative stress characteristics of community-acquired pneumonia in patients with chronic heart failure.

To achieve this goal, we set the following **objectives:**

1. To evaluate the clinical, paraclinical, and the disease course characteristics of patients with community-acquired pneumonia and concomitant chronic heart failure.
2. To assess oxidative stress markers in patients with community-acquired pneumonia and chronic heart failure.
3. Correlate inflammatory and oxidative stress indices with clinical and paraclinical data in patients with community-acquired pneumonia and chronic heart failure.
4. Determination of clinical and paraclinical data and progression in patients with community-acquired pneumonia and chronic heart failure, according to left ventricular ejection fraction and functional class of heart failure.
5. Analysis of the diagnostic accuracy of community-acquired pneumonia severity scores (PSI/PORT, CURB-65, DS-CRB-65) and development of our own model for predicting the severe progression of community-acquired pneumonia in chronic heart failure.

Scientific research methodology. The study was conducted within the Department of Internal Medicine, Clinical Syntheses Discipline, clinical base of Municipal Clinical Hospital "Holy Trinity". The study is a cohort, analytical, observational, prospective study, in which 210 patients were examined and subjected to complex treatment, of which 105 had community-acquired pneumonia and chronic heart failure (study group), 105 had community-acquired pneumonia and no chronic heart failure (control group). The primary endpoints were clinical improvement on day 3 and the secondary endpoints were clinical and radiological improvement on day 10 of treatment (complete disappearance/significant reduction of symptoms: cough, dyspnoea, disappearance of fever, normalization of heart rate, respiratory rate, blood pressure, SpO2 greater than 90% with FiO2=21%, disappearance of rales and crackles; radiologically - resorption of pulmonary infiltration), complications of community-acquired pneumonia, including death of patients included in the study.

The research was conducted based on clinical examination of patients, assessment of inflammatory and oxidative stress markers, assessment of comorbidities, and radiological data. The measurement of oxidative stress markers was performed in the biochemical laboratory of the "Nicolae Testemițanu" State University of Medicine and Pharmacy and inflammatory markers in the biochemical laboratory of the Municipal Clinical Hospital "Holy Trinity". Data analysis was performed using the functions and modules of Microsoft Excel, Medcalc, and SPSS Statistics for Windows, version 23, using various methods of assessing veracity.

Scientific novelty and originality. For the first time in the Republic of Moldova, community-acquired pneumonia in patients with chronic heart failure has been studied, and at present it is one of the few studies published in the specialized literature that addresses the problem of oxidative stress developed at the interface of two pathologies: pulmonary infection (community-acquired pneumonia) and cardiovascular disease (chronic heart failure). This research involved a comprehensive analysis aimed at determining the clinical and the disease course characteristics of oxidative stress and systemic inflammatory response in community-acquired pneumonia in chronic heart failure. It was demonstrated that in community-acquired pneumonia in patients with CHF, there is an excessive accumulation of pro-oxidative reaction products, manifested by higher values of ischemic modified albumin, partially counterbalanced by an increase in total antioxidant activity assessed by the CUPRAC method. Ischemic modified albumin, previously applied as a biological marker of acute cardio- and cerebrovascular events, was proposed in this study as a biomarker of community-acquired pneumonia severity in patients with CHF. NT-proBNP, currently used as a biomarker of heart failure, correlated positively with both the degree of heart failure and the severity of community-acquired pneumonia, and was proposed as a useful biomarker for predicting the severity of community-acquired pneumonia in the context of CHF. To predict the

severity of pneumonia, a method was developed to predict the severe progression of community-acquired pneumonia in patients with chronic heart failure.

The scientific problem addressed in the thesis consists in elucidating the clinical, paraclinical, and the disease course aspects of community-acquired pneumonia in chronic heart failure, predicting disease progression using biomarkers of heart failure and inflammation, oxidative stress, and radiological data. Inflammatory markers, imaging data in community-acquired pneumonia, and the correlations between them and the severity of clinical manifestations were evaluated. An essential point of the research was the analysis of echocardiographic indices, in particular the left ventricular ejection fraction, as an indicator of the severity of heart failure and a predictor of the evolution of pneumonia. By evaluating these parameters, the present study aimed not only to describe the clinical characteristics of patients with CAP and CHF, but also to identify those patients who are at risk for an unfavorable disease progression. Therefore, the scientific problem addressed in the thesis is a current one and reflects a medical reality frequently encountered in clinical practice. It proposes an evidence-based approach to optimizing the diagnosis and prognosis of patients with community-acquired pneumonia in the context of chronic heart failure.

Theoretical importance and practical value of the study. The study aimed to identify the clinical, paraclinical, and the disease course characteristics of community-acquired pneumonia in patients with pre-existing chronic heart failure. The pattern of systemic inflammatory response and oxidative stress in these patients was studied, demonstrating a positive correlation between the severity of community-acquired pneumonia, the radiological extent of the pneumonic infiltrate, the presence of pleural effusion, the length of hospitalisation, the need for oxygen therapy and the degree of pro-oxidative status (ischemic modified albumin, advanced oxidation protein products, advanced glycation end products) and proinflammatory status (lactate dehydrogenase, fibrinogen). This study highlighted the mutual influence of community-acquired pneumonia and chronic heart failure: the progression of chronic heart failure is associated with the presence of pleural effusion on chest X-ray, higher levels of oxidative stress (advanced glycation end products, advanced oxidation protein products), partially offset by the production of antioxidants (total antioxidant activity assessed by the CUPRAC method).

Using logistic regression, an algorithm was developed to predict the severe progression of community-acquired pneumonia in patients with CHF, integrating clinical (respiratory rate per minute) and paraclinical (left ventricular ejection fraction, modified ischemic albumin, platelet count, peripheral blood oxygen saturation, NT-proBNP value, and the presence of pleural effusion on chest X-ray).

To assess the severity of community-acquired pneumonia, threshold values for ischemic modified albumin and NT-proBNP in patients with chronic heart failure were

determined and proposed for practical application. We also assessed the sensitivity and specificity of community-acquired pneumonia severity scores in chronic heart failure, with the DS-CRB-65 score demonstrating the highest diagnostic accuracy in this patient category. The results obtained will contribute to improving the diagnosis and prediction of the evolution of community-acquired pneumonia in patients with chronic heart failure.

Implementation of scientific results. The results of the study were approved and applied in the teaching process in the Clinical Syntheses discipline within the Internal Medicine Department of the "Nicolae Testemițanu" State University of Medicine and Pharmacy and implemented in the practical activity of the Pneumology and General Therapy Departments of the Municipal Clinical Hospital "Holy Trinity".

Approval of scientific results. The research results were reported at national and international forums: Annual scientific conference within the USMF "Nicolae Testemiţanu" Days, Chișinău, October 17, 2019; The 26th National Congress of the Romanian Society of Pneumology, held online, November 5-8, 2020; The First National Congress of Geriatrics and Gerontology, Chișinău, September 23-24, 2021; International Congress for Students and Young Researchers: BIMCO, 8th edition, online, Chernivtsi, Ukraine, April 6-9, 2021; INSPIR Pneumology Conference – virtual edition. Iași, June 8-11, 2021; Annual Scientific Conference within the USMF "Nicolae Testemițanu" Days, Chișinău, October 19-21, 2022; The 27th National Congress of the Romanian Society of Pulmonology, Sinaia, November 3-6, 2022; The 9th International Medical Congress for Students and Young Doctors, Chișinău, May 12-14, 2022; Annual Scientific Conference within the USMF "Nicolae Testemiţanu" Days, Chișinău, October 20-23, 2023; The 6th International Conference on Nanotechnologies and Biomedical Engineering, ICNBME-2023. Chisinau, September 20–23, 2023; Congress of Internal Medicine of the Republic of Moldova with International Participation, 4th edition, Chișinău, September 13-14, 2024; 28th National Congress of the Romanian Society of Pneumology. Romania, Sinaia, November 13–16, 2024; The European Respiratory Society Congress, Netherlands, Amsterdam, September 27–October 1, 2025; The 7th International Conference on Nanotechnologies and Biomedical Engineering, ICNBME-2025, Chisinau, October 7–10, 2025.

Publications related to the thesis topic. The scientific results obtained in this research were published in 21 scientific papers, including 8 articles (4 of which were published in SCOPUS journals) and 13 abstracts of oral presentations.

Volume and structure of the thesis. The thesis is written in Romanian as a manuscript. The thesis consists of an introduction, 4 chapters, conclusions and practical recommendations, bibliographical references (305 sources) and appendices. The work is illustrated with 47 tables, 31 figures and 4 appendices.

1. CONTEMPORARY CONCEPTS REGARDING COMMUNITY-ACQUIRED PNEUMONIA IN PATIENTS WITH CHRONIC HEART FAILURE

This chapter reflects a synthesis of the specialized literature dedicated to the clinical, paraclinical, and the disease course characteristics of community-acquired pneumonia in patients with chronic heart failure. The role of inflammatory biomarkers and oxidative stress, clinical presentation and imaging, as well as contemporary approaches to the diagnosis of pneumonia in patients with chronic heart failure were described. Existing studies on the prognostic role of community-acquired pneumonia severity scores (PSI/PORT, CURB-65, DS-CRB-65) for assessing the disease course possibilities in chronic heart failure were analyzed. Similarly, the impact of pre-existing chronic heart failure on the evolution of community-acquired pneumonia was addressed. At the same time, the chapter discusses the value of applying our own model for predicting the severe progression of community-acquired pneumonia in chronic heart failure.

2. MATERIALS AND RESEARCH METHODS

2.1.General characteristics of the research

This study was conducted within the Department of Internal Medicine, Clinical Syntheses Discipline, Municipal Clinical Hospital "Holy Trinity" clinical base, between October 2018 and October 2023. It is a prospective, observational, analytical, cohort study, in which 210 patients were examined and underwent complex treatment, of which 105 had community-acquired pneumonia and pre-existing chronic heart failure (study group), and 105 had community-acquired pneumonia and no heart failure (control group) (Figure 1.).

Patients were enrolled in the study in the order of admission and signed an informed consent form for participation in the study, approved by the Research Ethics Committee of the "Nicolae Testemițanu" State University of Medicine and Pharmacy, approval number 18 of 12.04.2019. The study was conducted in accordance with the ethical guidelines specified in the 1975 *Declaration of Helsinki.* The clinical diagnosis of community-acquired pneumonia was established according to the clinical and paraclinical criteria stipulated in national and international guidelines: fever, cough, expectoration, dyspnea, and/or chest pain and symptoms of infectious impregnation (unexplained asthenia, fatigue, night sweats), signs of respiratory failure, and radiological confirmation of pulmonary infiltrate [20].

The diagnosis of chronic heart failure was based on typical signs and symptoms: dyspnea, increased jugular venous pressure, reduced exercise tolerance, laterally displaced apical shock, fatigue, and leg edema. The diagnosis was confirmed in patients who showed evidence of structural or functional heart damage on echocardiography: low ejection fraction, enlarged heart chambers, diastolic dysfunction, ventricular hypertrophy, or moderate to severe valvular lesions,

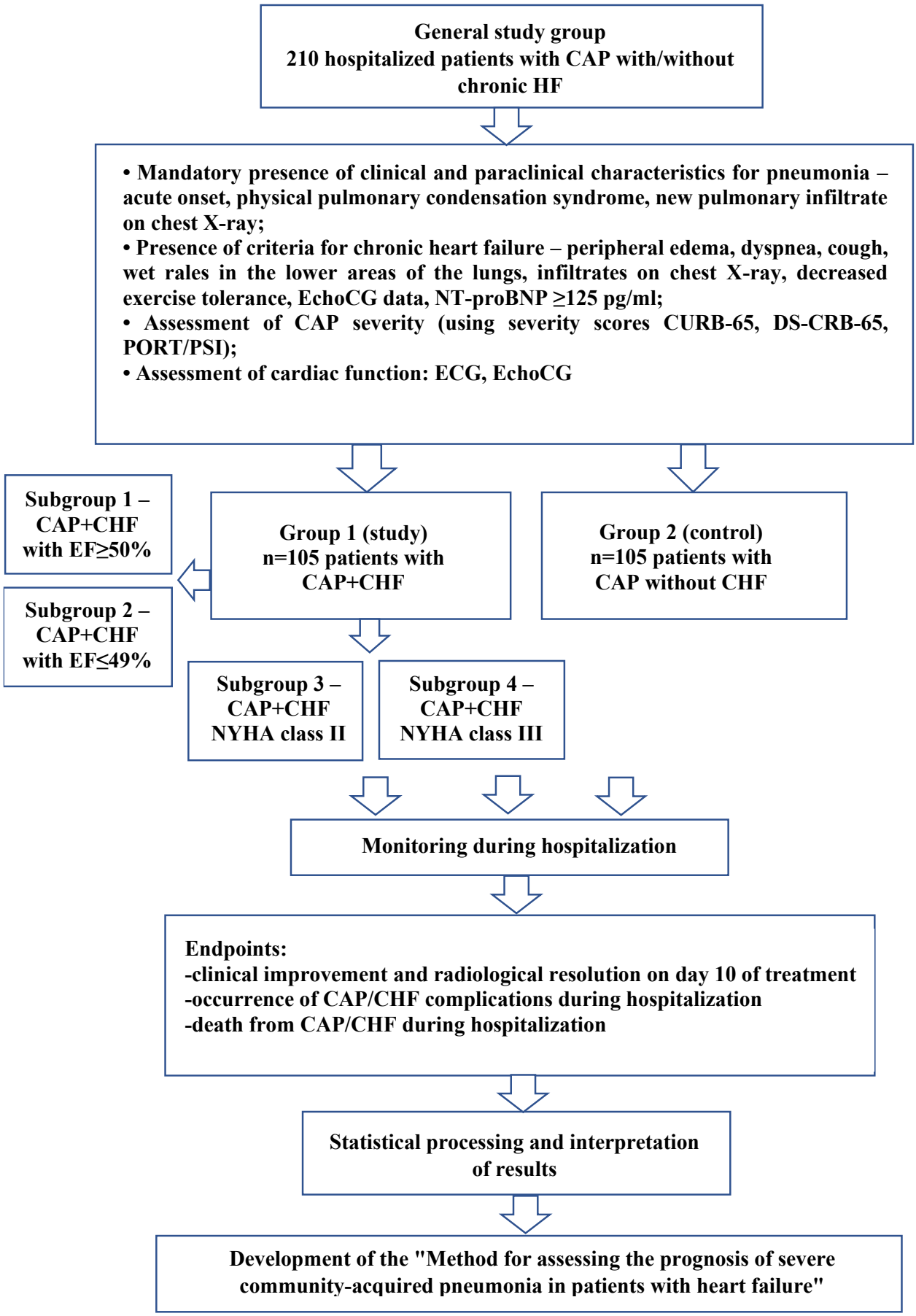

Figure 1. Study design

associated with at least one of the following two criteria: elevated serum natriuretic peptide levels and/or imaging or hemodynamic evidence of cardiac pulmonary or systemic congestion at rest or during exercise.

The primary endpoints involved clinical improvement on day 3, and the secondary endpoints involved clinical and radiological improvement on day 10 of treatment (complete disappearance/significant reduction of symptoms: cough, dyspnea, disappearance of fever, normalization of heart rate, respiratory rate, blood pressure, SpO2>90% with FiO2-21%, disappearance of rales, crepitations; radiologically – resorption of pulmonary infiltration). The research was conducted based on the clinical examination of patients, daily monitoring of the evolution of the inflammatory process, assessment of comorbidities, and paraclinical investigations. The measurement of oxidative stress markers was performed in the biochemical laboratory of the "Nicolae Testemițanu" State University of Medicine and Pharmacy and inflammatory markers in the biochemical laboratory of the Municipal Clinical Hospital "Holy Trinity". The severity of community-acquired pneumonia was determined based on clinical and evolutionary classification, according to the National Clinical Protocol "Community-acquired pneumonia in adults" [20].

Inclusion criteria:

1. Patients with and without chronic heart failure with community-acquired pneumonia and the mandatory presence of clinical and paraclinical characteristics for pneumonia – acute onset, physical syndrome of pulmonary condensation, new radiological pulmonary infiltrate;
2. Presence of criteria for chronic heart failure (dyspnea, orthopnea, fatigue, leg edema, increased jugular venous pressure, laterally displaced apical impulse, evidence of structural and/or functional cardiac abnormalities, and/or elevated natriuretic peptides);
3. Patients over 50 years of age;
4. Patients' ability to communicate well with the researcher and their ability to understand and comply with the study requirements;
5. Signing of the informed consent form for inclusion in the study.

Exclusion criteria:

1. Pregnancy, breastfeeding;
2. Immunocompromised patients: HIV/AIDS, tuberculosis, cancer, advanced liver failure (Child Pugh C), renal failure requiring dialysis;
3. Inability to provide informed consent or persons who have expressed their disagreement to participate in the study;
4. Patients for whom it is difficult to obtain medical history data, complete the questionnaire, physical data, and paraclinical investigations;
5. Chronic heart failure class I and IV (NYHA);

6. Patients with chronic pulmonary heart disease;
7. Patients with acute myocardial infarction;
8. Patients with acute pulmonary edema.

2.2. Research methods

Patients were evaluated based on their medical history, clinical and paraclinical data, using the following methods:

- The survey was conducted using an examination protocol developed by us, including a standardized survey of patients with chronic heart failure and community-acquired pneumonia, which includes general patient data, the presence of cardiovascular risk factors, clinical manifestations, aggravated medical history, and the presence of comorbidities;
- The clinical examination was performed by detailed and standardized clinical assessment, according to the study protocol. A comprehensive examination of the respiratory and cardiovascular systems was performed, which included data on the presence of community-acquired pneumonia: typical pulmonary condensation syndrome, infectious impregnation syndrome, as well as data for chronic heart failure: pulmonary rales, peripheral edema, heart murmurs, jugular turgidity, hepatomegaly;
- Bacteriological examination of sputum to determine the causative agent, with antibioticogram – using classical methods of bacterial culture, microbial resistance was determined by the disc diffusion method. The examinations were performed in the Bacteriological Laboratory of the Municipal Clinical Hospital "Holy Trinity" in accordance with current national and international standards;
- Laboratory investigations were performed in the laboratory of the Municipal Clinical Hospital "Holy Trinity" and in the Biochemical Laboratory of the "Nicolae Testemițanu" State University of Medicine and Pharmacy, using the reference values approved by the respective laboratories.

2.3. Statistical processing methods

The obtained data were statistically processed using IBM SPSS Statistics 23.0 and Microsoft Office Excel 2010. Quantitative values were represented by the mean, standard deviation, median, and interquartile range. Several methods were used for statistical data analysis, depending on the type of variables and the purpose of the analysis. The Fisher test (or exact χ^2 test) was applied to compare frequencies in 2x2 contingency tables, being applied in particular for small samples and dichotomous categorical variables. The One-Way ANOVA test, a parametric test that required compliance with conditions such as normal data distribution, homogeneity of variances, and a balanced experimental model, was used to compare means between independent groups. Differences were considered statistically significant at a threshold

of $p<0.05$, and the results were represented graphically by boxplots. To evaluate the relationships between continuous variables, the Pearson correlation coefficient (r) was used, which measures the strength and direction of a linear relationship, with values ranging from -1 to 1. In addition, Spearman's correlation coefficient (R) was used as a nonparametric alternative to identify monotonic relationships between ordinal variables without requiring normal data distribution. The threshold values for interpreting statistical significance were determined by the conventional method, using the lower limit of the confidence interval of the mean. The ROC curve was used for the qualitative comparison of two or more diagnostic tests. Logistic regression was used to predict the severity of the disease based on different variables.

3. CLINICAL, PARACLINICAL, AND THE DISEASE COURSE CHARACTERISTICS OF COMMUNITY-ACQUIRED PNEUMONIA IN PATIENTS WITH CHRONIC HEART FAILURE

3.1. Clinical and paraclinical characteristics of community-acquired pneumonia in patients with chronic heart failure

Clinical and paraclinical characteristics were evaluated in 210 patients with community-acquired pneumonia with/without chronic heart failure. Depending on the presence of criteria for CHF, patients were divided into 2 groups: group 1 – 105 patients with CAP and CHF (study group), group 2 – 105 patients with CAP without CHF (control group). The age of patients in group 1 ranged from 50 to 92 years and averaged 70.6±8.89 (95% CI [68.8-72.3]) years, (Mn=70.0; IIQ=11). In group 2, the average age was 68.7±7.56 (95% CI [64.2-68.2]) years (Mn=68.0; IIQ=11), with no significant differences between groups (F=18.109; p=0.205). The groups were balanced in terms of gender distribution, with no significant differences between them. In group 1, the proportion of women was 57 (54.3%; 95% CI [44.8-64.1]), and that of men was 48 (45.7%; 95% CI [35.9-55.2]). In group 2, the proportion of men was higher than that of women: 54 (51.4%; 95% CI [42.3-61.0]) men and 51 (48.6%; 95% CI [39.0-57.7]) women, respectively ($\chi2=0.686$; gl=1; p=0.407).

When assessing the severity of chronic heart failure according to the NYHA class in patients in group 1, the following was found: NYHA class II was present in 42 (40.0%; 95% CI [30.5-49.5]) patients, and NYHA class III in 63 (60.0%; CI 95% [50.5-69.5]) patients. According to the etiology, CHF had several causes: ischemic – 16 patients (15.2%; CI 95% [8.8-22.2]), valvular – 1 patient (1.0%; CI 95% [0.0-3.2]), mixed – 88 (83.8%; CI 95% [76.6-90.7]) patients. The mixed etiology of CHF included the following causes: ischemic, hypertensive, valvular, or arrhythmogenic. Analysis of the anamnestic data revealed that in group 1, 21 (20.0%; 95% CI [13.0-27.5]) patients had a history of myocardial infarction, 6 (5.7%; 95% CI [1.8-10.3]) patients underwent angioplasty with stent implantation, 1 (1.0%; 95% CI [0.0-3.5]) patient underwent

angioplasty without stent implantation, and 2 (1.9%; 95% CI [0.0-5.2]) patients underwent coronary artery bypass grafting. Next, we analyzed the presence and role of comorbidities in both groups. Hypertension, which is both a comorbidity of CAP and a cause of chronic heart failure, was the most common condition in both group 1 and group 2: 103 (98.0%) patients and 84 (80.1%) patients, respectively ($\chi2$=19.552; gl=1; p<0.0001). Type 2 diabetes mellitus was found in 41 (39.0%; 95% CI [29.9-48.4]) patients in group 1, with a frequency twice as high as in group 2, where it was recorded in only 25 (23.8%; 95% CI [15.8-32.4]) patients, ($\chi2$=5.657; df=1; p=0.017). Cerebrovascular disease was present in 47 (44.8%; CI 95% [35.5-54.3]) patients in group 1 and in 25 (23.8%; 95% CI [16.0-32.3]) patients in group 2 (p=0.001). Chronic kidney disease was more common in group 1 than in group 2: 21 (20.0%; 95% CI [12.6-27.4]) patients and 6 (5.7%; 95% CI [1.9-10.8]) patients, respectively, (p=0.002). Atrial fibrillation was present only in patients in group 1 – 54 (51.4%; 95% CI [42.2-61.0]) cases, (p<0.0001).

Subsequently, we evaluated the symptoms that patients had at the onset of the disease triggered at the prehospital stage. Patients in group 1 had 7.18±0.51 days from symptom onset to hospitalization, and patients in group 2 had 7.18±0.51 days, which was not statistically significant (F=0.303; p=0.583). The worsening of respiratory symptoms against the background of pre-existing cardiovascular disease can be evidenced from the onset of pneumonia. Thus, dyspnea was present at the onset of the disease in most patients in group 1: 98 (93.3%; CI 95% [87.6-98.0]) patients, compared to group 2, where it was present in 73 (69.5%; 95% CI [60.5-78.1]) patients, the difference being statistically significant ($\chi2$=19.681; gl=1; p<0.0001). In the group with CAP and chronic HF, worsening of pre-existing dyspnea occurred in 50 (47.6%; 95% CI [38.5-57.5]) patients. Cough was another symptom, more frequently present at disease onset in patients without pre-existing CHF: 41 (39.0%; 95% CI [29.7-48.5]) patients in group 1 and 58 (55.2%; 95% CI [45.2-65.3]) patients in group 2. Productive cough was present in 26 (24.8%; 95% CI [17.0-32.8]) patients with CAP and CHF and 36 (34.3%; 95% CI [24.6-43.7]) without CHF, $\chi2$=19.410; gl=2; p<0.0001. Chest pain at onset was present in 8 (7.6%; 95% CI [2.9-12.7]) patients in group 1 versus 21 (20%; 95% CI [12.5-28.3]) patients in group 2 ($\chi2$=6.761; df=1; p=0.009).

Mild infectious impregnation syndrome was observed at the onset of the disease in 49 (46.7%; CI 95% [37.3-55.8]) patients, and pronounced intensity – in 42 (40.0%; 95% CI [31.3-49.6]) patients, with no significant differences between groups. In patients with pre-existing CHF, pneumonia onset without fever was observed in 75 (71.4%; 95% CI [61.9-80.0]) patients, and in 14 (13.3%; 95% CI [7.4-20.0]) patients, pneumonia onset with a temperature between 37.1-37.9°C, in 12 (11.4%; 95% CI [5.6-18.4]) patients it was between 38.0-38.9°C, and in 2 (3.8%; 95% CI [0.9-7.9]) patients it was between 39.0-39.9°C.

Subsequently, we analyzed the clinical picture and characteristic symptoms of patients with CAP and CHF at their first visit. Respiratory symptoms at the first visit were: dry cough – 42 (40.0%; 95% CI [30.6-49.4]) patients, cough with mucous expectoration – 13 (12.4%; 95% CI [6.6-18.6]) patients, mucopurulent cough – 21 (20.0%; 95% CI [11.4-26.8]) patients and bloody cough – 1 (1.0%; 95% CI [0.0-3.2]) patient. In the control group, we obtained the following data: dry cough – 42 (40.0%; 95% CI [31.3-50.5]) patients, cough with mucous expectoration – 19 (18.1%; 95% CI [10.7-25.6]) patients, mucopurulent cough – 34 (32.4%; 95% CI [19.6-36.0]) patients and bloody cough – 2 (1.9%; 95% CI [0.0-4.9]) patients. Pleural pain was experienced by 7 (6.7%; 95% CI [2.1-11.9]) patients in group 1, compared to 15 (14.3%; 95% CI [7.1-19.6]) patients in group 2 ($\chi2$=3.524; df=1; p=0.140). Mixed-type dyspnea at the first visit was reported by 62 (59.0%; 95% CI [50.0-68.8]) patients in group 1, twice as often as in group 2, where it was present in 32 (30.5%; 95% CI [22.2-39.5]) patients, ($\chi2$=28.750; df=1; p<0.0001). These data confirm the presence of the two components (obstructive and restrictive) of chronic heart failure, caused by reduced cardiac output and the development of pulmonary congestion. Inspiratory dyspnea was present in 37 (35.2%; 95% CI [25.7-44.3]) patients in the study group and in 42 (40.0%; 95% CI [30.5-50.0]) patients in the control group ($\chi2$=29.748; gl=1; p<0.0001). Expiratory dyspnea was observed in 1 (1.0%; 95% CI [0.0-3.0]) patient in the study group and in 6 (5.7%; 95% CI [1.8-10.4]) patients in the control group.

At the first visit (day of admission), in accordance with the clinical-evolutionary classification of CAP from the National Clinical Protocol "Community-acquired pneumonia in adults", in group 1 there were 57 (54.3%) patients with moderate severity evolution versus 82 (78.1%) patients in group 2. Severe evolution of CAP was present in 48 (45.7%) patients in group 1 versus 23 (21.9%) patients in group 2 ($\chi2$=12.257; gl=1; p= 0.0005). We continued to analyze patients with CAP and chronic HF during the objective examination and to highlight relevant indicators for this category of patients. Thus, the respiratory rate per minute was higher in patients with CAP and CHF – 23.83±1.46 breaths per minute, compared to group 2 – 21.40±0.95 breaths per minute, statistically significant (F=6.305; p=0.013). Peripheral oxygen saturation, determined by pulse oximetry, had a mean value of 90.26±4.61% in group 1 and 94.01±3.73% in group 2, with statistically significant differences. Systolic BP values in the study group were 132.82±19.57 mm/Hg, diastolic BP – 80.71±10.38 mm/Hg, and mean BP – 97.70±12.29 mm/Hg, with no significant differences between groups. The heart rate per minute was 86.64±18.97 and 87.08±12.07 in group 1 and group 2, respectively (F=0.040; p=0.842).

According to the data presented in Table 1., regarding the objective examination of the patients, we have to mention that significant differences between groups were observed in relation to the presence of peripheral edema, local diminution of the vesicular murmur, bilateral crepitant rales, sibilant rales and peripheral blood oxygen saturation less than or equal to 92%.

Table 1. Determined changes during the objective examination in patients with community-acquired pneumonia and chronic heart failure at the first visit

	Study group (CAP+CHF) n=105		Control group (CAP) n=105		P df=1
	Abs.	%	Abs.	%	
Altered consciousness	3	2.9	0	0	$\chi2$=3.043; p=0.081
Peripheral edema	56	53.3	0	0	$\chi2$=76.364; p<0,0001
Increased vocal tremor	21	20.0	22	21.0	$\chi2$=0.029; p=0.864
Subduedness/dullness	13	12.4	8	7.6	$\chi2$=1.323; p=0.250
Diminished vesicular murmur	74	70.5	55	52.4	$\chi2$=7.255; p=0.007
Hardened murmur	37	35.2	46	43.8	$\chi2$=1.614; p=0.204
Unilateral crepitant rales	27	25.7	29	27.6	$\chi2$=1.512; p=0.250
Bilateral crepitant rales	41	39.0	20	19.0	$\chi2$=11.183; p=0.004
Unilateral subcrepitant rales	10	9.5	8	7.6	$\chi2$=0.068; p=0.805
Bilateral subcrepitant rales	5	4.7	7	6.6	$\chi2$=0.088; p=0.766
Whistling rales	6	5.7	15	14.3	$\chi2$=4.286; p=0.038
$SpO_2 \leq 92\%$	64	61.0	42	40.0	$\chi2$=8.401; p=0.004

Analyzing the extent of lung involvement in patients with CAP and CHF, bilateral extension of pulmonary infiltrates was more frequently determined – 63 (60.0%; 95% CI [50.5-69.1]) patients, followed by polysegmental extension – 27 (25.7%; 95% CI [17.7-34.3]) patients, segmental (1-2 segments) – 10 (9.5%; 95% CI [4.3-15.5]) patients, and lobar – 5 patients (4.8%; 95% CI [1.0-9.3]). In the CAP group without CHF, bilateral extension of the pulmonary infiltrate was found in 57 (54.3%; 95% CI [45.1-64.0]) patients, polysegmental extension – 29 (27.6%; 95% CI [19.3-35.6]) patients, segmental (1-2 segments) – 9 (8.6%; 95% CI [3.0-12.8]) patients, and lobar – 10 patients (9.5%; 95% CI [4.3-15.5]). The presence of pleural effusion in the first radiological investigation was significantly higher in patients in group 1 compared to those in group 2: 41 (39.0%; 95% CI [30.6-49.5]) patients and 14 (13.3%; 95% CI [7.3-20.0]) patients, respectively ($\chi2$=17.958; gl=1; p<0.0001). Bilateral pleural effusion was present in 25 (23.8%; 95% CI [18.6-39.5]) patients in group 1 and 8 (7.6%; 95% CI [7.3-18.0]) patients in group 2, while unilateral localization was present in 16 (15.2%; 95% CI [4.6-19.2]) patients in group 1 and 6 (5.7%; 95% CI [5.3-12.0]) patients in group 2, respectively, with no statistically significant differences.

Subsequently, we compared the results of laboratory investigations (Table 2). The results of the hemogram analysis revealed that the erythrocyte distribution width (RDW-SD) was significantly higher CAP and CHF group (48.05±6.33 fL), compared to those without CHF (45.96±8.39 fL), (F=4.131; p=0.043), and monocytes were significantly lower in group 1 compared to group 2: 7.60±3.52 % and 8.75±3.71 %, Mn=7.40; IIQ=5.30 and Mn=8.50; IIQ=4.50, respectively, (F=5.274; p=0.023). We observed a lower platelet count in patients in group 1 (236.95±81.74 x10^9/L) compared to group 2 (284.46±113.67 x10^9/L), (F=12.087; p=0.001), and the median value was:

Mn=250.00; IIQ=155.00 versus Mn=238.00; IIQ=85.00. The mean ESR value was significantly higher in group 1 compared to group 2: 29.89±19.47 mm/h and 21.17±15.98 mm/h (F=12.561; p<0.0001), the median values being as follows: Mn=26.0; IIQ=29.0 compared to Mn=17.0; IIQ=20.0, respectively.

Table 2. General blood count parameters in patients with community-acquired pneumonia with/without chronic heart failure

	Study group (CAP+CHF), n=105		Control group (CAP), n=105		F	P
	Average	SD±	Average	SD±		
Erythrocytes (x10^{12}/L)	4.41	0.75	4.41	0.64	0.000	0.987
Hemoglobin, g/L	128.67	22.42	130.03	25.58	0.168	0.682
Hematocrit, %	39.06	6.37	39.34	6.77	0.093	0.761
RDW-SD, fL	48.05	6.33	45.96	8.39	4.131	0.043
Leukocytes (x10^{9}/L)	10.36	7.13	10.52	5.58	0.033	0.856
Neutrophils, %	71.56	16.33	69.64	14.41	0.817	0.367
Lymphocytes, %	18.24	11.38	18.96	9.92	0.244	0.622
Monocytes, %	7.60	3.52	8.75	3.71	5.274	0.023
Eosinophils, %	1.07	0.35	1.55	0.48	3.047	0.082
Basophils, %	0.37	0.26	0.38	0.34	0.008	0.928
Immature granulocytes, %	0.61	0.27	0.89	0.47	2.824	0.094
Platelets (x10^{9}/L)	236.95	81.74	284.46	113.67	12.087	0.001
Erythrocyte sedimentation rate, mm/h	29.89	19.47	21.17	15.98	12.561	0.0001

Analyzing serum lactate dehydrogenase values in both groups, we found that they were significantly higher in the group of patients with CAP and CHF compared to the group without CHF: 232.65±109.80 u/L and 192.40±44.98 u/L, respectively (F=12.076; p=0.001). The median values were as follows: Mn=216.0; IIQ=76.0 and Mn=180.0; IIQ=46.0, respectively. The mean prothrombin values were significantly lower in group 1 compared to group 2: 77.35±22.65% and 93.96±22.52%, respectively, F=28.396; p<0.0001. These data reflect an impairment of prothrombin synthesis in the liver in patients with pre-existing CHF, as well as more frequent use of anticoagulant drugs. The mean fibrinogen values were higher in group 1 (5.24±1.78 g/L) compared to group 2 (4.51±1.60 g/L), statistically significant (F=9.692; p=0.002), and the median values were as follows: Mn=4.80; IIQ=2.90 and Mn=4.20; IIQ=2.25, respectively.

The mean NT-proBNP values in patients with community-acquired pneumonia and chronic heart failure were 1371.88±498.91 pg/ml, compared to the group without CHF: 58.19±48.22 pg/ml, (F=721.54; p<0.0001). Subsequently, by applying the conventional method of determining threshold values, namely using the lower limit of the confidence interval of the mean for NT-proBNP values, a threshold value of 1665.73 pg/ml was identified. This value is associated with the prediction of severe community-acquired pneumonia in patients with chronic heart failure.

To determine the etiology of community-acquired pneumonia, biological material

(sputum) was collected before initiating empirical antibiotic therapy. Bacteriological examination of sputum was performed in 37 (35.2%; CI 95% [25.7-44.6]) patients in group 1 and in 56 (53.3%; 95% CI [43.7-62.5]) patients in group 2 ($\chi 2$=6.967; gl=1; p=0.008). Viral etiology was determined by polymerase chain reaction (PCR) in 10 (9.5%; 95% CI [4.3-15.9]) patients in group 1 and 11 (10.5%; 95% CI [5.3-16.5]) patients in group 2 ($\chi 2$=0.053; df=1; p=0.495). The most common causative agents of community-acquired pneumonia in both group 1 and group 2 were streptococci (*Streptococcus viridans, Streptococcus pneumoniae,* and *Streptococcus pyogenes*) – 24 (64.8%; 95% CI [45.2-85.9]) cases and 32 (57.0%; 95% CI [38.1-69.4]) cases, respectively. *Streptococcus viridans* was determined in 12 (32.4%; 95% CI [27.6-37.8]) patients in group 1 and in 22 (39.2%; 95% CI [33.7-45.2]) patients in group 2, ($\chi 2$=1.405; gl=2; p=0.818). *Staphylococcus aureus* was detected in 7 (18.9%; 95% CI [10.9-21.9]) patients with CHF and in 8 (14.2%; 95% CI [5.2-15.9]) patients without CHF, respectively. *Klebsiella pneumoniae* was detected in sputum culture in 2 (5.4%; CI 95% [2.2-8.4]) patients in the CAP and CHF group, and in only one patient (1.7%; CI 95% [0.0-3.1]) in the group without CHF. Influenza A (H1N1) virus was identified in only one patient in the study group. At the same time, *Moraxella catarrhalis* and mixed infection (influenza A (H1N1) virus and *Streptococcus viridans*) were detected in only one case in patients in group 2.

Subsequently, we continued by comparing echocardiographic parameters in patients with chronic heart failure. In the echocardiographic evaluation, it should be noted that aortic valve stenosis was found in 7 (6.7%; 95% CI [2.7-12.0]) patients in group 1, compared to group 2, where it was not found in any patient. Left ventricular hypertrophy was determined more frequently in group 1 compared to group 2: 92 (87.6%; 95% CI [80.7-93.5]) patients versus 32 (30.5%; 95% CI [21.8-39.3]) patients. The presence of hypo/akinesia areas was observed in 13 (12.4%; 95% CI [6.5-18.9]) patients in group 1, ($\chi 2$=13.858; gl=1; p<0.0001). In group 2, no patient showed changes in myocardial contractility on echocardiographic examination. Pericardial effusion was more common in patients with CAP and chronic HF compared to those without chronic HF: 16 (15.2%; 95% CI [8.8-22.4]) patients versus 1 (1.0%; 95% CI [0.0-3.0]) patient, ($\chi 2$=14.401; gl=1; p<0.0001).

3.2.The disease course characteristics in patients with community-acquired pneumonia and chronic heart failure

The evolution of community-acquired pneumonia was assessed at the end of treatment by determining the length of hospital stay and clinical, laboratory, and radiological parameters. Thus, patients with community-acquired pneumonia and pre-existing chronic heart failure were hospitalized for more days compared to those without chronic HF: 11.96±0.36 versus 10.82±0.28 days, statistically significant (F=6.020; p=0.012). Positive clinical dynamics on the 10th day of hospitalization, manifested by

improvement in dyspnea presented 95 (96.2%; 95% CI [92.0-99.5]) patients in group 1 compared to 104 (99.8%; 95% CI [100.0]) patients in group 2, ($\chi2$=4.078; gl=1; p=0.143). Peripheral oxygen saturation greater than or equal to 92%, measured by pulse oximetry, was determined at the end of treatment in 98 (93.3%; IÎ 95% [87.9-97.9]) patients in group 1, a significantly lower number compared to group 2 – 104 (99.0%; IÎ 95% [96.6-100.0]) patients, ($\chi2$=4.678; gl=1; p=0.131). The return of body temperature to normal values was recorded in 26 (86.6%; 95% CI [82.0-95.1]) patients in group 1 versus 56 (100%; 95% CI [100.0]) patients in group 2, ($\chi2$=4.078; df=1; p=0.043). The disappearance of pulmonary rales also occurred at a lower rate in patients with CAP and CHF versus those without CHF: 101 (96.2%; 95% CI [92.3-99.1]) patients and 105 (100%; 95% CI [100.0]) patients, respectively ($\chi2$=2.294; df=1; p=0.129).

On the 10th day of treatment, radiological picture manifested by total reabsorption of the pulmonary infiltrate was determined in 88 (83.8%; 95% CI [74.7-90.6]) patients in group 1 and in 76 (72.3%; 95% CI [62.1-80.8]) patients in group 2. Final radiological evolution characterized by partial reabsorption of the pulmonary infiltrate was encountered in 13 (12.3%; 95% CI [4.4-15.9]) patients in group 1 versus 29 (27.6%; 95% CI [17.8-30.3]) patients in group 2. Progression of pneumonia occurred in 4 (3.8%; 95% CI [0.0-6.5]) patients in group 1 and in no patients in group 2. Then we assessed the need for oxygen support in patients with CAP and CHF. Non-invasive positive pressure ventilation was required significantly more frequently in patients in group 1 - 23 (21.9%; 95% CI [18.5-29.1]), compared to group 2, where there were 19 (9.5%; 95% CI [8.9-11.2]) patients. At the same time, oxygen therapy via mask/nasal cannula was required in 41 (39.0%; 95% CI [29.3-46.5]) patients in group 1 and 32 (30.5%; 95% CI [27.9-35.9]) patients in group 2. A positive final outcome on day 10 of treatment, manifested by improvement in clinical and paraclinical symptoms, was observed in 101 (96.2%; 95% CI [92.3-99.1]) patients in group 1 and in 4 (3.8%; 95% CI [0.9-7.7]) patients death occured. At the same time, in group 2, all patients had a positive outcome ($\chi2$=4.078; gl=1; p=0.043).

Acute respiratory failure occurred significantly more frequently in patients in group 1–64 (60.9%; 95% CI [52.5–71.5]), as well as in those in group 2–42 (40.0%; 95% CI [30.0–49.1]) patients ($\chi2$=0.840; gl=1; p=0.004). The presence of pleural effusion had a significantly higher rate in patients in group 1 versus group 2: 41 (39.0%; 95% CI [30.0-48.9]) and 14 (13.3%; 95% CI [7.1-20.7]), respectively, statistically significant ($\chi2$=17.958; df=1; p<0.0001). Pericardial involvement was observed in 16 (15.2%; 95% CI [8.8-22.4]) patients, more frequently in group 1 compared to group 2, where it was observed in only one patient (1.0%; 95% CI [0.0-3.0]), ($\chi2$=14.401; df=1; p<0.0001). The rate of cardiogenic pulmonary edema was more frequent in patients with CAP and CHF – 5 (4.8%; 95% CI [1.1-9.2]) patients versus those without CHF, where no cases were reported ($\chi2$=5.122; df=1; p=0.024). In one patient (1.0%) in the

CAP and CHF group, the following complications were encountered: acute respiratory distress syndrome, pneumomediastinum and cerebral edema. Cardiogenic shock and pulmonary embolism were more frequent in group 1 – 2 (1.9%; 95% CI [0.0-5.1]) patients each, compared to group 2, where these complications were not attested. Multiple organ dysfunction syndrome (MODS) was diagnosed exclusively in the CAP and CHF group – 8 (7.6%) of the cases.

3.3.Oxidative stress markers in patients with community-acquired pneumonia and chronic heart failure

In this study, we aimed to evaluate the oxidative status in patients with community-acquired pneumonia and chronic heart failure. Thus, the values of prooxidant markers (ischemic modified albumin, advanced glycation end products, advanced oxidation protein products, malondialdehyde) and antioxidants (total antioxidant activity, superoxide dismutase, catalase) were determined and compared (Table 3.). The expression of prooxidant status was more evident in patients with CAP and CHF. Thus, ischemic modified albumin had significantly higher values in patients in group 1 compared to group 2: 236.60±64.35 μM/L and 229.77±57.23 μM/L, respectively (F=0.660; p=0.045). By applying the conventional method for determining threshold values (using the lower limit of the confidence interval of the mean for AIM values), the AIM threshold value of 218.98 μM/L was determined for patients with CHF and severe community-acquired pneumonia. Compensatory activation of antioxidant status in patients with CAP and CHF was manifested by the increase in total antioxidant activity by the CUPRAC method, which had higher values in patients in group 1 (6.70±4.62 μM/L), compared to those in group 2 (4.99±2.29 μM/L), the median being: Mn=5.45; IIQ=6.19 and Mn=3.38; IIQ=4.01, respectively, (F=7.647; p=0.006).

Table 3. Oxidative stress markers in patients with community-acquired pneumonia and chronic heart failure

Oxidative stress parameters	Study group (CAP+CHF), n=105		Control group (CAP), n=105		F	P
	Average	SD±	Average	SD±		
IMA, μM/L	236,60	64,35	229,77	57,26	0,660	0,045
AGE- pentosidin-like, μM/L	598,79	251,68	544,55	197,20	3,021	0,084
AGE-vesperlisin-like, μM/L	449,14	169,38	455,24	160,66	0,072	0,789
AOPP, μM/L	95,21	63,05	105,95	55,21	1,726	0,190
MDA, μM/L	17,46	6,94	16,07	4,72	2,869	0,092
Catalase, μM/L	21,88	10,01	23,16	11,54	0,740	0,391
TAA with CUPRAC, μM/L	6,70	4,62	4,99	4,29	7,647	0,006
TAA with ABTS, μM/L	132,22	21,48	128,23	22,21	1,748	0,188
SOD, u/c	62,72	13,37	62,33	16,47	0,034	0,853
MDA/TAA with CUPRAC ratio	5,09	3,24	3,79	2,48	10,575	0,001

IMA – Ischemic modified albumin; AGE – Advanced glycation end products; AOPP – Advanced oxidation protein products; MDA – Malonic dialdehyde; TAA – Total antioxidant activity; SOD – Superoxide dismutase

By calculating the lower limit of the confidence interval of the mean total antioxidant activity for patients with CHF and severe CAP, a threshold value of total antioxidant activity by the CUPRAC method of 4.90 μM/L was determined. The mean value of the MDA/AAT ratio with CUPRAC was significantly higher in patients with CAP and CHF, compared to those without CHF: 5.09±3.24 versus 3.79±2.48 (F=10.575; p=0.001).

3.4.Correlation of inflammatory indices and oxidative stress with clinical and paraclinical data in patients with community-acquired pneumonia and chronic heart failure

To confirm the data obtained in the study, we performed correlation analysis of inflammatory indices and oxidative stress with clinical and paraclinical data. Thus, a significant positive correlation was determined with the mean value of LDH and the presence of productive cough (rs=0.203; p=0.038), with the radiological extension of the pulmonary infiltrate (rs=0.394; p=0.025), with the left ventricular ejection fraction (rs=0.193; p=0.048). A significant positive correlation existed between LDH values and modified ischemic albumin values (rs=0.420; p=0.010), which reflects an intense systemic activation of inflammatory and oxidative processes in patients with CAP and CHF. Subsequently, we determined the degree of correlation between fibrinogen values and clinical and paraclinical parameters. Thus, a positive average correlation was attested with modified ischemic albumin (rs=0.487; p=0.045) and with erythrocyte sedimentation rate (rs=0.522; p<0.0001). Significant positive correlations of NT-proBNP with pneumonia severity scores were determined. Thus, the best correlation was determined with the PORT/PSI score (rs=0.650; p<0.0001), followed by the DS-CRB-65 score (rs=0.326; p=0.001) and the CURB-65 score (rs=0.299; p=0.002). NT-proBNP levels also had a positive correlation with pleural effusion on chest radiography (rs=0.340; p=0.040) and with the need for oxygen therapy (rs=0.475; p=0.005).

The usefulness of ischemic modified albumin in stratifying the severity and prognosis of CAP in patients with CHF was demonstrated by a positive correlation with the serum fibrinogen value (rs=0.487; p=0.045), with the RDW-SD value (rs=0.314; p=0.025) and with the PORT/PSI score (rs=0.450; p=0.025). In the same context, the close link between oxidative stress, systemic inflammation and clinical severity of community-acquired pneumonia in patients with CHF is reflected by the following correlations: advanced oxidation protein products with total length of hospital stay (rs=0.341; p=0.041), malonic dialdehyde with leukocyte levels (rs=0.388; p=0.050), advanced glycation end products pentosidine-like with the presence of pleural effusion on chest radiography (rs=0.334; p=0.001). Total antioxidant activity determined by the CUPRAC method had a positive correlation with the presence of pericardial effusion (rs=0.357, p=0.023), with interventricular septal thickness (rs=0.392, p=0.005) and with creatine kinase MB fraction values (rs=0.351, p=0.029). A significant negative correlation was determined with the mean value of erythrocyte sedimentation rate (rs=-0.454, p=0.026).

4. ASSESSMENT OF CLINICAL-PARACLINICAL PECULIARITIES BASED ON THE DEGREE OF HEART FAILURE AND THE SEVERITY OF COMMUNITY-ACQUIRED PNEUMONIA

4.1. Community-acquired pneumonia evolution according to left ventricular ejection fraction

Depending on the left ventricular ejection fraction, the group of patients with CAP and CHF was divided into 2 subgroups: subgroup 1 (EF≥50%) - n=90 (restrictive phenotype of CHF) and subgroup 2 (EF≤49%) - n=15 (dilatory phenotype of CHF). The clinical and paraclinical criteria of these two subgroups were compared. Thus, dyspnea at the onset of the disease was determined in 85 (94.4%; 95% CI [90.2-98.3]) patients from subgroup 1 and 13 (86.6%; 95% CI [81.1-92.0]) patients from subgroup 2, statistically insignificant ($\chi2$=2.808; gl=2; p=0.246). The radiological picture manifested by the presence of alveolar infiltrate was presented in 31 (34.4%; 95% CI [31.2-39.1]) patients from subgroup 1 and in 7 (46.6%; 95% CI [42.4-50.2]) from subgroup 2, ($\chi2$=0.858; gl=2; p=0.651). Pleural effusion on chest radiography was present in 32 (35.5%; 95% CI [32.8-40.2]) patients from subgroup 1 and in 9 (60.0%; 95% CI [58.4-62.2]) patients from subgroup 2, statistically insignificant ($\chi2$=3.744; gl=2; p=0.154).

Subsequently, we determined the systemic inflammatory response in these patients. Thus, the mean leukocyte values in subgroup 1 were 10.55±7.57 x10^9/L, and in subgroup 2 they were 9.21±3.48 x10^9/L, statistically insignificant (F=0.454; p=0.502). RDW-SD values were insignificantly lower in patients in subgroup 1 (47.56±5.84 fL) compared to those in subgroup 2 (50.97±8.40 fL), (F=3.821; p=0.053). Subsequently, we continued by comparing the values of oxidative stress markers. Thus, the ischemic modified albumin had lower values in patients from subgroup 1 compared to subgroup 2: 228.49±58.96 μM/L and 237.46±46.52 μM/L, respectively, without statistical significance. The values of AGE-pentosidine-like, AGE-vesperlysin-like, advanced oxidation protein products, malonic dialdehyde did not have statistically significant differences between the compared subgroups. The total antioxidant activity with CUPRAC, the total antioxidant activity with ABTS, the values of superoxide dismutase did not differ significantly between the compared subgroups. The mean values of NT-proBNP were significantly higher in the subgroup with left ventricular ejection fraction less than 49%: 1142.54±362.30 pg/ml versus 1365.62±402.25 pg/ml, respectively (F=183.342; p<0.0001). A weak negative correlation was determined between NT-proBNP values and left ventricular ejection fraction (rs=-0.314; p=0.027).

Analyzing the presence of pneumonia complications in these patients, we found that acute respiratory failure was the most common complication encountered in both groups: 54 (51.4%; 95% CI [47.2-59.5]) patients in subgroup 1 and 10 (66.6%; 95% CI [59.8-75.5]) patients – subgroup 2, ($\chi2$=0.042; gl=1; p=0.838). Acute respiratory failure was followed by pericardial involvement, which occurred in 9 (10.0%; 95% CI

[8.4-12.7]) patients in subgroup 1 and in 7 (46.6%; 95% CI [41.5-50.2]) patients in subgroup 2, statistically significant ($\chi 2$=15.366; gl=2; p<0.0001).

4.2. Evolution of community-acquired pneumonia depending on the NYHA class of chronic heart failure

Depending on the NYHA class of chronic heart failure, the group of patients with CAP and CHF was divided into 2 subgroups: subgroup 3 (NYHA class II) - n=42 patients and subgroup 4 (NYHA class III) - n=63. We analyzed the clinical-paraclinical and laboratory data of these two subgroups. Thus, dyspnea at the onset of the disease was presented by 38 (90.4%) patients from subgroup 3 and 60 (95.2%) patients from subgroup 4, statistically significant ($\chi 2$=20.058; gl=2; p=0.0001). The presence of alveolar infiltrate at the radiological examination was presented in 17 (40.4%) patients from subgroup 3 and in 21 (33.3%) patients from subgroup 4, ($\chi 2$=0.574; gl=2; p=0.750). Pleural effusion on chest X-ray was determined in 13 (30.9%) patients from subgroup 3 and in 38 (60.3%) patients from subgroup 4, statistically significant ($\chi 2$=20.331; gl=2; p=0.0001).

Subsequently, we evaluated the oxidative stress markers values. The increase in oxidative stress as chronic heart failure progresses is reflected by higher values of the prooxidant AGE-pentosidine-like in patients in subgroup 4 (648.12±268.95 μM/L), compared to subgroup 3 (524.78±204.78 μM/L), (F=5.431; p=0.005). AGE-vesperlysin-like had the following values: in subgroup 3 - 401.81±133.88 μM/L and in subgroup 4 - 480.70±183.69 μM/L, statistically insignificant (F=2.981; p=0.053). Advanced oxidation protein products had lower values in patients in subgroup 3 (80.18±45.35 μM/L) versus subgroup 4 (105.23±71.08 μM/L), (F=3.168; p=0.044). It is worth mentioning that, as chronic heart failure progresses, the activation of the prooxidant system (AGE-pentosidine-like) is counterbalanced by the increase in the activity of the antioxidant system. Thus, the total antioxidant activity by the CUPRAC method had lower values in patients in subgroup 3 (6.06±4.05 μM/L), compared to those in subgroup 4 (7.12±4.95 μM/L), (F=4.547; p=0.012).

At the same time, some parameters of the inflammatory response were more expressed in patients with CAP and CHF NYHA class III, compared to those with CAP and CHF NYHA class II. Thus, the erythrocyte sedimentation rate was higher in patients in subgroup 4 compared to those in subgroup 3: 22.95±7.98 mm/h versus 19.98±4.53 mm/h, statistically significant (F=6.621; p=0.002). Serum lactate dehydrogenase values, likewise, differed between subgroups: 239.43±111.40 u/L in subgroup 4 and 228.13±109.38 u/L in subgroup 3, respectively, F=6.250; p=0.002. The mean values of NT-proBNP were significantly different in subgroup 3 and subgroup 4, depending on the functional class of the CHF: 1232.74±461.30 pg/ml versus 1464.64±504.75 pg/ml, F=384.352; p<0.0001. A positive correlation was determined between NT-proBNP values and the NYHA class of heart failure (rs=0.413; p=0.014). Analyzing the severity of community-acquired pneumonia in patients with CHF depending on the NYHA

functional class, we determined that according to the mean value of the PORT/PSI score, pneumonia had a more severe course in patients with CAP and CHF class III NYHA compared to those in the subgroup with CAP and CHF class II NYHA: 92.32±18.91 versus 89.69±20.58 (F=51.720; p<0.001). According to the CURB-65 and DS-CRB-65 scores, we did not observe significant differences between the subgroups.

4.3. The diagnostic accuracy analysis of community-acquired pneumonia severity scores (PSI/PORT, CURB-65, DS-CRB-65) in chronic heart failure

According to the National Clinical Protocol "Community-acquired pneumonia in adults", regarding the clinical-evolutionary classification of CAP, in group 1 there were 48 (45.7%) patients with severe evolution and 57 (54.3%) patients with moderate evolution. In group 2 there were 23 (21.9%) patients with severe pneumonia and 82 (78.1%) patients with moderate pneumonia ($\chi2$=12.257; gl=1; p= 0.0005). In Table 4., a more severe evolution of community-acquired pneumonia can be observed in patients with pre-existing CHF (group 1), compared to those without CHF (group 2), depending on the PORT/PSI class.

Table 4. Distribution of patients with community-acquired pneumonia and chronic heart failure according to the PSI/PORT score severity

PORT/PSI score	Study group (CAP+CHF), n=105		Control group (CAP), n=105		P df=1
	Abs.	%	Abs.	%	
I (<51 points)	0	0	2	1.9	$\chi2$=7.514; p=0.512
II (51-70 points)	16	15.2	58	55.2	$\chi2$=58.414; p<0.0001
III (71-90 points)	38	36.2	42	40.0	$\chi2$=34.420; p=0.002
IV (91-130 points)	47	44.8	3	2.9	$\chi2$=68.758; p<0.0001
V (>131 points)	4	3.8	0	0	$\chi2$=11.201; p=0.405

Evaluating the diagnostic accuracy of the PORT/PSI score, we observed that it had a sensitivity of 59.45% and specificity of 29.99% for patients with severe CAP, who required hospitalization in the intensive care unit, and the area under the ROC curve was 0.84. According to the CURB-65 score, a trend towards more severe CAP evolution was also observed in group 1 compared to group 2: 1.27±0.69 and 0.83±0.72, respectively, the difference being statistically significant (F=19.876; p<0.0001). The DS-CRB-65 score also recorded a higher mean value in patients in group 1 (2.30±0.82) compared to group 2 (0.90±0.77), respectively, (F=160.570; p<0.0001). In patients with community-acquired pneumonia and chronic heart failure, who had a severe course of pneumonia and required hospitalization in the intensive care unit, the CURB-65 score had 47.12% sensitivity and 87.96% specificity, the area under the ROC curve – 0.65. At the same time, the DS-CRB-65 score demonstrated a sensitivity of 92.51% and specificity of 88.74%, and the area under the ROC curve was 0.88.

4.4. Development of the "Method for assessing the prognosis of severe community-acquired pneumonia in patients with chronic heart failure"

Identifying patients with chronic heart failure and high risk of severe development of community-acquired pneumonia remains a challenge in clinical practice. In this regard, we aimed to develop a method for predicting the severe development of CAP in these patients. The innovation refers to the application in the clinical practice of internists and cardiologists of a calculation formula (Table 5.), which includes parameters from the clinical examination, laboratory data and echocardiographic examination, which will help identify patients with high risk of severe development of community-acquired pneumonia (Innovator Certificate No. 6263 of 25.06.2024).

Table 5. Clinical and paraclinical parameters included in the logistic regression analysis

Variable	Coefficient (β)	ES	Wald Criteria (χ^2)	P
1. Respiratory rate per minute	0,283	0,151	3,096	0,078
2. Left ventricular ejection fraction, %	-0,039	0,036	1,205	0,272
3. Modified ischemic albumin, μM/L	-0,042	0,051	0,694	0,405
4. Platelets x10⁹/L	-,0003	0,003	1,300	0,254
5. Peripheral blood oxygen saturation, %	-0,087	0,032	7,369	0,007
6. Presence of pleural effusion	1,406	0,433	10,559	0,001
7. NT-proBNP, pg/ml	3,096	0,677	20,932	0,000
Calculated constant	-2,511	3,692	0,463	0,496

The result of the logistic regression analysis is the calculation of the coefficients b1, b2... from the equation: y=b0+b1X1+b2X2+...+biXi, where X1...Xi – independent prognostic variables. Subsequently, all variables that were statistically significant were included in the calculation formula (Table 6.).

Table 6. Calculation formula for determining the prognosis of severe community-acquired pneumonia in patients with chronic heart failure

Variable	Coeficient (β)	ES	Wald criteria (χ^2)	P
Pleural effusion	1.406	0.433	10.559	0.001
NT-proBNP ≥125 pg/ml	3.096	0.677	20.932	0.000
Peripheral blood oxygen saturation <92%	-0.087	0.032	7.369	0.007
Constant	-2.511	3.692	0.463	0.496

The value y in the regression equation is the natural logarithm of the odds ratio for the studied event, thus, *the proposed calculation formula* is as follows:

Y = c + (k1 × 1) + (k2 × 1) + (k3 x 1), where: c – constant equal to -2.511; k1 – β coefficient related to pleural effusion equal to 1.406; k2 – β coefficient related to NT-proBNP equal to 3.096; k3 – β coefficient related to peripheral blood oxygen saturation

<92% equal to -0.087. The probability of the event (of severe evolution of community-acquired pneumonia in chronic heart failure) can be calculated by the formula:

$P = \frac{e^y}{1+e^y}$, where *e* represents a mathematical constant equal to 2.72.

Example: In the case of the presence of all positive prognostic variables we obtain the following equation: Y = -2,511 + (1,406 × 1) + (3,096 × 1) + (-0,087 x 1) = 1,904

$$P = \frac{2{,}72^{1{,}904}}{1 + 2{,}72^{1{,}904}} = 0{,}870$$

Thus, the probability of developing severe evolution of community-acquired pneumonia in patients with chronic heart failure, when applying the calculation formula, is equal to 0.870 or 87.0%.

Explanation: in a person in whom all risk factors are present (presence of pleural effusion, NT-proBNP ≥125 pg/ml and peripheral blood oxygen saturation <92%), the probability of developing severe evolution of community-acquired pneumonia is 87.0%. Obviously, if one of the listed factors is missing, the probability of severe evolution of community-acquired pneumonia decreases. Thus: if pleural effusion is missing, then the probability of severe evolution is 0.622 (62.2%), if the NT-proBNP value is less than 125 pg/ml – 0.233 (23.3%), if peripheral blood oxygen saturation ≥92% – 0.440 (44.0%). The innovation result consists in objectifying the prognosis of severe evolution of community-acquired pneumonia in chronic heart failure. The advantages of the proposed method consist in: early detection in 87.0% of cases of patients with high risk of death, which dictates early therapeutic management, with the aim of early hospitalization in the intensive care unit, correction of possible complications and avoidance of unfavorable evolution.

GENERAL CONCLUSIONS

1. Community-acquired pneumonia in patients with chronic heart failure was manifested by a more severe course, by a more frequently bilateral clinical-radiological extension of the pneumonic infiltrate and a systemic inflammatory reaction dominated by increased fibrinogen values, erythrocyte sedimentation rate, serum lactate dehydrogenase and erythrocyte distribution width; and the complications that occurred included pleural effusion, pericardial effusion, acute respiratory failure and multiple organ failure syndrome, requiring non-invasive ventilatory support and a longer duration of hospitalization.
2. The coexistence of community-acquired pneumonia and chronic heart failure resulted in an excessive accumulation of protein oxidation reaction products, manifested by higher values of ischemic modified albumin, counterbalanced by increased total antioxidant activity, assessed by the CUPRAC method, and the oxidative stress index confirmed the predominance of oxidation processes.

3. In community-acquired pneumonia in patients with chronic heart failure, proinflammatory markers correlated with prooxidative markers and with clinical and radiological data: lactate dehydrogenase correlated with the extent of the pneumonic infiltrate and with modified ischemic albumin; fibrinogen – with erythrocyte sedimentation rate and modified ischemic albumin; the level of modified ischemic albumin – with the severity of community-acquired pneumonia and with the values of the erythrocyte distribution width; advanced protein oxidation products – with the duration of hospitalization; and advanced glycation end products – with the presence of pleural effusion. The amino-terminal fragment of the brain natriuretic prohormone is not only a diagnostic biomarker of heart failure, but also correlates with the severity of community-acquired pneumonia and the need for oxygen therapy in these patients.
4. Studying the evolution of community-acquired pneumonia on the background of chronic heart failure, depending on the degree of heart failure, highlighted the mutual influence of both pathologies: the progression of chronic heart failure is associated with the severe evolution of pneumonia, a more expressed prooxidant status (advanced glycation end products, advanced oxidation protein products), more expressed values of antioxidant status markers: total antioxidant activity assessed by the CUPRAC method. The amino-terminal fragment of the brain natriuretic prohormone correlated with both the degree of heart failure and the severity of community-acquired pneumonia.
5. Among the community-acquired pneumonia severity scores evaluated by us (CURB-65, DS-CRB-65, PORT/PSI), only the DS-CRB-65 score demonstrated high specificity and sensitivity (92.51% and 88.74%), with the area under the ROC curve – 0.88, which makes it useful in predicting the severity of community-acquired pneumonia in patients with chronic heart failure.
6. Our own model to evaluate the prognosis of severe community-acquired pneumonia in patients with chronic heart failure was developed, which allows early identification, in 87.0% of cases, of patients at high risk of unfavorable outcome, being a useful tool in guiding clinical decisions regarding early hospitalization in the intensive care unit and preventing the progression of community-acquired pneumonia.

PRACTICAL RECOMMENDATIONS

1. At the prehospital level, the DS-CRB-65 score is recommended as a useful working tool for predicting the evolution of community-acquired pneumonia in patients with pre-existing chronic heart failure.
2. At the hospital healthcare level, we recommend the use of NT-proBNP threshold values - 1665.73 pg/ml, to assess the severe evolution of community-acquired pneumonia in patients with chronic heart failure.
3. At the hospital healthcare level, we propose the use of threshold values of ischemic modified albumin – 218.98 μM/L to assess the severe evolution of community-acquired pneumonia in patients with chronic heart failure.

4. At the hospital healthcare level, to determine the risk of unfavorable evolution of community-acquired pneumonia in patients with chronic heart failure, it is recommended to use in practice the "Method for assessing the prognosis of severe evolution of community-acquired pneumonia in patients with chronic heart failure".

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22. **Caşcaval V.,** Dumitraș T., Grib L., Matcovschi S., Fetco-Mereuță D. *Metodă de apreciere a evoluției severe a pneumoniei comunitare la pacienții cu insuficiență cardiacă.* Act de implimentare a inovației, Nr. 6263, din 25 iulie 2024.

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  - ✓ **national**

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  - ✓ **national with international participation**

26. **Cașcaval V.** Oxidative stress markers in patients with heart failure and community-acquired pneumonia. *The 9th International Medical Congress for Students and Young Doctors.* Chișinău, 12-14 mai, 2022.
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  - ✓ **international**

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ADNOTARE

Cașcaval Virginia „Pneumonia comunitară la pacienții cu insuficiență cardiacă cronică”,

teză de doctor în științe medicale,

Chișinău, 2026

Structura tezei: teza este expusă pe 135 pagini text de bază ce include introducere, 4 capitole și concluzii. Lucrarea citează 305 surse bibliografice, fiind ilustrată prin 47 tabele, 31 figuri, 4 anexe. Rezultatele obținute sunt publicate în 21 lucrări științifice.

Cuvinte cheie: pneumonie comunitară, insuficiență cardiacă, particularități clinico-paraclinice, stres oxidativ.

Domeniul de studiu: 321.01 Boli interne (cu specificarea: Pulmonologie).

Scopul studiului: evaluarea particularităților clinico-paraclinice, evolutive și ale stresului oxidativ în cadrul pneumoniilor comunitare la pacienții cu insuficiență cardiacă cronică.

Obiectivele studiului: evaluarea particularităților clinico-paraclinice și evolutive la pacienții cu pneumonie comunitară și insuficiență cardiacă cronică concomitentă; aprecierea markerilor stresului oxidativ la pacienții cu pneumonie comunitară și insuficiență cardiacă cronică; corelarea indicilor inflamatori și ai stresului oxidativ cu datele clinico-paraclinice, la pacienții cu pneumonie comunitară și insuficiență cardiacă cronică; determinarea datelor clinico-paraclinice și evolutive la pacienții cu pneumonie comunitară și insuficiență cardiacă cronică, în funcție de fracția de ejecție a ventriculului stâng și în funcție de clasa funcțională a insuficienței cardiace; analiza acurateții diagnostice a scorurilor de severitate a pneumoniilor comunitare (PSI/PORT, CURB-65, DS-CRB-65) și elaborarea propriului model de prezicere a evoluției severe a pneumoniilor comunitare în insuficiența cardiacă cronică.

Noutatea și originalitatea științifică: au fost analizate datele clinico-paraclinice și evolutive ale pneumoniilor comunitare la pacienții cu insuficiență cardiacă cronică, a fost determinată importanța markerilor inflamatori și a stresului oxidativ la pacienții cu pneumonie comunitară și insuficiență cardiacă cronică.

Problema științifică soluționată în teză: rezultatele studiului au permis elaborarea unui model de prezicere a evoluției nefavorabile a pneumoniilor comunitare în insuficiența cardiacă cronică preexistentă.

Semnificația teoretică și valoarea aplicativă a lucrării: cercetarea aspectelor clinico-paraclinice și evolutive ale pneumoniilor comunitare în insuficiența cardiacă cronică a permis elaborarea recomandărilor practice privind managementul diagnostic, atât la etapa de asistență medicală prespitalicească, cât și spitalicească.

Implementarea rezultatelor științifice: Recomandările practice sunt utilizate în secția Terapie Generală și secția Pneumologie a IMSP SCM „Sfânta Treime” și în procesul didactic în cadrul Departamentului Medicină Internă, Disciplina de sinteze clinice, a IP Universității de Stat de Medicină și Farmacie „Nicolae Testemițanu”.

АННОТАЦИЯ

диссертации соискателя Кашкавал Вирджиния «Внебольничная пневмония у пациентов с хронической сердечной недостаточностью»,

докторская диссертация по медицинским наукам,

Кишинев, 2026 г.

Структура диссертации: диссертация представлена на 135 страницах основного текста, включая введение, 4 главы и заключение. Работа имеет 305 библиографических источника, 47 таблиц, 31 рисунка, 4 приложения. Полученные результаты опубликованы в 21 научных работах.

Ключевые слова: внебольничная пневмония, сердечная недостаточность, клинико-параклинические особенности, оксидативный стресс.

Область исследования: 321.01 Внутренние болезни (с уточнением: Пульмонология).

Цель исследования: оценка клинико-параклинических, особенностей течения и особенностей оксидативного стресса при внебольничной пневмонии у пациентов с хронической сердечной недостаточностью.

Задачи исследования: оценка клинико-параклинических особенностей и особенностей течения у пациентов с внебольничной пневмонией и сопутствующей хронической сердечной недостаточностью; оценка маркеров оксидативного стресса у пациентов с внебольничной пневмонией и сопутствующей хронической сердечной недостаточностью; корреляция показателей воспаления и оксидативного стресса с клинико-параклиническими данными у пациентов с внебольничной пневмонией и сопутствующей хронической сердечной недостаточностью; определение клинико-параклинических и эволюционных данных у пациентов с внебольничной пневмонией и сопутствующей хронической сердечной недостаточностью в зависимости от фракции выброса левого желудочка и функциональной класса сердечной недостаточности; анализ диагностической точности шкал оценки тяжести внебольничной пневмонии (PSI/PORT, CURB-65, DS-CRB-65) и разработка собственной модели прогнозирования тяжелого течения внебольничной пневмонии при хронической сердечной недостаточности.

Научная новизна и оригинальность: были проанализированы клинические и эволюционные данные пневмоний внебольничного происхождения у пациентов с хронической сердечной недостаточностью, определена значимость маркеров воспаления и оксидативного стресса у пациентов с пневмонией внебольничного происхождения и хронической сердечной недостаточностью.

Научная задача, решенная в диссертации: результаты исследования позволили разработать модель прогнозирования неблагоприятного течения внебольничной пневмонии у пациентов с хронической сердечной недостаточностью.

Теоретическая значимость и прикладная ценность работы: исследование клинико-параклинических и аспектов течения внебольничной пневмонии при хронической сердечной недостаточности позволило разработать практические рекомендации по диагностике как на этапе амбулаторной, так и госпитальной медицинской помощи.

Внедрение научных результатов: Практические рекомендации используются в отделениях общей терапии и пулъмонологии ГКБ «Сфынта Треиме», а также в учебном процессе в рамках дисциплины Клинического синтеза, Департамента Внутренней Медицины, Государственного Университета Медицины и Фармации «Николае Тестемицану».

SUMMARY

Cascaval Virginia "Community-acquired pneumonia in patients with chronic heart failure",

PhD thesis in medicine,

Chisinau, 2026

Structure of the thesis: the thesis is presented on 135 pages of basic text that includes an introduction, 4 chapters and conclusions. The work cites 305 bibliographic sources, being illustrated by 47 tables, 31 figures, 4 appendixes. The obtained results are published in 21 scientific papers.

Key words: community-acquired pneumonia, heart failure, clinical-paraclinical features, oxidative stress.

Field of study: 321.01 Internal diseases (with specification: Pulmonology).

Aim of the study: assessment of clinical, paraclinical peculiarities, the disease course and oxidative stress characteristics in community-acquired pneumonia in patients with chronic heart failure.

Study objectives: assessment of clinical, paraclinical peculiarities and the disease course in patients with community-acquired pneumonia and concomitant chronic heart failure; assessment of oxidative stress markers in patients with community-acquired pneumonia and chronic heart failure; correlation of inflammatory and oxidative stress indices with clinical and paraclinical data in patients with community-acquired pneumonia and chronic heart failure; determination of clinical, paraclinical peculiarities and the disease course in patients with community-acquired pneumonia and chronic heart failure, depending on the left ventricular ejection fraction and the functional class of heart failure; analysis of the diagnostic accuracy of community-acquired pneumonia severity scores (PSI/PORT, CURB-65, DS-CRB-65) and development of a model for predicting the severe progression of community-acquired pneumonia in chronic heart failure.

Scientific novelty and originality: the clinical-paraclinical and evolutionary data of community-acquired pneumonia in patients with chronic heart failure were analyzed, the importance of inflammatory and oxidative stress markers in patients with community-acquired pneumonia and chronic heart failure was determined.

The scientific problem solved in the thesis: the results of the study allowed the development of a model to predict the unfavorable outcome of community-acquired pneumonia in patients with pre-existing chronic heart failure.

The theoretical significance and applied value of the work: the research into the clinical, paraclinical, and the disease course aspects of community-acquired pneumonia in chronic heart failure has enabled the development of practical recommendations for diagnostic management, both at the prehospital and hospital stages of care.

Implementation of the scientific results: The practical recommendations are used in the General Therapy Department and the Pneumology Division of Municipal Clinical Hospital "Holy Trinity" and in the didactic process within the Discipline of Clinical Syntheses, Department of Internal Medicine of "Nicolae Testemițanu" State University of Medicine and Pharmacy.

CAȘCAVAL Virginia

COMMUNITY-ACQUIRED PNEUMONIA IN PATIENTS WITH CHRONIC HEART FAILURE

321.01 Internal Medicine (Pneumology)

Summary of the PhD thesis in medical sciences

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