Doctoral school in medical sciences

With manuscript title

C.Z.U: 616.233-007.64-07(043.2)

MUNTEANU OXANA

CLINICAL, IMAGING, FUNCTIONAL AND MICROBIOLOGICAL MANIFESTATIONS OF BRONCHIECTASIS IN ADULTS

321.01 – INTERNAL MEDICINE (PNEUMOLOGY)

SUMMARY OF THE HABILITATION THESIS IN MEDICAL SCIENCES

Chișinău, 2022

The thesis was elaborated within the Discipline of Pneumology and allergology, Department of Internal Medicine, Nicolae Testemitanu State University of Medicine and Pharmacy.
Doctoral school in medical sciences.

Scientific advisor:
Botnaru Victor, hab. dr. in med. science, univ. prof., Emeritus

The Committee Members for the Public Defense:

The President:
Matcovschi Sergiu, hab. dr. in med. science, univ. prof.

Members:

Iavorschi Constantin, hab. dr. in med. science, research prof.
Ghinda Serghei, hab. dr. in med. science, research prof.
Haidarlî Ion, hab. dr. in med. science, research prof.
Grosu Aurel, hab. dr. in med. science, research prof.
Ivanov Victoria, hab. dr. in med. science, research prof.
Codreanu Ion, hab. dr. in med. science, associate prof.

Official reviewers:

Șciuca Svetlana, hab. dr. in med. science, univ. prof.
Pisarenco Serghei, hab. dr. in med. science, research prof.
Jimborean Gabriela, hab. dr. in med. science, univ. prof. (Romania)

The thesis defense will take place on November 9, 2022, at 14:00 at Nicolae Testemitanu University, 165, Stefan Cel Mare si Sfant Bd., office 205, at the meeting of the Committee for public defense of the doctoral thesis, approved by Senate Decision no. 7/6 from 23. 06. 2022 of the PI Nicolae Testemitanu State University of Medicine and Pharmacy.

The thesis and its summary can be found at the library of PI Nicolae Testemitanu State University of Medicine and Pharmacy and on the website of ANACEC (www.cnaa.md).
The thesis summary was submitted on 7/10/2022
Scientific Secretary of the Public Defense Committee:
Dumitraș Tatiana,
dr. in med. science, associate prof. _____

Scientific advisor*:*
Botnaru Victor,
hab. dr. in med. science, univ. prof., Emeritus _____

Author*:*
Munteanu Oxana _____

SUMMARY

CONCEPTUAL LANDMARKS OF THE RESEARCH

The relevance and significance of the research study

Bronchiectasis is irreversible dilatation of the large airways, bronchi and bronchioles associated with recurrent infections and walls inflammatory changes with progressive damage to the airways and adjacent lung parenchyma. They are characterized radiologically by permanent dilations of the bronchi and clinically by coughing, sputum expectoration and recurrent respiratory infections [1-3].

Considered a rare and often neglected disease, bronchiectasis has become a hot topic in the last decade [3-5]. In the pre-antibiotic era, the highest incidence was in childhood, in the first decade of life. Currently (due to the vaccination program and antibiotic treatment), most cases are in adulthood. Being historically underdiagnosed disease, the actual prevalence of bronchiectasis is not known. Estimated prevalence of bronchiectasis in adults increased from 2,4 million in 2012 to 3 million in 2020. One of the recent editorials defines this disease as the third most common chronic lung disease after COPD and asthma [6].

Despite the expectations to decrease the bronchiectasis prevalence, due to a better control of respiratory infections, an increasing prevalence explained by an improved diagnostic capacity (increased accessibility to imaging methods) and by the association of bronchiectasis with some systemic diseases, the increase of population survival. In developed countries, the epidemiological characteristics have changed, with fewer post-infectious bronchiectasis, but with a greater number of cases associated with another prevalent disease such as COPD [7].

Patients with bronchiectasis show impressive heterogeneity in both etiology and clinical course [1, 8, 9]. A systematized analysis of the underlying etiology according to an algorithm, proposed in this study, offers an economically efficient approach to establishing the diagnosis and management of bronchiectasis patients with a better resource management. The clinical course of bronchiectasis patients is variable, with some patients having few symptoms and others having daily symptoms that affect their activity, quality of life and have a progressive loss of lung function.

The concept of phenotyping, in relation to the type of inflammation, has as practical implications possible differentiated therapeutic approaches and is currently a topic of great interest [10]. Different clinical and functional manifestations, presence of systemic inflammation and comorbidities, frequency of exacerbations, microbiological characteristics are potential candidates in defining phenotypes of bronchiectasis.

Aspergillosis occurs in pulmonary practice as a relatively rare condition, but the chronic lung patient, including those with bronchiectasis, should be considered as a patient at risk for the association of *Aspergillus* infection.

In the Republic of Moldova there is a lack of statistical data on bronchiectasis, these patients are included in the group of obstructive diseases together with chronic bronchitis and COPD. The study confirmed the assumption of a higher proportion of patients with post-infectious bronchiectasis, due to the high incidence and prevalence of tuberculosis infection in the Republic of Moldova, which in a significant number of

cases were underestimated, and these patients in periods of infectious exacerbations being tested only for the presence or absence of M. tuberculosis, although the association of colonization with P. aeruginosa as well as Aspergillus species has been shown to be an important cause of morbidity and mortality, which has also been proven by other studies [11-13].

Antibacterial treatment given empirically, for an insufficient duration of time and without bacteriological testing over several years are realistic findings, which argue the need to study the microbiological profile in patients with bronchiectasis. Knowledge of the microbiological profile would allow the assessment of the long-term impact of these actions in order to detect bacterial resistance, and the existence of correlations with the treatment administered since diagnosis, the frequency of exacerbations and their impact on lung function decline would be analysed.

Increased pulmonary artery pressure, due to vasoconstriction from hypoxia and vascular bed destruction, may develop in patients with severe bronchiectasis and longer disease duration. Relatively few well-systematized studies have examined the prevalence of pulmonary hypertension in patients with bronchiectasis [14].

The importance of assessing the impact of bronchiectasis on population health, with steadily increasing epidemiological indices, highlights the need for a comprehensive study assessing multidimensional indices and phenotypes correlated with quality of life indicators to develop new diagnostic, prognostic and treatment strategies for patients with bronchiectasis.

Keywords: bronchiectasis, etiology, imaging, Pseudomonas, phenotype, aspergillosis.

Studied area: internal medicine, pulmonology

Aim of the study: To determine the etiological and phenotypical peculiarities, correlated with the clinical, imaging, functional and microbiological patterns in bronchiectasis for the proposal of the management strategy in adult patients.

Objectives of research:

1. revealing of the etiological profile of bronchiectasis in adults;
2. highlighting the microbiological spectrum in bronchiectasis in correlation with the functional and imaging patterns;
3. assessment of the imaging diagnostic and prognostic significance of bronchiectasis;
4. defining the role of the multidimensional approach in the management of patients with bronchiectasis, including severity (BSI, FACED, E-FACED) and comorbidity assessment tools (BACI, Charlson);
5. estimation of the impact of pulmonary hypertension in patients with bronchiectasis;
6. evaluation of some inflammatory markers in the evolution of bronchiectasis and their role in estimating the severity of exacerbations;
7. revealing phenotypes in bronchiectasis and their potential role in the personalized treatment;
8. highlighting the factors for an unfavorable evolution in different degrees of severity bronchiectasis.

Scientific research methodology

The research hypothesis and design were based on the objectives for achieving the study aim; the scientific research being carried out in 4 stages consecutively. The positive diagnosis of bronchiectasis was based on the imaging signs identified at chest HRCT, later additional tests were applied to establish the etiology of bronchiectasis, according to the recommendations of the ERS guide and of the National Clinical Protocol. A descriptive and analytical cross-sectional observational complex study was carried out with the evaluation of a 448 consecutive patients' group. An investigation plan for each patient was drawn up recording the results of clinical, paraclinical examinations, imaging scores and calculated multidimensional indices. Data were analyzed using MS Excel 2016, TIBCO Statistica 12 and MedCalc (v 20.006).

Novelty and originality of the research: Based on the study, the etiological diversity of bronchiectasis in adults was demonstrated, including the rare etiological forms, with the presentation of imaging features and the needed paraclinical tests for their confirmation. Sputum cultures monitoring revealed the prevalence and the types of pathogenic germs in the airways, as well as the spectrum of bacterial resistances. For the first time, the utility of the immunochromatographic rapid test (Aspergillus ICT IgG-IgM lateral flux) was demonstrated for the identification of cases of aspergillosis among bronchiectasis patients. Several bronchiectasis phenotypes were revealed based on the analysis of clinical, radiological, microbiological and ventilatory patterns and their role in the personalized approach for patients with bronchiectasis in the Republic of Moldova was shown. The study demonstrated the prognostic value of imaging scores and multidimensional indices in assessing the severity of the disease and the impact on the quality of life of patients with bronchiectasis.

Fundamentally new scientific and practical results.

Based on the study, the role of several inflammatory markers in the evaluation of the exacerbation severity, as well as the value of various clinical and paraclinical tools in the multidimensional assessment of bronchiectasis patients was demonstrated, highlighting the predictors. The spectrum of comorbidities and their prognostic role were assessed. The usefulness of imaging signs for the diagnosis of PH and of coronary lesions by using chest HRCT examination was demonstrated, underlying the role of modern diagnostic and treatment strategies in certain bronchiectasis patient sub-populations.

The theoretical significance consists in the proposal of a new complex conceptual framework for scientific and practical evaluation of the bronchiectasis heterogeneity. The long-term monitoring of the bronchiectasis patients from a multidimensional perspective highlighted some correlations according to the etiological, imaging, ventilatory patterns and chronic airway infections in the bronchiectasis patients. The analysis of the determinants responsible for the disease severity and the identification of poor evolution predictors have led to the elaboration of a new diagnostic and treatment algorithm, contributed to improving the management of the disease and the quality of patients care.

The applicative value. The results of the study were applied for the development of diagnostic and treatment algorithms for bronchiectasis, included in national clinical protocols.

Personal contribution of the author to the elaboration of the work.

The concept of the study, the collection of clinical material, the selection of research methods, the elaboration and completion of investigation forms for each patient, the direct participation in the evaluation of the clinical diagnosis, the analysis of anamnestic data, the indication and evaluation of paraclinical tests for the confirmation of aspergillosis, the calculation of disease severity scores, comorbidity indices, the statistical analysis of all the accumulated material and the commentary of the obtained results were carried out by the author. Evaluation of imaging lesions identified on chest HRCT, calculation and evaluation of imaging scores for bronchiectasis and emphysema was performed by the author assisted by the radiologist and the scientific advisor. The author also developed the diagnostic algorithm and the management algorithm in the light of etiological, imaging, functional, microbiological aspects and phenotypes identified in the Republic of Moldova population.

Implementation of scientific results. The results of the study are used in undergraduate and postgraduate education at the Discipline of Pneumology and Allergology, in the Phthisiopulmonology ward of the IFP "Chiril Draganiuc" and General Therapy and Allergology ward of the RCH "Timofei Moșneaga". There were registered 3 certificates of innovations and 3 acts of implementation of the results. A central database of patients with non-cystic fibrosis bronchiectasis (NCFB) was created by the collaboration with the polyclinics' department of the Phthisiopneumology Institute "Chiril Draganiuc". The data can be used as a database for the elaboration of a National Registry for Bronchiectasis patients, by monitoring them for a longer period of time and by assuring a continuity of the research direction, analyzing the effects of new diagnostic and management methods implementation.

Approval of scientific results.

The thesis materials were presented and discussed at: ERS Congress (Amsterdam, The Netherlands 2015); Conference dedicated to the 70th anniversary of the founding of USMF "Nicolae Testemitanu" (Chisinau, Republic of Moldova, 2015); 1st World Bronchiectasis Conference (Hanover, Germany, 2016); 24th Congress of the Romanian Society of Pulmonology (Brasov, Romania, 2016); ERS Congress (London, UK, 2016); IX National Bronchiectasis Conference (Oradea, Romania, 2017); Scientific conference in the framework of the World COPD Day (Chisinau, Republic of Moldova, 2016); Differential diagnosis of cough - Conference organized by Berlin-Chemie/Menarini (Chisinau, 2016); Anniversary Conference of IMSP Republican Clinical Hospital "Timofei Mosneaga" at 200 years since its foundation (Chisinau, Republic of Moldova, 2017); ERS Congress (Milan, Italy, 2017); 2-nd World Bronchiectasis Conference (Milan, Italy, 2017); ERS Congress (Paris, France. 2018); ISHAM Congress (Amsterdam, The Netherlands, 2018); Scientific-Practical Conference „Este timpul" (Chisinau, Republic of Moldova, 2019); National conference with international participation "Bronchoscopy and thoracic ultrasonography - modern means of diagnosis and treatment in pleuropulmonary diseases" (Chisinau, Republic of

Moldova, 2019); Scientific conference in the framework of the World Day against Chronic Obstructive Pulmonary Disease, with the title "All together to stop COPD" (Chisinau, Republic of Moldova, 2019); National Congress of Internal Medicine (Călimănești-Căciulata, Romania, 2019); ERS Scientific Seminar: The interaction between airways disease and bronchiectasis - An initiative of the EMBARC and SHARP CRCs (Barcelona, Spain, 2019); ERS Congress (Madrid, Spain, 2019); Meetings of the Society of Respirology of Moldova "VIAREMO" (Chisinau, Chisinau, Republic of Moldova, 2019-2020); ERS Congress (Online 2020); 26th Congress of the Romanian Society of Pneumology Congress (Romania ,online, 2020); Congress dedicated to the 75th anniversary of the founding of USMF "Nicolae Testemitanu" (Chisinau, Republic of Moldova, 2020); INSPIR "Pneumologia altfel – progrese, previziuni și provocări contemporane" (online, Iași, Romania, 2021); 31st European Congress of Clinical Microbiology and Infectious Diseases (ECCMID, online, 2021); International Conference "Interferențe în pneumologie. Patologia post-COVID episodul 2" (online, Iași, Romania, 2021); International conference "PNEUMOLOGIA ROMÂNEASCĂ DE O PARTE ȘI ALTA A PRUTULUI" (online, 2021).

Publications on the thesis topic.

67 scientific papers were published on the topic of the thesis, including 28 articles and 29 theses, 6 articles in journals with impact factor, 4 in international journals indexed in SCOPUS/PubMed, 5 articles without co-authors, 1 article in national journals, 1 monograph, 1 methodological-didactic paper, 2 manuals and 2 National Clinical Protocols. The scientific results of the thesis were approved at 17 international scientific forums and at 11 national scientific forums.

Summary of the thesis' chapters.

The thesis is presented on 249 pages of basic text, processed on the computer and includes annotations in Romanian, Russian and English, introduction, 6 chapters, general conclusions, practical recommendations. The iconographic material contains 92 tables, 86 figures.

THESIS CONTENT

1. BRONCHIECTASIS IN ADULTS – AETIOLOGICAL, IMAGING, MICROBIOLOGICAL AND FOLLOW-UP ASPECTS (LITERATURE REVIEW)

The chapter presents a synthesis of publications in the literature highlighting the key elements in the approach to a patient with bronchiectasis, in the context of changing views on both the diagnostic methods used and the multidimensional approach, designed to combine the assessment of several aspects (clinical, functional, imaging, microbiological). The assessment of multidimensional indices allows a more accurate stratification of disease severity, which will contribute to the choice of different therapeutic approaches in the management and prognosis of the disease.

Based on the positive diagnosis of bronchiectasis, CT allows the assessment of its severity by identifying dominant imaging patterns, characterising the extent of bronchiectasis (diffuse or localised), and calculating different imaging scores. Imaging scores simplify and systematize the vast information provided by HRCT of the chest,

serving as a tool to categorize patients into severity groups, helping to identify phenotypes and guide the management of patients with bronchiectasis.

Exacerbation can be a way of detecting the disease, which certainly influences the bronchiectasis patient's prognosis by its frequency and severity. Exacerbations remain to be considered as events involving several causal factors, and the identification of subtypes of exacerbations is one of the research directions in bronchiectasis with a major impact on the choice of treatment. The severity of exacerbations and the increased risk of multidrug-resistant (MDR) germ infections are factors influencing the choice of antibiotic therapy.

Bronchiectasis is a heterogeneous and at the same time complex disease, through its consequences from the persistence of a systemic inflammatory process, which may initiate or aggravate comorbidities, which in turn may interact differently synergistically, incidentally or as a cause of bronchiectasis. Some interactions between host-related factors (such as the peculiarities of the immune system) in correlation with the severity of the disease, the type of germs colonising the airways and the type of inflammatory response are presented. The role of identifying subgroups of patients with high susceptibility for chronic P. aeruginosa infection or Aspergillus-associated diseases among bronchiectasis patients, for which prevention mechanisms and earlier initiation of treatment can be applied, has been noted.

2. CLINICAL DATA AND RESEARCH METHODS

The development of the research concept and design was based on the objectives outlined to achieve the intended purpose, the scientific research was carried out in several stages.

In the **1st stage**, the literature data were analysed, the problems that need to be solved were defined and the research concept and study design were created (figure 1).

Stage II included the collection of the study material, including bronchiectasis patients hospitalized or consulted at the "Chiril Draganiuc" Phthisiopneumology Institute during 2014-2019, based on which a descriptive and analytical cross-sectional observational study was conducted. The study group included 448 consecutive patients, for each patient an investigation form was elaborated which included detailed complaints (presence, character and duration of chronic cough; presence of chronic bronchorrhea; dyspnoea, being quantified by the mMRC scale), complete medical history (duration of illness, exacerbation rate/year, previous treatment given, severe lung infections in history), physical examination data, laboratory tests, bacteriological tests, data obtained from fibrobronchoscopy, spirometry, bodyplethysmography, DLCO and results of imaging investigations (X-ray, HRCT chest, EchoCG).

The data obtained were used both for the descriptive study with the presentation of demographic, clinical, microbiological, functional and imaging characteristics of the patients included in the study, and for the constitution of subgroups (based on etiology, bacteriological characteristics, imaging characteristics) for the analytical study by comparative evaluation of these subgroups with the analysis of clinical, microbiological, functional and imaging features, possible correlations and identification of bronchiectasis phenotypes.

Stage III included the follow-up of patients collected in stage II, for a period of 36 months after enrolment, by performing a cohort study with the evaluation of the patients' evolutionary profile according to aetiology, disease severity, severity of imaging scores, multidimensional indices and comorbidity indices, and predictors for lethality were identified.

Stage IV included the development of diagnostic and management algorithms and practical recommendations for patients with bronchiectasis based on the identified phenotypes, taking into account the diagnostic and treatment gaps attested at different stages of care in the conditions of the Republic of Moldova.

The positive diagnosis of bronchiectasis was established based on the imaging signs identified on chest HRCT, and subsequently additional tests were applied to establish the etiology of bronchiectasis according to the recommendations of the ERS guidelines and those of the National Clinical Protocol [15, 16]. Informed consent was obtained from all subjects.

Inclusion criteria: presence of bronchiectasis confirmed by chest HRCT; age ≥18 years; patient consent to participate in the study.

Exclusion criteria: patients with traction bronchiectasis due to diffuse interstitial lung disease; patient refusal to participate in the study; patients with cystic fibrosis.

Each patient was given an investigation form which included detailed complaints (presence, character and duration of chronic cough; presence of chronic bronchorrhoea; dyspnoea, being quantified by the mMRC scale), complete medical history (duration of illness, exacerbation rate/year, previous treatment given, severe lung infections in history), physical examination data, laboratory tests, bacteriological tests, data obtained from fibrobronchoscopy, spirometry, bodyplethysmography, DLCO and results of imaging investigations (X-ray, chest HRCT, EchoCG).

Evaluation of bronchiectasis severity was performed by applying validated imaging scores: the mReiff score (a simplified score from the Reiff score) [17], the Bhalla score [18], the BRICS score [19]. Quantification of emphysema severity was performed by applying the Goddard visual score [20]. Assessment of the imaging anatomy of the large endothoracic vessels and imaging signs of PH at HRCT thorax was performed by measuring the diameter of the ascending aorta, descending aorta, pulmonary artery trunk, right and left pulmonary artery branches. The data were correlated with signs of PHT identified on echocardiography by measuring PAPs on EchoCG.

Multidimensional indices combining clinical, functional, microbilogical and imaging variables were calculated: BSI [21], FACED and E-FACED [22] to assess disease severity and prognosis. The Charlson Comorbidity Index and the Bronchiectasis Aetiology Comorbidity Index (BACI) have been the tools to assess the weight of different comorbidities but also their impact on survival rates [23, 24].

The original questionnaire validated in Romanian and Russian QOL-B (Quality of Life Questionnaire-Bronchiectasis) was used to assess quality of life in patients with non-cystic fibrosis bronchiectasis.

Methods of statistical analysis

TIBCO Statistica 12, MS Excel 2016 and MedCalc (v20.006) programs were used for data analysis. Modern statistical processing tools were selected and applied, which included descriptive, correlational and multivariate statistics, ROC analysis, logistic regression analysis, cluster analysis, the Kaplan-Meier method and the Cox model.

The ethical principles in clinical research

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 no. 30 of 30/03/2015 and no. 18 of 21.11.2017).

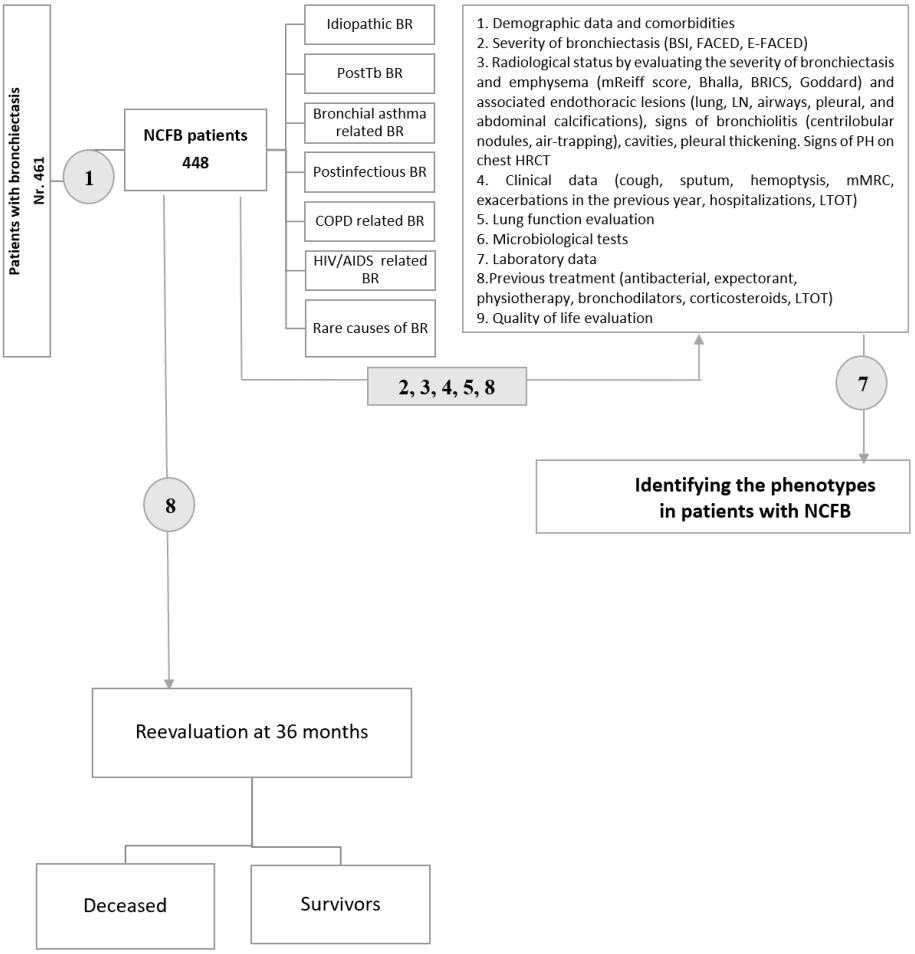


Figure 1 ***Study design***

3. AETIOLOGICAL ASPECTS, CLINICAL, IMAGING, MICROBIOLOGICAL AND FUNCTIONAL CHARACTERISTICS IN PATIENTS WITH BRONCHIECTASIS

3.1 General characteristics of the study group

The demographic characteristics of the study group (448 patients with NCFB) are presented in table 1. Predominance of male subjects (57%), age over 60 years old (51%), rural area (53%), and important rate of smokers (41%) are among the basic demographic characteristics of the study group.

Table 1 The demographic characteristics of the study group

Demographic characteristics	**Number n = 448**	**% (95%CI)**
Age, years		
< 60 years	221	49% (44,3-53,8)
≥ 60 years	227	51% (46,1-55.6)
Sex		
men	255	57% (52,1-61,5)
women	193	43% (38,4-47,8)
Rural/urban status		
urban	210	47% (42,4-51,8)
rural	238	53% (48,1-57,6)
Smoking history		
non-smokers	264	59% (54,2-63,5)
current smokers	111	25% (21-29,2)
ex-smokers	73	16% (12,7-19,8)
Death within 36 months of study entry		
deceased	121	27% (22,9-31,3)
survivors	327	73% (68,6-77)

The study highlighted a significant diagnostic delay of patients with NCFB, including the symptomatic ones, and the lack of treatment administration (table 2). In a big number of cases, no medication and no physiotherapy treatment have been done.

In 278 cases (62%; 95%CI: 57,5-66,5) of the 448 patients included in the study, the diagnosis of bronchiectasis was established for the first time, and there was a long period from the onset of symptoms till the diagnosis was confirmed by chest HRCT (median 8 years (IQ 2-19)).

When evaluating the diagnosis of patients until the presence of bronchiectasis was established, it was observed that these patients were assigned under the umbrella of another diagnosis, or the underlying disease such as COPD, BA, post-tuberculosis sequelae. Most frequently these patients were classified as having chronic bronchitis (30%; 95%CI: 25,7-34,2) or COPD (23%; 95%CI: 19,1-26,9). In 7% of cases (95%CI: 4,6-9,4) slow resolution of pneumonia conditioned chest HRCT and identification of pre-existing bronchiectasis.

Assessment of the patient's treatment until they have been included in the study determined that only 216 patients (48%; 95%CI: 43,4-52,6) have taken any treatment at home. The combination of salmeterol+fluticasone was reported by 73 patients (16%; 95%CI: 12,6-19,4). Only 86 patients (19%; 95%CI: 15,4-22,6) have taken expectorants and mucolytics. Physiotherapy and a nebulized medication with hypertonic saline solution were reported by only 32 patients (7%; 95%CI: 4,6-9,4). Surgical treatment for bronchiectasis was applied to 43 patients (9,5%; 95%CI: 6,7-12,2), of which only in one case pneumonectomy, in the others lobectomy or segmentectomy was performed.

Tabelul 2 Demographic characteristics of NCFB patients with a known diagnosis and with no prior diagnosis of bronchiectasis

	NCFB known diagnosis N=170	NCFB no prior diagnosis N=278	Mann-Whitney test, U	p
Duration of symptoms, years; median (IQ)	20 (9-34)	10 (4-20)	15175	p<0,0001
Time from symptom onset to diagnosis, years; median (IQ)	5 (2-15)	8 (2-19)	21059	p=0,05
Illness duration, years; median (IQ)	6 (3-15)	-	-	-
Age, years; median (IQ)	57,5 (46-64)	61 (52-68)	19484	p=0,001

The evaluation of the clinical characteristics of patients with NCFB revealed a high proportion of cases with severe dyspnea (mMRC 3-4 - 65%), with daily sputum production (92%), with a purulent appearance of sputum (52%) and with hemoptysis (25%) – table 3.

Chest radiography is a first-line tool in detecting pulmonary diseases, including bronchiectasis. Chest X-ray allows to evaluate more severe airway lesions, for mild or moderate severity bronchiectasis a lower sensitivity and specificity of the chest-X ray was reported. The diagnosis of bronchiectasis can be suspected on chest radiography, which demonstrated a sensitivity of 83,9% (95%CI: 80,1-87,2) for the "tram track" sign and of 37,3% (95%CI: 31,2-43,7) for the ring opacities sign. It is mandatory to perform a chest HRCT scan for bronchiectasis confirmation and the integration of the radiological criteria with the clinical elements of the disease.

A large proportion of patients presented a combination of the classical morphological categories described by Reid [1] (cylindrical, varicose or cystic), which could be clearly determined on chest HRCT. The diagnostic role for establishing the etiology of bronchiectasis (in particular, for rare etiologies group of BR) of direct signs identified on chest HRCT (connected with the severity of bronchial dilatations, their distribution), as well as the indirect signs, was demonstrated. A number of complications were also reported (pulmonary emphysema, pleurisy, empyema, pneumothorax, fibrothorax, atelectasis, "destroyed lung").

There are a handful of conditions when HRCT features are highly suggestive of a specific underlying cause. The prevalence of different accompanying signs in bronchiectasis identified on radiography is shown in table 4, and of those identified on chest HRCT in table 5.

Table 3 Clinical and paraclinical characteristics of the study group (N=448)

Characteristics	N=448	%	95%CI
Nr. exacerbations			
≤ 2 exacerbations/year	279	62%	57,5-66,5
≥3 exacerbations/year	169	38%	33,5-42,5
Nr. hospitalizations /year			
< 2 hospitalizations /year	240	54%	49,3-58,6
≥2 hospitalizations /year	208	46%	41,3-50,6

Nr. emergency call /year due to worsen BR symptoms 0 call/ year 1-3 calls/ year >3 calls/ year	 329 95 24	 73% 21% 6%	 68,8-77,1 17,2-24,7 3,8-8,1
BMI, *kg/m²*, median (IQ) ≤18,5 >18,5-25 25-29,9 ≥30	24,1 (20,76–28,45) 64 192 108 84	24,1 (20,76–28,45) 14% 43% 24% 19%	 10,7-17,2 38,4-47,5 20-27,9 15,3-22,6
SaO_2, % median (IQ) ≥96% 90-95% <90%	94 (91-96) 140 237 71	94 (91-96) 31% 53% 16%	 26,7-35,2 48,3-57,6 12,6-19,3
Dry cough daily sputum production	34 414	8% 92%	5,4-10,5 89,4-94,5
Amount of sputum, *ml/24 ore* during exacerbation, median (IQ), *ml*	30 (20-50)	30 (20-50)	
Assessment of sputum purulence mucous aspect mucopurulent aspect purulent aspect	 32 149 233	 7% 33% 52%	 4,6-9,3 28,6-37,3 47,3-56,6
Hemoptysis	114	25%	20,9-29
Dyspnea, mMRC mMRC 1 mMRC 2 mMRC 3 mMRC 4	3 (2-4) 27 117 180 113	3 (2-4) 6% 26% 40% 25%	 3,8-8,1 21,9-30 35,4-44,5 20,9-29
Clubbing	27	6%	3,8-8,1
Signs of hyperinflation syndrome • On percussion • Auscultation (diminished vesicular murmur)	 134 215	 30% 48%	 25,7-34,2 43,3-52,6

Table 4 Chest X-ray features in NCFB patients (N=448)

	Nr n = 448	**% (95%CI)**
Bronchiectasis		
Tram track sign	376	84% (80,6-87,3)
Ring opacities	90	20% (16,2-23,7)

Rosette pattern	217	48% (43,3-52,6)
Air-fluid levels	37	8% (5,4-10,6)
Bronchiectasis		
Localized	255	57% (52,4-61,5)
Diffuse	193	43% (38,4-47,5)
Bilateral	372	83% (79,5-86,4)
Unilateral	76	17% (13,5-20,4)
Associated radiological features		
Hyperinflation syndrome	277	62% (57,5-66,4)
Segmental/lobar atelectasis	103	23% (19,1-26,8)
Fibrothorax	87	19% (15,3-22,6)
Pleural effusion	45	10% (7,2-12,7)
Pleural calcifications	12	3% (1,4-4,5)
Pneumothorax	1	0,2% (0-0,6)
Hydropneumothorax	1	0,2% (0-0,6)
"Destroyed lung"	11	2% (0,7-3,2)
Tracheomegaly	3	0,7% (0-1,4)

Table 5 HRCT scan features in NCFB patients (N=448)

	Număr n = 448 (%)	**95% CI**
Bronchiectasis		
Bronchiectasis		
Tubular	134 (30 %)	25,7-34,2
Varicose and tubular	73 (16 %)	12,6-19,4
Saccular, varicose and tubular	241 (54%)	49,4-58,6
Bronchiectasis		
Localized	255 (57%)	52,4-61,5
Diffuse	193 (43%)	38,4-47,6
Unilateral	76 (17%)	13,5-20,5
Bilateral	372 (83%)	79,5-86,5
Accompanying radiological features in NCFB		
Bronchiolitis	231 (51%)	46,3-55,6
Diffuse centrilobular nodules	140 (31%)	26,7-35,2
Localized centrilobular nodules	91 (20%)	16,3-23,7
Signs of emphysema		
Emphysema	303 (67%)	62,6-71,3
Centrilobular	238 (53%)	48,3-57,6
Panacinar	59 (13)	9,9-16,1
Paraseptal	156 (35%)	30,6-39,4
Bullous	56 (12%)	9-15
Surgical treatment with segmentectomy/lobectomy/ pneumonectomy		
Segmentectomy/lobectomy	42 (9%)	6,3-11,6
Pneumonectomy	1 (0,2%)	0-0,6
Lobar/segmental atelectasis		
Atelectasis	113 (25%)	21-29

Tracheal lesions		
Tracheomegaly	3 (0,7%)	0-1,4
Tracheal diverticulum	90 (20%)	16,3-23,7
multiple	53 (12%)	9-15
Accompanying pleural lesions		
Thickening of the apical visceral pleura		
right	311 (69%)	64,7-73,3
left	305 (68%)	63,7-72,3
Fibrothorax	153 (34%)	29,6-38,4
Pleural effusion	45 (10%)	7,2-12,8
Calcification of the pleura		
right	33 (7%)	4,6-9,4
left	24 (5%)	3-4
Calcifications		
Calcifications	217 (48%)	43,4-52,6
Pulmonary calcification	136 (30%)	25,7-34,2
LN	76 (17%)	13,5-20,5
Right hilar lymph nodes calcification	59 (13%)	9,9-16,1
Left hilar lymph nodes calcification	35 (8%)	5,5-10,5
Paratracheal calcified lymph nodes	40 (9%)	6,3-11,6
Infracarinal calcified lymph nodes	23 (5%)	3-7
Airway calcification	125 (28%)	23,8-32,2
Pericardial calcifications	1 (0,2%)	0-0,06
Hepatic calcification	25 (6%)	3,8-8,2
Splenic calcification	15 (3%)	1,4-4,5

The spectrum of functional impairment in the study group was dominated by obstructive functional defect (81% with decreased FEV1 and 90% with decreased MMEF25-75, translating small airway obstruction), with restrictive defect reported in 10% of cases. *Air-trapping* was reported in 43% of cases - table 6.

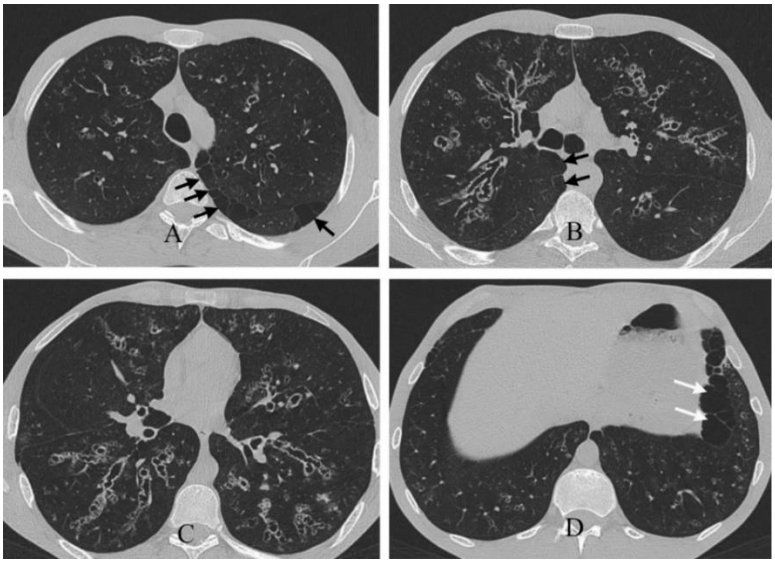


Figure 2 The diffuse distribution pattern in bronchiectasis

A 26-year-old patient with idiopathic BR. Axial sections performed at different levels (A-D) highlighted the presence of all morphological categories of bronchiectasis (tubular, varicose, cystic),

diffusely spread with a predilection for the middle and central fields, illustrating the radiological signs ("signet ring", "tram track". Signs of paraseptal emphysema have been also noted (A, B – black arrows) and emphysematous bullae (D – white arrows).

Table 6 Ventilatory dysfunctions in patients with NCFB (N=448)

Defectul funcțional		**Modificarea parametrilor funcționali**	**Nr. cazuri (%)**	**95%CI**
Obstructive pattern	Obstruction	↓ FEV1/FVC	265/448 (59%)	54,4-63,5
	Central airway obstruction	↓ FEV1 ↓ FEV1 mild ↓ FEV1 moderate ↓ FEV1 severe	361/448 (81%) 122/361 (34%) 157/361 (43%) 82/361 (23%)	77,4-84,6 29,6-38,4 38,4-47,6 19,1-26,9
	Small airway obstruction	↓$MMEF_{25-75}$	405/448 (90,4%)	87,7-93,1
	Air-trapping	↑RV and TLC↔	176/406 (43,3%)	38,7-47,9
	Hyperinflation syndrome	↑RV and ↑ TLC	155/406 (38,1%)	33,6-42,6
Restrictive pattern	Restriction on spirometry	↓FVC and ↑ FEV1/FVC	46/448 (10%)	7,2-12,8
	Restriction on bodypletismografie	↓TLC and FEV1/FVC ↔	7/406 (1,7%)	0,5-2,9
Mixt pattern	Mixt pattern	↓TLC and ↓ FEV1/FVC	2/406 (0,5%)	0-1,1
Diffusion of gases through the alveolar membrane	The impairment in gas diffusion	↓DLCO	314/395 (79%)	75,2-82,8
Blood oxygen level	Blood oxygen saturation level	≥96% ↓SaO_2 90-95% <90%	140/448 (31%) 308/448 (69%) 237/308 (77%) 71/308 (23%)	26,7-35,3 64,7-73,3 73,1-80,9 19,1-26,9

The microbiological examination was performed on sputum and LBA samples, if necessary pleural fluid cultures were performed (table 7). According the microbiological examination in 65% of cases the identification of germs was possible, with a rate of 75% for germs without resistance or resistance to a single antibacterial class and a rate of 22% for MDR germs (*P.aeruginosa* being the most prevalent one 72%, 38/53 cases). Fiberoptic bronchoscopy (FBS) procedure obtained specimens

(table 8) increased the positivity rate for MBT (2 cases) and for NTM (1 case); but the rate of bacteria detection was reduced, probably related to the time of FBS, usually done after a several days of antibiotic therapy.

Table 7 Germs identified in sputum cultures (N=292)

The germs	**n**	**%**	**95%CI**
P.aeruginosa *P.aeruginosa+ M. tuberculosis* *P.aeruginosa+Aspergillus*	74 2 5	25	20-30
K.pneumoniae	39	13	9,1-16,8
S.aureus	20	7	4-9,9
H.influenzae	16	5	2,5-7,5
E.coli	14	5	2,5-7,5
S.pneumoniae	9	3	1-4,95
Acinetobacter spp.	3	1	0-2,1
M.catarrhalis	7	2	0,3-3,6
Neisseria spp.	10	3	1-4,95
S.heamolyticus	18	6	3,2-8,7
Proteus mirabilis	4	1	0-2,1
S.viridans	30	10	6,5-13,4
Aspergillus spp.	7	2	0,2-3,6
M. tuberculosis	22	7,5	4,5-10,5
M.chelonae	1	0,3	0-0,9
M.kansasii	1	0,3	0-0,9
Candida spp.	128	44	38,3-49,7

P.aeruginosa was the most frequently isolated pathogenic germ (25% of cases), representing a risk factor for severe forms of the disease and for severe deterioration of lung function. In all patients with bronchiectasis, significant obstructive ventilatory defect was found (significantly more severe in patients with *P.aeruginosa* and *Aspergillus*, in which the most extensive imaging lesions were identified). Following risk factors for chronic colonization with P.aeruginosa was identified in univariate analysis:

- lobar or segmental atelectasis (OR – 5,1; 95%CI 2,9-8,9; p<0,0001);
- cystic bronchiectasis (OR – 3,1; 95%CI 2,9-8,9; p=0,0003);
- hemoptysis (OR – 2,3; 95%CI 1,34-4,1; p=0,003);
- duration of symptoms, years (OR – 1,02; 95%CI 1,01-1,05; p<0,0001).

The presence of cystic bronchiectasis, although in the univariate analysis showed a correlation with the presence of *P.aeruginosa* colonization, in the logistic regression model it was removed from the model (Nagelkerke R2=0.18; p<0.0001; Hosmer & Lemeshow test=0.68):

- lobar or segmental atelectasis (OR – 3,7; 95%CI 1,98-6,81; p<0,0001);
- cystic bronchiectasis (OR – 0,67; 95%CI 0,3-1,3; p=0,26);
- hemoptysis (OR – 1,99; 95%CI 1,1-3,6; p=0,02);
- duration of symptoms, years (OR – 1,02; 95%CI 1,01-1,05; p=0,004).

Table 8 Spectrum of germs identified by bronchoalveolar aspirate (N=52)

The germs	n	%	95%CI
P.aeruginosa	21	40	26,7-53,3
K.pneumoniae	8	15	5,3-24,7
S.aureus	3	6	0-12,4
H.influenzae	2	4	0-9,3
S.pneumoniae	1	2	0-5,8
M.catarrhalis	2	4	0-9,3
S.heamolyticus	2	4	0-9,3
S.viridans	5	10	1,8-5,8
M. tuberculosis	8	15	5,3-24,7

Identification of bronchiectasis etiology was possible in 70% cases (347 patients), 30% of cases (95%CI: 25,7-34,2) being considered as idiopathic (table 9).

3.1.1 Characteristics of rare etiology forms of NCFB

The rare etiological forms of NCFB were also identified in the study, all patients (n=44) being primarily diagnosed according to the etiology at the stage of inclusion in the study. Treatable traits were identified in several cases (foreign body removal, intravenous substitution therapy with immunoglobulins) – table 9.

Table 9 Etiology of NCFB in the study group (N=448)

NCFB etiology	**N=448**	**%**	**%, CI**
Idiopathic	134	30	25,7-34,2
COPD	81	18	14,5-21,6
PostTB	92	20	16,8-24,3
Postinfectious	66	15	11,5-18
Bronchial asthma	16	4	1,9-5,3
Acquired immunodeficiency HIV	15	3	1,7-5,0
Rare causes of NCFB	44	9	7,1-12,6
Rare causes of NCFB	**N=44**	**%**	**%, CI**
Swyer-James syndrome	9	2,0	8,5 – 32,4
ABPA	6	1,3	3,5 - 23,8
Primary ciliary dyskinesia	5	1,1	2 - 20,7
Williams-Campbell syndrome	5	1,1	2 - 20,7
Mounier-Kuhn syndrome	3	0,7	0 - 14,3
Rheumatoid arthritis	3	0,7	0-14,3

Post iradiation	3	0,7	0 - 14,3
Alpha-1 antitrypsin deficiency	2	0,4	0 - 10,7
NTM	2	0,4	0 - 10,7
Tracheobronchial abnormality	2	0,4	0 - 10,7
Inborn immunodeficiency	1	0,2	0 - 6,7
(Bruton's disease)	1	0,2	0 - 6,7
Foreign body aspiration	1	0,2	0 - 6,7
Non-specific ulcerative colitis	1	0,2	0 - 6,7

The Swyer-James-MacLeod syndrome was the most frequent among the rare forms of bronchiectasis (9 cases). ABPA was identified in 6 cases. The radiological features with central distribution of bronchiectasis, high level of total IgE and sensitization to Aspergillus have been identified. Among the anatomical malformations, 5 cases with Williams-Campbell syndrome, 3 cases with Mounier-Kuhn syndrome, 1 case with tracheal bronchus, 1 case with cystic adenomatoid malformation have been described. Genetic diseases were demonstrated in 5 cases with primary ciliary dyskinesia, 2 cases with alpha-1 antitrypsin deficiency, and 1 patient with Bruton's disease. Although reported in large numbers, especially in American countries, but also in some European countries, in our group the prevalence of bronchiectasis caused by NTM was very law (0,4% - 2 cases). Bronchiectasis caused by NTM were attributed to the category of rare forms in the population of the Republic of Moldova.

3.2 Characteristics of bronchiectasis patients related to the etiology

The clinical particularities were defined for the 7 etiological groups (table 10):

- the youngest patients were in the group of patients with BR related to HIV/AIDS (34 years; IQ 29-45 years), followed by the rare etiological forms group of BR (475 years; IQ 36-65 years), and the oldest were represented by the BR group associated with COPD (63 years; IQ 58,75-70 years);
- according to the dyspnea severity mMRC scale, the most severe degree of dyspnea was determined in the group of BR associated with COPD, demonstrating statistically significant differences with all other etiological groups ($p<0,0001$), the mildest degree of dyspnea was appreciated in postinfectious BR group;
- smokers were the most prevalent in the BR group associated with COPD - 90,1%. A high rate of smokers was noted in the group of BR associated with HIV/AIDS (53,3%), postTB BR (44,6%) and post-infectious BR (28,8%), reaching the threshold of statistical differences ($p<0,05$) with the other groups (idiopathic BR – 20,9% and BR of rare etiologies – 22,7%);
- hemoptysis was identified with a higher frequency in the postinfectious BR (37,9%) and postTB BR (34,8%) groups.

The radiological features for various etiological groups were shown in table 11:

- according to the number of involved lobes, the highest number of lobes affected by bronchiectasis was found in the rare etiology BR group and the idiopathic BR group,

demonstrating statistically significant differences compared to the COPD-associated BR, postTB BR and postinfectious BR groups (KW 33,63; df=6; p<0,0001).

- localized type of BR was found to be more prevalent in the postTB BR group (20,7%) and in the postinfectious BR group (24.2%), with statistically significant differences compare with the other etiological groups.

- segmental/lobar atelectasis was more common in the postTB BR group (35,9%), rare etiology group of BR (29.5%) and idiopathic BR (27,6%).

Statistical differences compared to other etiological groups were determined for the presence of radiological signs of pulmonary emphysema, with the highest rate in the COPD-related BR group (91,4%). A high number of patients with emphysema was also noted in the rare etiologies group of BR (79,5%). Emphysema was less commonly identified in the HIV/AIDS-related BR group (33,3%) and post-infectious BR (47%) group (table 11).

Pulmonary function tests demonstrated statistically significant differences between etiological groups. Thus, a less severe deterioration of lung function was noted in the group of patients with BR associated with BA. The group of BR associated with COPD demonstrated a sever compromised lung function with statistically significant differences compared to the other groups. For FEV1, the lowest values were observed in the BR group associated with COPD (median 38,5%; IQ 28-46,9%) and the rare etiologies BR group (median 40,8% IQ 28,8-56%), with statistical differences with the other groups (KW 36,58; df=6; p=0,0000002). The highest FEV1 values were appreciated in the postinfectious BR group (median 60,5% IQ 39-83,6%) and BA related BR group (median 58,5% IQ 39,9-93,3%).

Table 10 Characteristics related to the etiology of NCFB (N=448)

	Idiopathic BR[1] n=134	**COPD related BR[2] n=81**	**PostTB BR[3] n=92**	**Postinfec-tious BR [4] n=66**	**BA related BR[5] n=16**	**HIV/AIDS related BR[6] n=15**	**BR rare etiologies [7] n=44**	**p**
Duration of symptoms, years	15[, 6,7] (5-28)	10[, 6,7] (6-20)	13[, 6,7] (6-24,5)	10,5[, 6,7] (5-25)	12,5[,6] (6-22)	2[1,2,3,4,5,7] (2-3)	21,5[,1,2,3,4,6] (11-35)	KW 39,7; df=6; p<0,0001
Time from onset of symptoms to diagnosis, years	6 [6] (2-19)	10[, 3,6] (4-19)	5[, 2,6,7] (2-15)	7 [6] (2-12)	9[, 6] (3,5-19,5)	2 [1,2,3,4,5, 7] (0-2,75)	12,5[, 3,6] (3-24,5)	KW 21,1; df=6; p=0,001
Age, years	60[2,6,7] IQ 52-66	63[1,3,4,5,6,7] IQ 58,75-70	61[2,6,7] IQ 53-68	55[2,6] IQ 45-64	57[2,6] IQ 53-64,5	34[1,2,3,4,5,7] IQ 29-45	47.5[1,2,3,4,5,6] IQ 36-65	KW 49,54; df=6; p<0,001
Women	79 59%[2,3,7]	6 7,4%[1,3,4,5,6,7]	37 40,2%[1,2]	34 51,5%[2]	9 56,2%[2]	5 33,3%[2]	23 52,3%[1,2]	p<0,05
Smokers	28 20,9%[2,3,6]	73 90,1%[1,3,4,5,6,7]	41 44,6%[1,2,4,7]	19 28,8%[2,3]	4 25%[2]	8 53,3%[1,2,7]	10 22,7%[2,3,6]	p<0,05
BMI, median kg/m2 (IQ)	25,7[3,6] (21,2-29,3)	24,2[3,6] (20,4-29,5)	22,5[1,2,4,5,6] (20,1-25,6)	25,2[3,6] (21,9-28,4)	25,7 [3,6] (23,9-34,8)	17,4[1,2,3,4,5,7] (16,1-19,6)	24[6] (22,1-28,4)	KW 45,84; df=6; p<0,001
Nr. exacerbations/year	2 (IQ 2-3)	2 (IQ 2-3)	2 (IQ 1-3)	2 (IQ 1-3)	2,5 (IQ 2-3,5)	2 (IQ 2-3)	2 (IQ 1,25-3)	KW 4,4; p=0,57
Nr. admissions/year	1 (IQ 1-2)	1 (IQ 1-2)	1,5 (IQ 1-2)	1 (IQ 1-2)	1,5 (IQ 1-2)	2 (IQ 1-2)	2 (IQ 1-2)	KW 8,9; p=0,11
Amount of sputum/24h, ml	30 IQ 20-50	20 IQ 17,5-50	30 IQ 20-50	30 IQ 20-50	30 IQ 15-50	50 IQ 30-75	50 IQ 12,5-57,5	KW 10,23; df=6; p=0,1
mMRC, median (IQ)	3[2] (2-3)	3[1,3,4,5,6] (3-4)	3[2] (2-3)	2,5[2,6,7] (2-3)	3[2] (2-3)	3[2,4] (3-4)	3[4] (2-3,5)	KW 28,1; df=6; p<0.0001
Hemoptysis	31 (23,1%)[3,4]	13 (16%)[3,4]	32 34,8%)[1,2,5]	25 (37,9%)[1,2,5]	1 (6,2%)[3,4]	5 (33,3%)[3]	10 (22,7%)	p<0,05
Chronic *P.aeruginosa* infection	24 (17,9%)[4]	11 (13,6%)	14 (15,2%)	4 (6,1%)[1,7]	0	0	9 (20,5%)[4]	p<0,05

Analyzed variables were presented as percentage values or as medians with interquartile range (IQ). Note: with [1, 2, 3, 4, 5, 6, 7] are marked the groups between which significant differences were detected following the multiple comparative analysis (p<0,05).

Table 11 Imaging features related to the etiology of NCFB (N=448)

	BR idiopatice[1] n=134	**BR asociate BPOC[2] n=81**	**BR postTB[3] n=92**	**BR postinfecțioase[4] n=66**	**BR asociate AB[5] n=16**	**BR asociate HIV/SIDA[6] n=15**	**BR etiologii rare[7] n=44**	**p**
Nr of lobes involved	4[2,3,4,7] (3-6)	4[1,7] (2-5)	4[1,7] (2-5)	3[1,7] (2-5)	4[7] (2-5,5)	4 (3-6)	6[1,2,3,4,5] (4-6)	KW 33,63; df=6; p<0,0001
Localized bronchiectasis on chest HRCT	11 8,2%[3,4]	3 3,7%[3,4]	19 20,7%[1,2,7]	16 24,2%[1,2,7]	1 6,2%	1 6,7%	3 6,8%[3,4]	p<0,05
Segmental/lobar atelectasis	37 27,6%[2]	12 15%[1,3,4,7]	33 35,9%[2,4,5]	12 18,2%[2,3]	1 6,2%[3]	5 33,3%	13 29,5%[2]	p<0,01
Calcifications in the lung parenchyma	29 21,8%[3]	17 21,2%[3]	65 70,7%[1,2,4,5,6,7]	15 22,7%[3]	2 12,5%[3]	7 15,9%[3]	1 6,7%[3]	p<0,0001
Calcifications in the bronchial walls	38 28,6%[3]	25 31,2%	39 42,1%[1,4,5,6,7]	12 18,2%[3]	2 12,5%[3]	2 13,3%[3]	7 15,9%[3]	p<0,05
Tracheal diverticulum	29 21,6%[4]	19 23,5%[4]	26 28,3%[4]	7 10,6%[1,2,3]	1 6,2%	0	8 18,2%	p<0,05
Imaging signs of pulmonary emphysema	88 65,7%[2,6]	74 91,4%[1,3,4,5,6]	59 64,1%[2,4,6]	31 47%[2,3,7]	11 68,7%[2,6]	5 33,3%[1,2,3,5,7]	35 79,5%[4,6]	p<0,05
Imaging signs of fibrothorax	34 25,4%[3,7]	25 30,9%[3,6]	48 52,2%[1,2,4,6]	21 31,8%[3,6]	5 31,2%	1 6,7%[2,3,4,7]	19 43,2%[1,6]	p<0,05
Segmentectomy/ lobectomy	13 9,7%[2]	2 2,5%[1,3,4]	15 16,3%[2]	8 12,1%[2]	1 6,2%	1 6,7%	3 6,8%	p<0,05

Analyzed variables were presented as percentage values or as medians with interquartile range (IQ). Note: with [1, 2, 3, 4, 5, 6, 7] are marked the groups between which significant differences were detected following the multiple comparative analysis (p<0,05).

Noteworthy, a very low value for MMEF $_{25-75}$ was noted in all etiological groups, the lowest value has been recorded in the rare etiologies BR group (median 17,15%; IQ 13,6-51%); with statistical differences with the other groups (KW 32,69; df=6; p<0,0001).

The assessment of the quality-of-life bronchiectasis (QOL-B) questionnaire revealed the lowest scores for the "physical activity" and "health" domains in all the etiological groups. Statistical differences were notified between the BR group related to COPD, with the lowest score for the "physical activity" domain and for the "disease impact" domain compare with other etiological groups.

3.3 Gender differences in non-cystic fibrosis bronchiectasis

In our study, a greater number of males with NCFB was noted 57% (255/448). The female predominance was determined in the BA related BR group (56%; 9/16) and in the idiopathic BR group (59%, 79/134). Statistically significant differences according the etiology and gender prevalence were determined only for idiopathic BR whose prevalence was 40,9% for women and 21,6% for men ($\chi2$=19,5; p<0,0001) and for COPD related BR with a prevalence of 31% for women and 29,4% for men ($\chi2$=51,2; p<0,0001).

There were no differences between men and women (12 years (IQ 5-22 years) *vs* 15 years (6-27,2 years); p=0,17) in relation to the duration of symptoms, but it was noted a difference according the number of patients first time diagnosed with bronchiectasis (70,6% men (180/255) and 50,8% women (98/193); p<0.0001).

Among the clinical manifestations, there were differences linked to the dyspnea mMRC scale, which demonstrated a greater severity of dyspnea among men (p=0,0001). During exacerbations a bigger amount of daily sputum was registered for women (p=0,02). Related to the morphological types of bronchiectasis, there was a higher rate of cylindrical bronchiectasis in men – 36,1% compared to women – 21,8% ($\chi2$=10,7; p=0,001) and a higher rate of cystic BR in women 60,6% *vs* men – 48,3% ($\chi2$=6,3; p=0,01).

Pulmonary functional tests demonstrated significant differences for all analyzed parameters, a more severe hypoxemia in the male group, but also a more severe decrease in lung volumes on spirometry, and a more important increase of RV and TLC on body plethysmography. Women had a higher rate in the group of patients with preserved lung function (18,1% *vs* 7,5%, $\chi2$=11,6; p=0,0007), and the obstructive pattern being more frequent in men (82,4% *vs* 70,5%, $\chi2$=8,8; p=0,002). Restrictive pattern was more prevalent in women (11,6% *vs* 8,8%), but did not reach a statistical difference threshold ($\chi2$=0,47; p=0,4).

Sputum culture during exacerbations identified a higher prevalence of *P.aeruginosa* among women with statistically significant differences (20,7% *vs* 13,3%; $\chi2$=4.3; p=0,03). The evaluation of cases identified with *P.aeruginosa* colonization did not reach a threshold of statistical significance, although women had a higher rate than men (16,6% *vs* 11,8%; $\chi2$=2,1; p=0,06).

3.4 Microbiological profile correlated with clinical manifestations, ventilatory dysfunction, imaging pattern, aetiology and quality of life in patients with bronchiectasis

The correlation between the microbiological profile identified in patients with NCFB and the etiological groups, as well as the spectrum of ventilatory dysfunction was performed by dividing the group of NCFB (448 patients) into 5 subgroups:

1. Group A – 204 patients (45%) in whom sputum culture grew germs considered to be part of the oropharyngeal microflora and those in whom sputum culture growth was determined to be absent.

2. Group B – 67 (15%) patients identified with *P.aeruginosa*

3. Group C – 120 (27%) patients identified with pathogenic germs except *P.aeruginosa*

4. Group D – 31 (7%) patients with *Aspergillus* spp infection.

5. Group E – 26 (6%) patients identified with *M.tuberculosis* or NTM.

In the analyzed groups, patients from group B (P.aeruginosa) have been symptomatic for a longer period of time compared to the other groups (18 years; IQ 10-34,3 years), statistically significant differences were noted. A smaller time duration of symptoms shas been reported in the group E (5 years; IQ 2-12 years), which also showed significant differences. Patients with *Aspergillus* infection, as well, were symptomatic for a longer period of time (15 years; IQ 5-21,7 years), but showed significant differences only with group B and E.

According to the number of exacerbations during the last year, a higher number of frequent exacerbators (≥2 exacerbations per year) was identified in all groups, with the highest rate in group B - 91% (61/67) and the lowest in group E – 53,8% (14/26), both groups presenting statistically significant differences with the others in which the rate of frequent exacerbators was 77%. The median number of exacerbations showed similar results, with the highest values for group B (2; IQ 2-3,75) and group D (3 IQ 2-3) and the lowest value for group E (2; IQ 1-2), KW test=13.7; p=0,004.

In all microbiological groups bilateral localization (83%, 372/448) and diffuse distribution of BR (88%, 394/448) were the most frequent radiological identified appearances. Unilateral BR were more prevalent in group E (30,8%, 8/26), followed by group C (18,3%, 22/123) and group A (18,1%, 37/204). The highest rate of localized BR was in group E (23%, 8/26) and the lowest in group B (6%, 4/67). According to the imaging pattern evaluated linked to the morphological type of BR, in all groups the predominance of the cystic pattern was attested, the highest percentage being observed in group E (83,9%, 26/31) and group B (74,6 %, 50/64). Another marker of BR severity was the extension of BR involving multiple lobes. A higher number of involved lobes was in group B and group D with a median of 6 lobes for group B (IQ 4-6) and a median of 5 lobes for group D (IQ 3-6).

The highest mReiff imaging score and Bhalla imaging scores were appreciated in group B and group D, demonstrating significant differences related to other groups (KW= 43,9; p<0,0001 for mReiff score and KW=51,13, p<0,0001 for Bhalla score).

Thus, in group B the median mReiff score was 6 points (IQ 4-6), and in group D 5 points (IQ 3-6), the other groups had a median of 4 points (IQ 2-5). A median Bhalla score of 15 points in group B and C, and in groups A, C, E the median was ≤10 points.

Imaging signs of bronchiolitis with centrilobular distribution of nodules and with "tree-in-bud" pattern were registered in 52% (231/448). Group A showed a rate of 49% (99/203), group B - 63% (42/67), group C - 46% (55/120), group D - 48% (15/31), and group E - 77% (20/26). Radiological signs of localized bronchiolitis in one lobe or segment were demonstrated in a smaller number of cases in all groups: group A – 21,6% (44/204), group B – 10,4% (7/67), group C 20% (24/120), group D 25,8% (8/31), group E – 30,8% (8/26). Diffuse spread of centrilobular nodules as a manifestation of bronchiolitis was reported in higher percentage of cases in group B – 52,2% (35/67) and group E – 46,2% (12/26). In the other groups, a similar proportion of cases (less than 30%) were noted: group A – 27% (55/207), group C – 25,8% (31/120), group D – 22,6% (7/31).

The distribution of microbiological groups according to the BR etiology showed statistically significant differences ($\chi 2$=73,77; DF=24; p<0,0001). For group E, postTB BR had the highest rate (65,4%; 17/26), these being the patients with tuberculosis relapses, but also the 2 cases of NTM previously were treated for pulmonary TB. The other etiological forms had a smaller rate below 10%.

3.5 *Aspergillus* infection in patients with bronchiectasis

3.5.1 Characteristics of patients with NCFB and chronic pulmonary aspergillosis

Chronic pulmonary aspergillosis (CPA) was identified in 27 patients (6%, 95%CI 3,8-8,1). Patients with BR and chronic pulmonary aspergillosis, showed a higher number of lobes with BR, a higher rate of cystic bronchiectasis, a higher severity of imaging scores (mReiff, Bhalla, Goddard, BRICS), a smaller hemoglobin level and a higher thrombocyte number. Fibrotic form of chronic pulmonary aspergillosis was the most frequently identified (63%).

Most part of the patients (85%; 95%CI: 81.7-88.3) were first time diagnosed with aspergillosis when they were included in the actual study. The high proportion of patients with the fibrosing form of CPA could be the consequence of a diagnosis delay and of the progression of cavitary forms in the absence of antifungal and surgical treatment. The presence of fungus ball was identified in 18 cases (67%; 95%CI: 49,2-84,7), 4 of these cases presented the mycetoma inside the cystic bronchiectasis.

Posttuberculosis etiology (OR 2,39; 95%CI 1,03-5,57; p=0,04), residual cavities or cystic BR (OR 5,27; 95%CI 1,94-14,3; p=0,001) were identified as risk factors for the appearance of chronic pulmonary aspergillosis in univariate analysis as well as in the logistic regression model. BMI was identified as a protective factor (OR 0,91; 95%CI 0,84-0,99; p=0,01).

A 36-month follow-up of patients with CPA revealed a high mortality rate, 10/27 patients died (37%; 95%CI: 18,8-55,2), mostly young patients (56,1±12,6 years).

3.5.2 The role of the rapid immunochromatographic test Aspergillus ICT IgG-IgM in the identification of aspergillosis.

Ninety NCFB patients were tested for evaluating the role of the Aspergillus ICT IgG-IgM rapid immunochromatographic test (lateral flow) for the identification of aspergillosis. The positive diagnosis of aspergillosis was based on clinical, imaging, histological criteria, sputum cultures, serum level of IgG antiAspergillus fumigatus. The test showed a sensitivity of 75% and a specificity of 98,38%, which can recommend this test for the identification of patients with aspergillosis among NCFB patients.

3.6 Bronchiectasis exacerbations. The role of inflammatory biomarkers in highlighting pneumonic exacerbations of bronchiectasis.

The study group was distinguished by a big number of patients considered as frequent exacerbators (≥2 exacerbations/year, at least one required hospitalization) - 78% cases (95%CI: 74,2-81,8). Univariate logistic regression analysis identified as risk factors for frequent exacerbations: mMRC dyspnea scale, BMI, number of affected lobes, mReiff score, Bhalla score, BACI comorbidity index, FEV1, SaO2, *P. aeruginosa*. The multivariate logistic regression model demonstrated as independent risk factors for frequent exacerbations only 3 factors:

- mMRC dyspnea scale OR 1,7; 95% CI: 1,24-2,34; p=0,001
- BMI OR 1,04; 95% CI: 1,01-1,09; p=0,04
- *P.aeruginosa* OR 2,9; 95% CI: 1,17-7,23; p=0,02.

The evaluation of NCFB patients during exacerbations identified a high prevalence of pneumonic exacerbations (43%). Analysis of patient's subgroup with pneumonic and non-pneumonic exacerbations identified several significant differences. The radiological scores have identified significant differences only for the Bhalla score, which showed a higher value in the group of patients with pneumonic exacerbations (p=0,02). Diabetes mellitus and anemia were shown as a more frequent comorbidities in the subgroup of patients with pneumonic exacerbations.

Inflammatory markers (C-reactive protein and leukocyte count) showed statistically significant differences with higher values for the bronchiectasis group of pneumonic exacerbations versus the group of non-pneumonic exacerbations. There are no differences according to platelet count and erythrocyte sedimentation rate. ROC analysis determined poor discriminatory power in differentiating between pneumonic and non-pneumonic exacerbations, both for C-reactive protein and leukocyte count. These data support the recommendation to perform the chest radiography during BR exacerbations for identifying cases complicated by pneumonia.

4. IMAGING FEATURES IN PATIENTS WITH BRONCHIECTASIS

4.1 Imaging patterns in bronchiectasis

A huge variety of imaging lesions demonstrated at chest HRCT in patients with NCFB provide the identification of some radiological patterns that can help to evaluate the groups of patients with similar features. This can be used in finding of new therapeutic options. Three types of radiological patterns of bronchiectasis were identified according to the dominant morphological category visualized at the chest HRCT: tubular, varicose and cystic.

A clinical significance of the radiological pattern was demonstrated in NCFB patients: severe dyspnea, a big amount of sputum expectoration, sputum purulence and hemoptysis were the dominant clinical features in the group of patients with cystic pattern. *P.aeruginosa* as a frequent identified germ in patients with a cystic radiologic pattern argues the need for a more rigorous monitoring of sputum cultures and of using of airway clearance techniques. The multidimensional severity indices (BSI, FACED, E-FACED) demonstrated statistical differences with higher values in the cystic pattern group of patients.

According to the etiology a higher proportion of patients with cystic pattern was found in the group of idiopathic and posttuberculosis bronchiectasis. The tubular pattern was found as a dominant one in the group of COPD related BR and bronchial asthma related BR. Obstructive syndrome was present in all patterns, without statistically significant differences for small airways obstruction. These argues for the need of bronchodilator treatment in all patterns. An important decrease of FEV1 in the cystic pattern group suggests the need for a more frequent assessment of pulmonary function tests in this group.

Hemoptysis is a symptom that would suggest a more severe airways damage. So, the proportion of patients with hemoptysis in the cystic pattern group was statistically higher compared to the other 2 patterns – 33,2% *vs* 19,2% *vs* 17,2%. Similarly, there was a higher proportion of patients with *P.aeruginosa* infection in the cystic pattern group, compared to the other two – 22,8% *vs* 13,7% *vs* 6,7%.

The distribution of BR groups according the etiology in correlation with the imaging pattern identified statistically significant differences ($\chi 2=53,15$; DF=12; $p<0,0001$). The cystic pattern was more prevalent in the idiopathic BR group (33,6%) and postTB (22,8%) compared to the other etiologies where rate was below 20%. Tubular radiological pattern was a predominant one in asthma related BR, COPD related BR and BR associated with HIV/AIDS.

4.2 The role of radiological scores

The radiological scores (mReiff, Bhalla, BRICS, Goddard) in our study group were evaluated. A correlation between the scores as well as their correlation with clinical markers, lung function tests and identified germs were done. According to the mReiff score, patients with a mild severity (score below 6 points - 53%) have the highest rate. According to the Bhalla score, the group of patients with a moderate severity (53%) were the dominant one.

There were significant differences according various etiologic groups of BR and severity of radiological scores. All the scores (mReiff, Bhalla, BRICS) showed the highest values in the rare etiologies group of BR, presenting statistically significant differences with the other etiological groups. The Goddard score demonstrated the highest values in the BR group associated with COPD (9 points; IQ 4,7-13,25), but a severe degree of emphysema should also be mentioned in the group of rare etiologies of BR (6 points; IQ 3,5- 14). BR associated with COPD quantified according to severity by the mReiff score demonstrated mild or moderate forms, frequently associated with tubular BR, but evaluation with the Bhalla score quantifies them in the group of severe

due to the lesions associated with BR. Low radiological scores were seen in the BR group associated with BA. PostTB BR demonstrated the highest value for Bhalla radiological score. An excellent correlation was observed between mReiff and Bhalla score (r=0,78, p<0,05).

4.3 The diagnostic and prognostic role of imaging signs of PH on chest HRCT examination in patients with NCFB

The group of patients with PH (BR-PHP) included 137 cases (30.6%) and presented a PAPs value above 35 mmHg. Patients with BR in the BR-HTP group presented a higher average age, a higher number of exacerbations and hospitalizations per year, a more severe ventilatory dysfunction dominated by the obstructive pattern, and having a higher proportion of smokers, with Higher IF. In the BR-HTP group, there were higher imaging scores quantifying emphysema (Goddard score) and BR (mReiff score), as well as those assessing both types of lesions (bronchiectasis and emphysema) such as BRICS score and Bhalla score. In the BR-HTP group, higher values of the BSI, FACED, E-FACED indices were found. To estimate the predictive role for PH of the parameters measured using the HRCT examination - vessel diameters: diameter of the main pulmonary artery (MPAD), ascending aortic diameter (AsAoD), descending aortic diameter (DsAoD), axial diameters of the right (RPAD) and left main (LPAD), the ratio between MPA diameter and ascending aortic diameter (MPAD/AsAoD), the ratio between main PA diameter and descending aortic diameter (MPAD/DsAoD). ROC analysis was applied, with the identification of the cut off value for maximum sensitivity and specificity. The results were presented in figure 3. Area under the curve (AUC) demonstrated the highest accuracy in predicting PH for MPAD (0.815), followed by MPAD/AsAoD ratio (0,776), MPAD/DsAoD ratio (0,737), LPAD (0,735), RPAD (0,715).

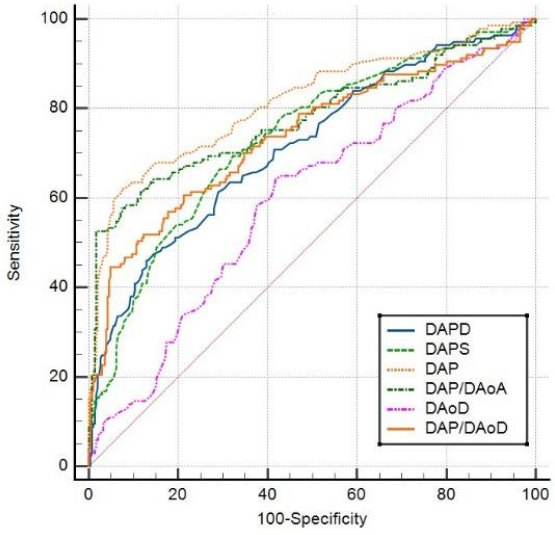


Figure 3 ROC curves for MPAD, RPAD, LPAD, AsAoD, DsAoD, MPAD/DsAoD, MPAD/AsAoD for the PH diagnosis

The measurement of pulmonary vessels and aorta diameters demonstrated a high specificity and good sensitivity for the identification of cases associated with

pulmonary hypertension, the diameter of the trunk of the pulmonary artery (with a threshold >29,8 mm) was shown to be the best index for this purpose.

5. MULTIDIMENSIONAL ASSESSMENT OF PATIENTS WITH BRONCHIECTASIS

5.1 Multidimensional indices in the assessment of bronchiectasis: applicability and clinical significance

The multidimensional severity indices (BSI, FACED) can be used for identifying severe forms of the disease with increased risk of death, although they have showed differences in the quantification of the disease severity with a degree of coincidence of only 25%. Significant differences between the Kaplan-Meier survival curves according the severity of the indices were identified (figure 5).

According to the BSI, the highest proportion (80%) had the severe form of BR, followed by moderate form of BR (16%) and mild form of BR (4%). According to the FACED, only 20% were classified as severe forms, and 40% as moderate and as mild forms. According to the E-FACED, the highest proportion was represented by the moderate form 54%, followed by mild forms 27% and severe forms 19%. The distribution according to the severity of indices (BSI, FACED, E-FACED) revealed statistically significant differences.

The BSI and FACED indices showed a good correlation, demonstrating a Spearman correlation index r=0,76; p<0,0001 (95% CI 0,71-079) and Kendall Tau correlation index 0,62; p<0,0001 (95% CI 0,57-0,65). The E-FACED and FACED indices showed an excellent correlation as well, demonstrating a Spearman correlation index r=0,96; p<0,0001 (95% CI 0,95-0,96).

5.2 Comorbidities in bronchiectasis and their impact on mortality

From the 30 identified comorbidities in patients with NCFB (figure 4), 18 were associated with increased mortality in the univariate Cox proportional hazard analysis. Subsequently, multivariate Cox proportional hazard analysis was performed, and the results showed as independent predictors for death only 3 comorbidities: pulmonary hypertension (HR 1,7; 95%CI: 1,17-2,7; p=0,006); COPD (HR 1,66; 95%CI: 1,08-2,6; p=0,01) and HIV infection (HR 4,9; 95%CI: 2,37-10,1; p<0,0001).

Comorbidity BACI and Charlson indices were calculated, in order to evaluate the impact of comorbidities on the severity of the disease, and also their predictive role, especially in multimorbid patients. The BACI index (median 3 points; IQ 0-7,5 points) and the Charlson index (median 2 points; IQ 1-3,5 points) demonstrated a good correlation r=0,6; p<0,0001.

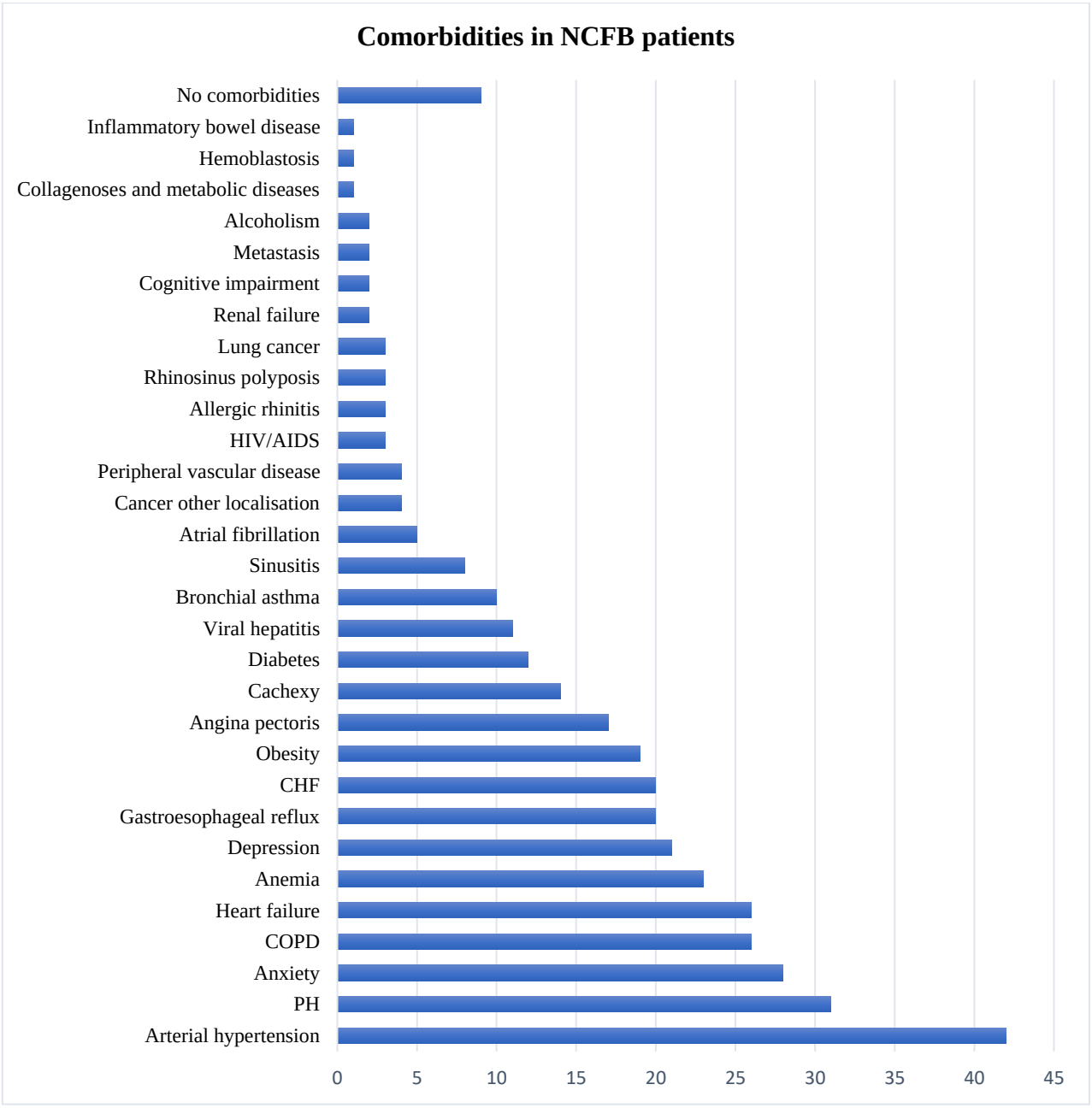


Figure 4 Comorbidities in NCFB patients

5.3 Poor outcome and its predictors in NCFB

Our analysis with a median follow-up of 36 months showed a mortality of 27% (121/448 cases). Descriptive statistics revealed significant differences ($p \leq 0,05$) between the characteristics of deceased and survived patients during the monitoring period.

Risk factors for death

The Kaplan–Meier curves and the logrank test highlighted the survival differences in various groups and represent a first step of the univariate analysis (figure 5). The variables under analysis were those suggested by the deceased patient profile and specific death rates. was completed with the proportional risk analysis (Cox model),

which suggests which of the clinical or paraclinical elements that characterized the patients' profile influence their survival.

According to the etiological groups, the proportion of deceased patients was higher in the groups of HIV/AIDS related BR (80%; 12/15 patients) and COPD related BR (42%, 34/81 patients). The Kaplan-Meier survival curve according to the etiological groups (figure 5) demonstrated statistically significant differences between the groups (Logrank test 58,2; df=6; p<0,0001). The lowest death rate was registered by the BR group associated with BA (6,2%, 1/16 patients). PostTB BR group (26,1%, 24/92 patients), rare etiologies BR group (25%, 11/44 patients), idiopathic BR group (20,1%, 27/134 patients) and postinfectious BR group (18%, 12/66) had a similar death rate.

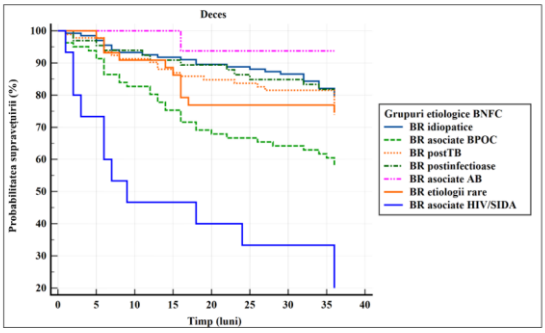
Related to the gender, a higher proportion of deaths was noted in men (36%, 91/255) *vs* women (15%; 30/193). The Kaplan-Meier survival curve (figure 5) showed a higher chance of survival in the women group. The logrank test confirms significantly lower survival probability in men (p<0,0001), with HR 2,31 (95%CI: 1,61-3,32).

Following univariate analysis, the factors that showed significant differences between survivors and those who died were entered into a Cox proportional hazard regression model to identify independent predictors of death. Multivariate analysis demonstrated which variables have an independent effect on mortality (table 12). Advanced age, severe dyspnea (mMRC), P.aeruginosa colonization, history of pneumonic exacerbations, decreased DLCO and reduced SaO2 were found to be independent predictors of death (table 12). Female gender and increased BMI in multivariate analysis were found to be protective factors.

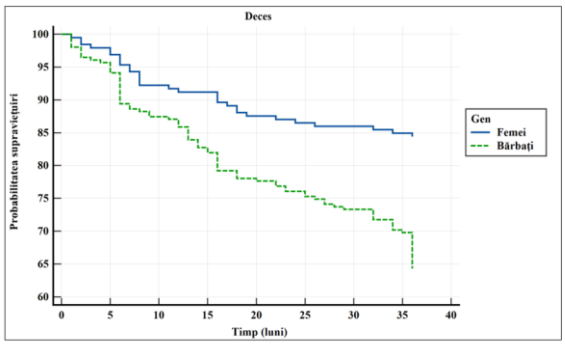
COX univariate analysis determined a predictive capacity for death for all multidimensional indices (BSI, FACED, E-FACED) and BACI comorbidity index:

- BSI (RR 1,18; 95%CI 1,12-1,24; p<0,0001);
- FACED (RR 1,44; 95%CI 1,29-1,61; p<0,0001);
- E-FACED (RR 1,41; 95%CI 1,27-1,57; p<0,0001);
- BACI (RR 1,14; 95%CI 1,1-1,18; p<0,0001).

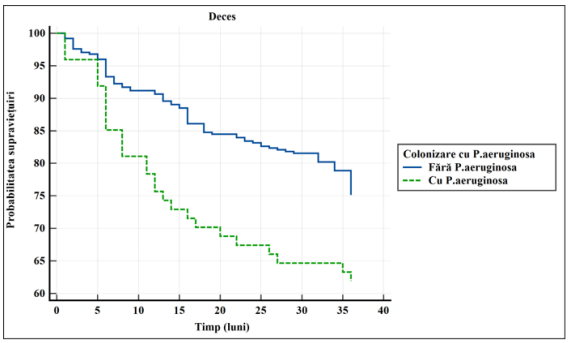
Cox multivariate analysis identified as independent predictive factors for death the BSI index (HR 1,08; 95%CI: 1,01-1,17; p=0,03), the FACED index (HR 1,18; 95%CI: 1,01-1,39; p=0,04) and BACI comorbidity index (HR 1,11; 95%CI: 1,07-1,15; p<0,0001).



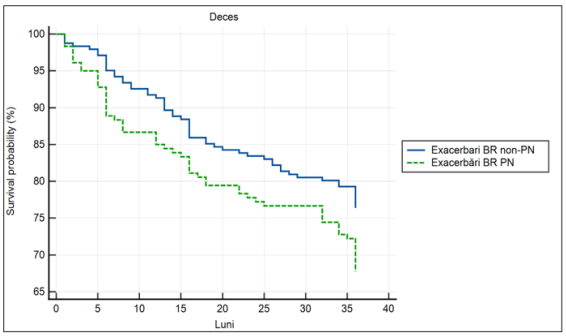
Logrank test; p<0,0001



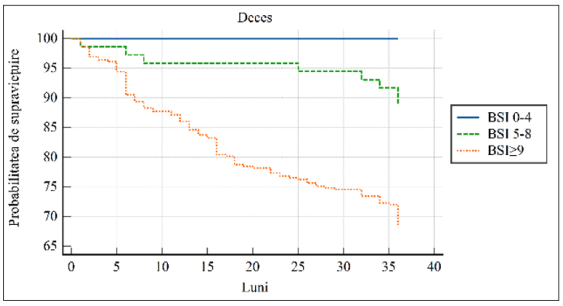
Logrank test; p<0,0001



Logrank test; p=0,02;

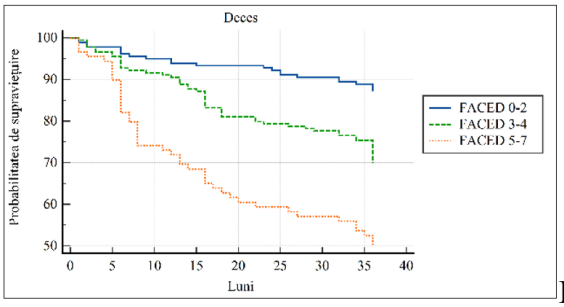


Logrank test; p=0,04



A

Logrank test; p<0,0001



B

Logrank test; p<0,0001

Figure 5 Kaplan-Meier curves illustrating the survival of NCFB patients

Table 12 Multivariate Cox regression analysis of factors associated with survival

Variabile	β- coeficient	SE	HR	95%CI	p
Female	-0,95	0,3	0,38	0,21-0,7	0,001
Age	0,02	0,01	1,02	1,01-1,04	0,002
mMRC	0,48	0,17	1,62	1,16-2,28	0,005
BMI	-0,04	0,01	0,95	0,92-0,99	0,03
History of pneumonic exacerbations	0,44	0,22	1,56	1,01-2,42	0,04
Cystic bronchiectasis	-0,21	0,29	0,8	0,44-1,44	0,47
Segmental/lobar atelectasis	0,06	0,3	0,8	0,58-1,94	0,84

mReiff score	0,01	0,04	1,01	0,92-1,09	0,84
Bhalla score	0,005	0,04	1,01	0,92-1,09	0,89
Goddard score	-0,03	0,02	0,96	0,92-1,01	0,1
FEV1	0,01	0,01	1,01	0,99-1,03	0,17
FVC	-0,01	0,01	0,98	0,96-1	0,12
DLCO	-0,02	0,01	0,97	0,96-0,99	0,004
SaO_2	-0,04	0,01	0,95	0,92-0,99	0,01
P.aeruginosa	0,53	0,26	1,7	1,01-2,87	0,04

Model: $\chi 2=113$; DF=16; $p<0,0001$
AUC: 0,82 (95%CI: 0,78-0,86)

5.4 Phenotypes in adult patients with bronchiectasis

The method of principal components analysis was used for the hierarchical clustering, and the components with Eigen values >1 have been included in the analysis. Thus, 3 main components were identified (table 13).

Table 13 Correlation of the variables with the three components selected by the method of principal components analysis

	Components		
	1	2	3
Number of affected lobes	0,229	**-0,563**	-0,051
P.aeruginosa	0,254	**-0,759**	-0,359
Men	**-0,819**	-0,105	-0,003
Smokers	**-0,858**	-0,156	0,013
BSI	-0,058	**-0,710**	-0,130
COPD	**-0,762**	-0,120	-0,114
Chronic pulmonary aspergillosis	-0,024	-0,261	**0,710**
TB treatment history	-0,034	0,190	**-0,681**

NB: marked values were statistically significant.

According to the obtained dendrograms, the optimal number of clusters was chosen, which in our group of patients identified 3 clusters (figure 6).
The characteristics of the three identified phenotypes are presented in table 14.

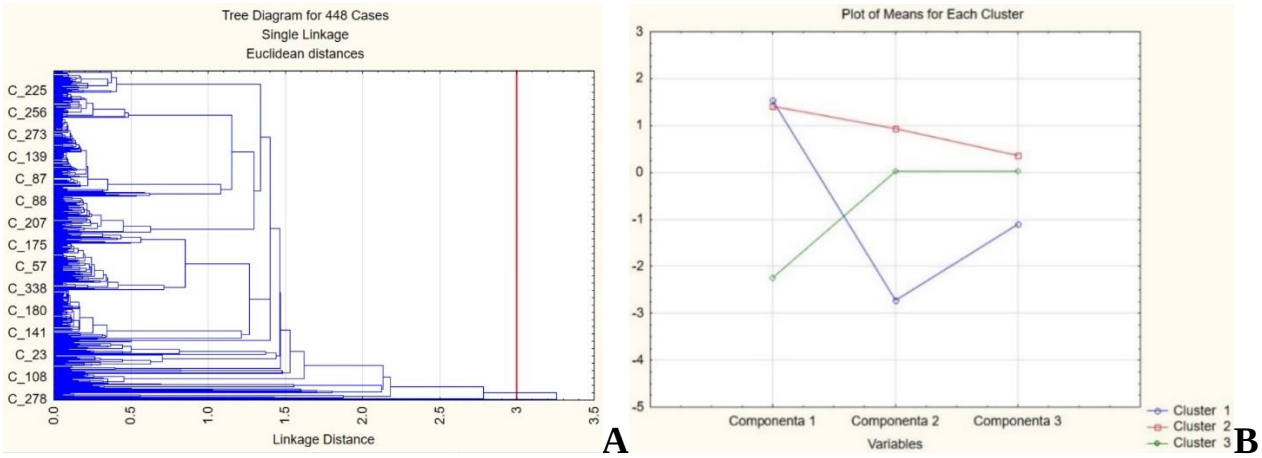


Figure 6
A - Dendrogram illustrating the results from the hierarchical cluster analysis
B - Differentiation of clusters by component means

Table 14 Characteristics of the three phenotypes of NCFB

	Phenotype 1 Elderly, diffuse BR, colonized with *P.aeruginosa*, severe disease, idiopathic etiology	**Phenotype 2** Young, women, moderate severity, postinfectious etiology	**Phenotype 3** Elderly, male, etiology COPD related BR, high number of comorbidities
Age, years	Elderly	Young	Elderly
Sex	Women	Women	Barbie
Obstruction	Severe	Moderate	Severe
Frequent exacerbations	Yes	Not	Yes
Severe emphysema	Not	Not	Yes
Extensive bronchiectasis	Yes	Not	Not
Frequent hemoptysis	Yes	Not	Not
Smoking	Smoking	Smoking	Smoking
Predominantly cystic bronchiectasis	Yes	Not	Not
Atelectasis	Yes	Not	Not
Etiology	Idiopathic	Postinfectious	COPD related BR
P.aeruginosa	Yes	Not	Not
High comorbidity index	Not	Not	Yes
Higher risk of death	Yes	Not	Yes

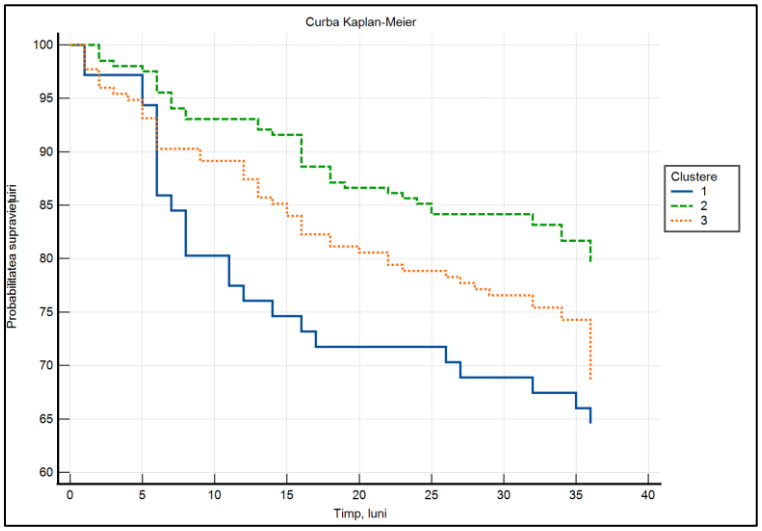
For each phenotype an association with the etiology was also been determined. Thus, phenotype 1 is characterized by idiopathic etiology, predominantly women, elderly, frequent exacerbators, non-smokers, with severe bronchiectasis, cystic pattern, severe obstructive syndrome, frequently associates lobar/segmental atelectasis, hemoptysis and colonization with *P.aeruginosa*, have an increased risk of death.

Phenotype 2 is characterized by post-infectious etiology, predominantly women, young age, non-smokers, moderate severity obstruction, low risk of death.

Phenotype 3 is characterized by the etiology of BR associated with COPD, predominantly male, elderly, smokers, frequent exacerbators with severe emphysema, high comorbidity index and increased risk of death.

For survival analysis in various clusters, we used the Kaplan-Meier method and the logistic regression method. Statistically significant differences in mortality rate were observed between the phenotypes (figure 7).

Phenotype 1 has the highest death rate compared to the other 2 phenotypes, with the largest difference being with phenotype 2 with an HR of 2.0 (95%CI 1,17-3,4). For phenotype 3 the HR was 1,21 (95%CI 0,7-2,11). Phenotype 3 presents a higher risk of death compared to phenotype 2 - HR 1,64 (95%CI 1,11-2,42).



Logrank 9,64; p=0,008

Figure 7 Kaplan-Meier survival curves for the three phenotypes identified in NCFB patients

An algorithm for bronchiectasis management was elaborated based on the identified phenotypes in the studied group (figure 8).

6. SYNTHESIZING STUDY RESULTS IN A SYSTEMATIC REVIEW

This chapter of own results' synthesis includes the theoretical results interpretations of other researchers with the results obtained in the current study, representing the largest published series of adult patients with NCFB from the Republic of Moldova.

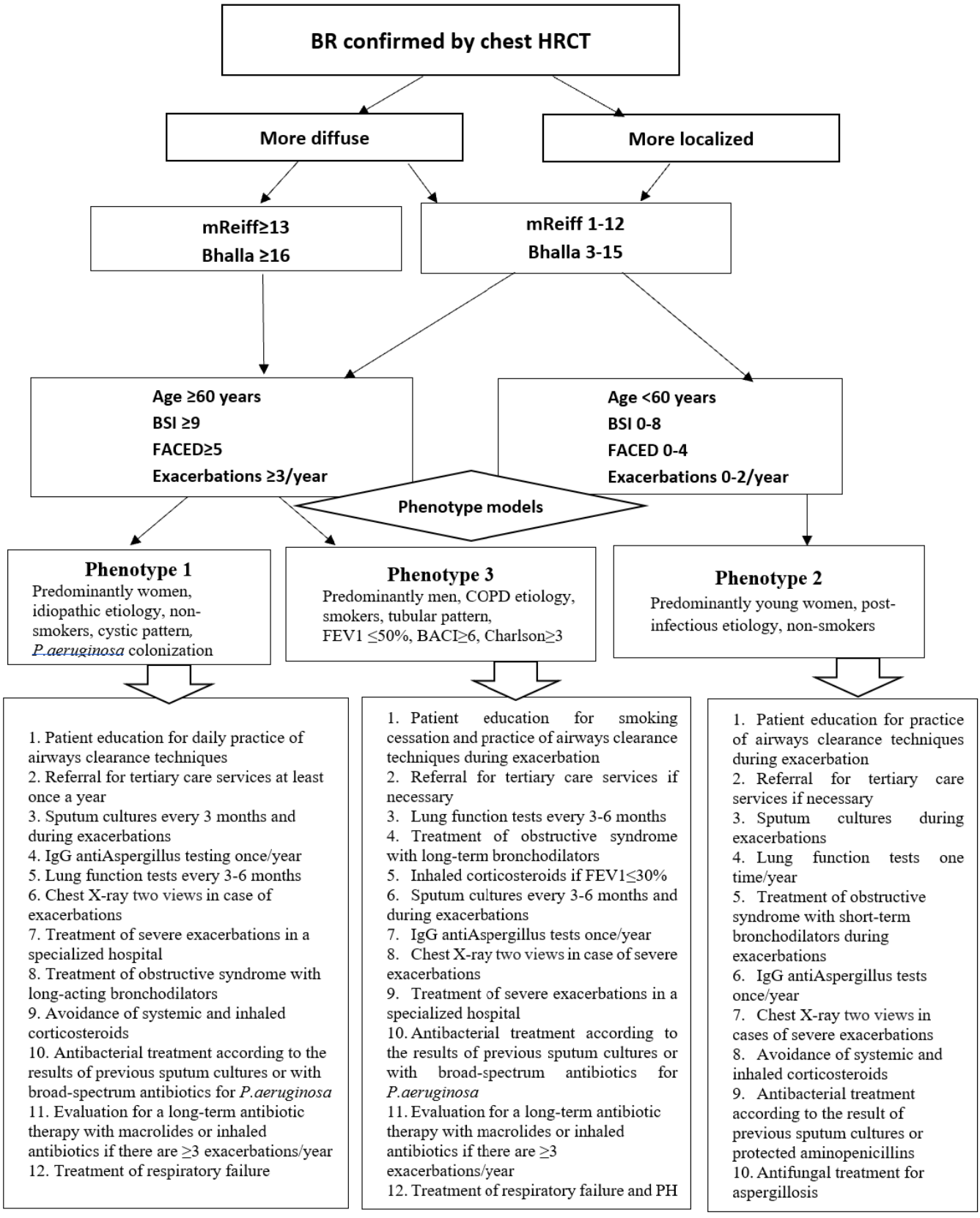


Figure 8 Management algorithm of the adult bronchiectasis patient according to the identified phenotype

GENERAL CONCLUSIONS

1. In adults, bronchiectasis have various causes, the most common being post-infectious (35%), idiopathic (30%) and COPD associated bronchiectasis (18%). Rare etiologies (9%) include congenital malformations, rare genetic diseases, systemic inflammatory conditions, gastroesophageal reflux, foreign body aspiration and opportunistic infections (mycoses, NTM). An important number of patients had a significant diagnostic delay, being diagnosed, on the occasion of this study, already in an advanced form of the disease, with colonization by potentially pathogenic germs, *P.aeruginosa* being the most frequent isolated germ.
2. Bacteriological examination of sputum in exacerbations was positive in 65% of cases (292/448), in most of these (62%, 182/292) pathogenic bacteria were identified, *Mycobacterium tuberculosis* (MBT) has been detected in 7,5% (22/292) and fungi of the genus *Aspergillus* in 2% (7/292). Fibrobronchoscopy specimens increased the positivity rate for MBT (2 cases) and NTM (1 case); however, the overall rate of bacteria isolation was reduced, probably due to the fact that fibrobronchoscopy was commonly performed after a few days of antibiotic therapy. In all patients with bronchiectasis, important obstructive ventilatory dysfunction was found (significantly more pronounced in patients with *P.aeruginosa* and *Aspergillus*, in whom the most severe imaging features were also noted).
3. High-resolution computed tomography of the chest (HRCT) is highly superior to radiography in detecting bronchiectasis, allowing the assessment of their morphology, distribution and extension, sometimes identifying suggestive signs for the bronchiectasis' etiology and disease activity (hydro-air levels, bronchiolitis, mucus plugging). The imaging patterns of bronchiectasis correlated with the disease severity, a greater frequency of the cystic pattern was seen in the group of idiopathic and posttuberculosis bronchiectasis, and the cylindrical pattern in the group of COPD and asthma associated BR. "Imaging severity" in bronchiectasis, especially when applying specific imaging scores, correlates with impaired lung function, isolation of *P.aeruginosa*, association of fungal infection, a greater number of exacerbations and hospitalizations.
4. Distribution of bronchiectasis severity grades when assessed by multidimensional indices is different of that evaluated by the imaging pattern. The bronchiectasis multidimensional indices (BSI, FACED, E-FACED) allowed identification of severe forms of the disease with an increased risk of death (statistically significant differences between the Kaplan-Meier survival curves depending on the severity of the indices were shown). The multidimensional severity indices correlate with patients' quality of life (on all domains of the quality of life questionnaire except for "treatment impact") and show a weak correlation with the BACI and Charlson comorbidity indices.
5. Out of 30 comorbidities identified in patients with NCFB, 18 were associated with increased mortality in univariate Cox proportional hazard analysis and only 3 comorbidities were identified in multivariate Cox analysis as independent predictors of death: PH (HR 1, 7; 95%CI: 1.17-2.7; p=0.006); COPD (HR 1.66; 95%CI: 1.08-2.6; p=0.01) and HIV infection (HR 4.9; 95%CI: 2.37-10.1; p<0, 0001).

6. Pulmonary artery trunk diameter (cut off >29.8 mm) measured by thorax HRCT has been shown to be a promising imaging parameter, for identification of patients requiring further evaluation for pulmonary hypertension. In patients with NCFB, pulmonary hypertension was found in a significant number of cases (30.6%), especially in those with BR associated with COPD (49%), as predictive factors being SaO2<90%, COPD, BSI index, Bhalla score, exacerbations ≥3/year. The presence of PH in patients with NSFB is associated with an increased risk for death (RR 1.77; p=0.006).
7. Serum levels of the inflammatory markers (C-reactive protein and leukocyte count) showed statistically significant differences between the group of bronchiectasis with pneumonic exacerbations (had higher values) versus those in non-pneumonic exacerbations group (p=0.000001), however there are no differences in platelet count and erythrocyte sedimentation rate. However, by ROC analysis the discriminatory power in differentiating between pneumonic and non-pneumonic exacerbations was found to be poor, both for C-reactive protein (AUC 0.63) and leukocyte count (AUC 0.57). Thus, it remains critically important to perform a chest radiography to identify cases complicated by pneumonia during exacerbations.
8. Cluster analysis identified 3 groups of patients with different clinical and paraclinical features (gender, age, imaging severity, bacterial colonization, etiology), which describe 3 phenotypes with different prognosis in long-term outcome (lung function impairment, frequency of exacerbations, mortality) with potential application in the individualized management of patients with NCFB.
9. Hemoptysis, cystic bronchiectasis, cirrhosis of lung segments or lobes have been identified as risk factors for chronic colonization with *P.aeruginosa*, which is associated with severe forms of the disease and more important impairment of lung function. Posttuberculosis etiology, presence of cystic bronchiectasis or residual cavities have been identified as risk factors for the development of chronic pulmonary aspergillosis. Among the clinical and paraclinical features, advanced age, severe dyspnea (mMRC), *P.aeruginosa* colonization, history of pneumonic exacerbations, decreased DLCO, and reduced SaO2 were found to be independent predictors of death. Multidimensional indices of severity [BSI (HR 1.08; 95%CI: 1,01-1,17; p=0,03), FACED (HR 1,18; 95%CI: 1,01-1,39; p=0,04)] and BACI comorbidity index (HR 1,11; 95%CI: 1,07-1,15; p<0,0001) were shown to be independent predictors of death in Cox multivariate analysis.
10. The complex evaluation of clinical data, functional parameters, imaging and bacteriological characteristics combined with the assessment of multidimensional indices allowed development of a diagnostic and management algorithm for adult patients with bronchiectasis which consider a personalized approach based on the identified phenotypes.

PRACTICAL RECOMMENDATIONS

1. The performed study showed an unexpectedly high prevalence of severe forms of bronchiectasis, marked by an important diagnostic delay, therefore bronchiectasis should be suspected in patients with long standing chronic respiratory diseases, being suggested by the clinical picture and confirmed on chest HRCT, radiography is a less

sensitive method, especially for mild forms of bronchiectasis and in patients with severe emphysema.

2. It is recommended to use the "Diagnostic Algorithm in Bronchiectasis" and the "Management Algorithm in Bronchiectasis" in order to optimize the management of patients with non-cystic fibrosis bronchiectasis.

3. Primary diagnosed patients with bronchiectasis on chest HRCT should be evaluated in a tertiary level institution to identify the etiology of bronchiectasis and potentially treatable causes.

4. BSI and FACED multidimensional indices are useful in the triage of patients with bronchiectasis to identify severe forms of the disease, which will require annual evaluation at the tertiary level.

5. The Aspergillus ICT IgG-IgM rapid test (based on lateral flow immunochromatography technology) should be used to identify cases of aspergillosis among patients with bronchiectasis.

6. The measurement of the diameter of the pulmonary artery trunk is recommended during HRCT scan performed in patients with bronchiectasis and in cases with a diameter over 29 mm the assessment by additional methods for PH to confirm and initiate treatment is recommended.

7. The initiation of antibiotic therapy will be preceded by sputum sampling for culture and drug susceptibility testing for optimal management during of current and future exacerbations.

8. Mandatory bacteriological monitoring every 3 months (by sputum cultures) for patients with at least one positive *P.aeruginosa* sputum isolate , in order to identify patients who require eradication treatment r long-term antibiotic treatment.

9. Use of nebulization with hypertonic solution with chronic sputum production.

10. Use of kinesitherapy techniques in patients with imaging signs of mucoid impaction.

11. Use of long-acting bronchodilators in patients with obstructive syndrome confirmed by pulmonary function tests and avoidance of ICS, except for patients with GOLD III-IV asthma and COPD.

12. Mandatory chest radiography (in two incidences) in patients with exacerbations with C-reactive protein above 24 mg/dl to identify cases complicated by pneumonia.

SELECTIVE BIBLIOGRAPHY

1. CHALMERS, J.D., et al. The bronchiectasis severity index. An international derivation and validation study. *Am J Respir Crit Care Med*, 2014, 189(5), p. 576-585.
2. ALIBERTI, S., et al. Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations. *Lancet Respir Med*, 2022, 10(3), p. 298-306.
3. MUNTEANU, O. Bronșiectaziile la adult. 2021, Chisinau: Print Caro. 222 p.
4. GOEMINNE, P.C., DE SOYZA, A. Bronchiectasis: how to be an orphan with many parents? *Eur Respir J*, 2016, 47(1), p. 10-13.
5. ALIBERTI, S., et al. Comparison of different sets of immunological tests to identify treatable immunodeficiencies in adult bronchiectasis patients. *ERJ Open Res*, 2022, 8(1).
6. MARTINEZ-GARCIA, M.A., POLVERINO, E., AKSAMIT, T. Bronchiectasis and Chronic Airway Disease: It Is Not Just About Asthma and COPD. *Chest*, 2018, 154(4), p. 737-739.
7. HURST, J.R., et al. COPD-bronchiectasis overlap syndrome. *Eur Respir J*, 2015, 45(2), p. 310-313.
8. LONNI, S., et al. Etiology of Non-Cystic Fibrosis Bronchiectasis in Adults and Its Correlation to Disease Severity. *Ann Am Thorac Soc*, 2015, 12(12), p. 1764-1770.
9. MARTINEZ-GARCIA, M.A., et al. The Multiple Faces of Non-Cystic Fibrosis Bronchiectasis. A Cluster Analysis Approach. *Ann Am Thorac Soc*, 2016, 13(9), p. 1468-1475.
10. ALIBERTI, S., et al. Clinical phenotypes in adult patients with bronchiectasis. *Eur Respir J*, 2016, 47(4), p. 1113-1122.
11. DENNING, D.W., et al. Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. *Eur Respir J*, 2016, 47(1), p. 45-68.
12. POLVERINO, E., CACHERIS W, SPENCER C, OPERSCHALL E, DONNELL AE. Global burden of non-cystic fibrosis bronchiectasis: A simple epidemiological analysis. *ERJ* 2014, 40(56), p. P3983.
13. MUNTEANU, O., et al. Chronic pulmonary aspergillosis in patients with post-tuberculosis bronchiectasis. *European Respiratory Journal*, 2018, 52(suppl 62), p. PA2743.
14. DEVARAJ, A., et al. Pulmonary hypertension in patients with bronchiectasis: prognostic significance of CT signs. *AJR Am J Roentgenol*, 2011, 196(6), p. 1300-1304.
15. BOTNARU, V., MUNTEANU O., CALARAȘ D. Bronșiectaziile la adult. *Protocol Clinic Național 275*, 2017, p. 49.
16. POLVERINO, E., et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J*, 2017, 50(3).
17. REIFF, D.B., et al. CT findings in bronchiectasis: limited value in distinguishing between idiopathic and specific types. *AJR Am J Roentgenol*, 1995, 165(2), p. 261-267.
18. BHALLA, M., et al. Cystic fibrosis: scoring system with thin-section CT. *Radiology*, 1991, 179(3), p. 783-788.
19. BEDI, P., et al. The BRICS (Bronchiectasis Radiologically Indexed CT Score): A Multicenter Study Score for Use in Idiopathic and Postinfective Bronchiectasis. *Chest*, 2017.
20. GODDARD, P.R., et al. Computed tomography in pulmonary emphysema. *Clin Radiol*, 1982, 33(4), p. 379-387.
21. MCDONNELL, M.J., et al. Multidimensional severity assessment in bronchiectasis: an analysis of seven European cohorts. *Thorax*, 2016, 71(12), p. 1110-1118.
22. MARTINEZ-GARCIA, M.A., et al. Predicting high risk of exacerbations in bronchiectasis: the E-FACED score. *Int J Chron Obstruct Pulmon Dis*, 2017, 12, p. 275-284.
23. CHARLSON, M., et al. Validation of a combined comorbidity index. *J Clin Epidemiol*, 1994, 47(11), p. 1245-1251.

24. MCDONNELL, M.J., et al. Comorbidities and the risk of mortality in patients with bronchiectasis: an international multicentre cohort study. *Lancet Respir Med*, 2016, 4(12), p. 969-979.
25. REID, L.M. Reduction in bronchial subdivision in bronchiectasis. *Thorax*, 1950, 5(3), p. 233-247.

LIST OF PUBLICATIONS

1. Monographs

1.1. MUNTEANU, Oxana. Bronșiectaziile la adult. Chișinău: Tipografia *Balacron*, 2021, 222 p. ISBN 978-9975-56-913-2.

2. Articles

2.1. **Cited in SCOPUS and *ISI-Thomson***

2.1.1 MUNTEANU, Oxana, SALZER, Helmut. Non-cystic fibrosis bronchiectasis: from programmatic management to personalized medicine. In: *Respiration*. 2017, 93: pp. 404-405. DOI10.1159/000473885. ISSN 0025-7931.

2.1.2 MUNTEANU, Oxana. Granulomatous nodules: know the ropes. *In: Respiration*. 2017, 93: pp. 396-397. DOI 10.1159/000471926. ISSN 0025-7931.

2.1.3 BOTNARU, Victor, et al. A rare genetic cause of bronchiectasis. *In: Pneumologia*. 2016, vol. 65, nr. 4, pp. 216-221. ISSN 2067–2993.

2.1.4 GODET, Cendrine et al. A CPAnet consensus statement on research priorities for chronic pulmonary aspergillosis: a neglected fungal infection that requires attention. In: *J Antimicrob Chemother*. 2017, EISSN 1460-209, DOI10.1093/jac/dkx390, p. 1-7. ISSN 0305-7453.

2.1.5 ALASTRUEY-IZQUIERDO, Ana et al. Treatment of chronic pulmonary aspergillosis: current standards and future perspectives. In: *Respiration.* 2018; 6:1-12. ISSN 0025-7931.

2.1.6 MUNTEANU, Oxana et al. Pictorial essay in bronchiectasis: diagnosis and beyond. *In: Pneumologia*. 2018, vol. 67, nr. 3, pp. 108-118. ISSN 2067–2993.

2.1.7 MUNTEANU, Oxana et al. Long-term follow-up: tuberculosis, bronchiectasis and chronic pulmonary aspergillosis. In: *Pneumologia*. 2019, vol. 68, nr. 3, pp. 138-143. ISSN 2067–2993.

2.1.8 MUNTEANU, Oxana et al. Cystic echinococcosis: an attraction for fungal and bacterial pulmonary infections. In: *Pneumologia*. 2019, vol. 68, nr. 4, pp. 57-63. ISSN 2067–2993.

2.1.9 LAURSEN, Christian et al. CPAnet Registry - An International Chronic Pulmonary Aspergillosis Registry. In: *J. Fungi.* 2020, 6(3), 96. DOI 10.3390/jof6030096. ISSN: 2309-608X.

2.1.10 VAN BRAECKELM Eva et al. Treatment outcome definitions in chronic pulmonary aspergillosis: a CPAnet consensus statement. In: *European Respiratory Journal, 2022*, DOI: 10.1183/13993003.02950-2021. ISSN: 0903-1936.

2.2. **Articles in accredited national scientific journals:**

- ***grade B+***

2.2.1 MUNTEANU, Oxana et al. Assessment of bronchiectasis in adult HIV/AIDS patients. In: *The Moldovan Journal.* 2020, nr. 5 (63), pp. 19-25. DOI: 10.5281/zenodo.4018906.

- ***grade B***

2.2.2 MUNTEANU, Oxana, ONEA, Leonid, BOTNARU, Victor. Bronhia traheală – cauză rară de bronșiectazii. In: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale.* Chișinău, 2016, nr 1(50), pp. 366-368. ISSN 1857-0011.

2.2.3 CHESOV, Dumitru et al. Diagnosticul imagistic al tuberculozei în era multidrogrezistenței. In: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale.* Chișinău, 2016, nr. 1(50), pp. 299-304. ISSN 1857-0011.

2.2.4 BOTNARU, Victor, MUNTEANU, Oxana, RUSU, Doina. Strategiile tratamentului antibacterian la pacienții adulți cu bronșiectazii non fibroză chistică. In: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale.* Chișinău, 2016, nr 1(50), pp. 309-314. ISSN 1857-0011.

2.2.5 MUNTEANU, Oxana et al. Bronșiectazii, tuberculoză și Aspergillus: dificultăți și perspective. In: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale.* Chișinău, 2017, nr 3(55), pp. 48-53. ISSN 1857-0011.

2.2.6 BOTNARU, Victor, et al. Aprecierea calității vieții la pacienții cu bronșiectazii non-fibroză chistică. In: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale.* Chișinău, 2017, nr 3 55), pp. 53-57. ISSN 1857-0011.

2.2.7 BOTNARU, Victor et al. Hemoptizie din două boli severe. In: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale.* Chișinău, 2017, nr 3(55), pp. 128-132. ISSN 1857-0011.

2.2.8 BOTNARU, Victor, MUNTEANU, Oxana, CONDRAȚCHI, Diana. Calcificări multiple – un martor taciturn al bolii de altă dată. In: *Moldovan Journal of Health Sciences/Revista de Ştiinţe ale Sănătăţii din Moldova.* 2017, nr. 4, pp.123-126. ISSN 2345-1467.

2.2.9 BOTNARU, Victor et al. Anomalii traheobronșice și infecţii asociate. In: *Moldovan Journal of Health Sciences/Revista de Ştiinţe ale Sănătăţii din Moldova.* 2018, nr. 1, pp.102-109. ISSN 2345-1467.

2.2.10 BOTNARU, Victor et al. Amprente ale unei patologii pulmonare cronice. In: *Moldovan Journal of Health Sciences/Revista de Ştiinţe ale Sănătăţii din Moldova.* 2019, nr. 2, pp. 110-117. ISSN 2345-1467.

2.2.11 MUNTEANU, Oxana. Bronșiectaziile la pacienții adulți cu diskinezie ciliară primară. In: *Sănătate Publică, Economie şi Management în Medicină.* 2020, nr. 1(83), pp. 25-30. ISSN 1729-8687.

2.2.12 MUNTEANU, Oxana. Bronșiectaziile la pacientul vârstnic. In: *Sănătate Publică, Economie şi Management în Medicină*. 2020, nr. 4(86), pp. 52-58. ISSN 1729-8687.

2.2.13 MUNTEANU, Oxana. Fibroza chistică la adult: realizări și perspective în Republica Moldova. In: *Buletin de Perinatologie*. 2020; 4(89), pp. 33-38. ISSN 1810-5289.

2.2.14 BOTNARU, Victor, CHESOV, Dumitru, MUNTEANU, Oxana. Verum aut Falsum Cavitas. In: *Moldovan Journal of Health Sciences/Revista de Ştiinţe ale Sănătăţii din Moldova.* 2016, nr.1, pp. 113-115. ISSN 2345-1467.

2.2.15 BOTNARU, Victor, MUNTEANU, Oxana, ONEA, Leonid. Cauză rară de infecţii respiratorii recurente. In: *Moldovan Journal of Health Sciences/Revista de Ştiinţe ale Sănătăţii din Moldova.* 2015, nr. 4, pp.100-103. ISSN 2345-1467.

2.2.16 MUNTEANU, Oxana. Terapii antibiotice actualizate și riscul dezvoltării rezistenței la antibiotice la pacienții adulți cu bronșiectazii non-fibrochistice. In: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale.* Chișinău, 2019, nr. 2(62), pp.141-146. ISSN 1857-0011.

2.2.17 MUNTEANU, Oxana. Bronșiectaziile punct de plecare în diagnosticul aspergilozei bronhopulmonare alergice. In: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale.* Chișinău, 2019, nr. 3(63), pp.156-161. ISSN 1857-0011.

2.2.18 MUNTEANU, Oxana, BOTNARU, Victor. Micobacterii netuberculoase și bronșiectazii. In: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale.* Chișinău, 2021, nr. 1(69), pp. 202-208. ISSN 1857-0011.

2.2.19 CEBOTARU, Aurelia, et al. Aspergiloza pulmonară asociată infecției prin COVID-19. In: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale.* Chișinău, 2021, nr. 1(69), pp. 170-174. ISSN 1857-0011.

3. Abstracts

3.1 Abstracts of international scientific conferences proceedings

3.1.1 BOTNARU, Victor, MUNTEANU, Oxana, RUSU, Doina. Combination of non CF-bronchiectasis and calcifications: a hallmark of high burden TB country. In: *1st World Bronchiectasis Conference. Abstract Book.* Hanover, Germania, 2016, p. 4.

3.1.2 MUNTEANU, Oxana et al. Detection of tuberculous etiology of bronchiectasis in a high burden TB country. *In: European Respiratory Journal. 2015, 46(suppl59), PA2731. DOI: 10.1183/13993003.congress- 2015.PA2731. ISSN: 0903-1936.*

3.1.3 MUNTEANU, Oxana et al. *Non-CF bronchiectasis in a Moldovan population: etiologic, radiological, microbiological and functional profile. In: ERJ. 2016, 48 (suppl 60), PA2557. DOI: 10.1183/13993003.congress- 016.PA2557. ISSN: 0903-1936.*

3.1.4 MUNTEANU, Oxana et al. Malformație chistică adenomatoidă congenitală la adult – prezentare de caz. In: *Program științific și rezumate. XXIV Congres al SRP.* Brașov, România, 2016, p. 59. ISSN 2285-1607.

3.1.5 MUNTEANU, Oxana et al. *Overlap BPOC și bronșiectazii – este oare important?* In: *Program științific și rezumate. XXIV Congres al SRP* Brașov, România, 2016, p. 38. ISSN 2285-1607.

3.1.6 MUNTEANU, Oxana et al. Late diagnosed unilateral pulmonary vascular abnormalities in advanced non-CF bronchiectasis. In: *2-nd World Bronchiectasis Conference. Abstract Book.* Milano, Italy, 2017, pp.113-114.

3.1.7 MUNTEANU, Oxana et al. Clinical, imaging and functional correlations in patients with non-CF bronchiectasis and Pseudomonas aeruginosa: the experience of a country center. In: 2-*nd World Bronchiectasis Conference. Abstract Book.* Milano, Italy, 2017, p.115.

3.1.8 MUNTEANU, Oxana et al. What is the relevance of COPD–bronchiectasis overlap for patients who fulfil both diagnoses? In: *2-nd World Bronchiectasis Conference. Abstract Book.* Milano, Italy, 2017, p.112.

3.1.9 MUNTEANU, Oxana et al. Adult bronchiectasis patients: microbiological insight in the Moldovan Bronchiectasis Registry. *In: European Respiratory Journal. 2017, 50 (61).*PA4016; doi: 10.1183/1393003.congress-2017. PA4016. *ISSN: 0903-1936.*

3.1.10 MUNTEANU, Oxana et al. Chronic lobe collapse: another bronchiectasis phenotype or a marker of Pseudomonas colonisation? *In: European Respiratory Journal. 2017, 50 (suppl 61).* PA4065; doi**:** 10.1183/1393003.congress-2017. PA4065. *ISSN: 0903-1936.*

3.1.11 MUNTEANU, Oxana et al. *Chronic pulmonary aspergillosis in patients with bronchiectasis. In: Abstract book ISHAM 2018, Medical Mycology. 2018, 56, S1–S159, 111s., doi: 10.1093/mmy/myy036, p. 222.*

3.1.12 MUNTEANU, Oxana, et al. Paratracheal air cysts in patients with non-CF bronchiectasis. In: *European Respiratory Journal*. 2018, 52(62). PA2671; doi: 10.1183/1393003.congress-2018. PA2671. ISSN: 0903-1936.

3.1.13 MUNTEANU, Oxana et al. Chronic pulmonary aspergillosis in patients with post-tuberculosis bronchiectasis. *In: European Respiratory Journal, Sep 2018, 52(62).* PA2743; doi**:** 10.1183/1393003.congress-2018. PA2743. *ISSN: 0903-1936.*

3.1.14 *BOTNARU, Victor, MUNTEANU, Oxana.* Amprenta tuberculoasă și aspergiloza pulmonară cronică. In: *Al XXV –lea Congres al SRP.* 2018, Poiana Brașov, România. CD: ISBN:978-973-0-27977-1.

3.1.15 MUNTEANU, Oxana et al. Astm, bronșiectazii si *Aspergillus*: evidențe și întrebări. In: *Al XXV –lea Congres al Societății de Pneumologie*, 2018, Poiana Brașov, România. CD: ISBN:978-973-0-27977-1.

3.1.16 MUNTEANU, Oxana et al. Two cases of endobronchial aspergilloma in patients with non-CF bronchiectasis. In*: ERS Research Seminar: The interaction between airways disease and bronchiectasis - An initiative of the EMBARC and SHARP CRCs.* 2019, Barcelona, Spania, p. 42.

3.1.17 MUNTEANU, Oxana et al. Dueling diseases - seven cases of Swyer-James-MacLeod syndrome in non-CF bronchiectasis adult patients. *In: European Respiratory Journal. 2019, 54(suppl 63).* PA4579; doi: 10.1183/13993003.congress-2019. PA4579. *ISSN: 0903-1936.*

3.1.18 BRAECKEL, Eva et al. Late Breaking Abstract - CPAnet Registry – An International Chronic Pulmonary Aspergillosis Registry. In: *European Respiratory Journal*. 2020, 56(64) 4929; DOI: 10.1183/13993003.congress-2020. *ISSN: 0903-1936.*

3.1.19 CHESOV, Dumitru et al. Role of bronchial aspirate samples for the diagnosis of pulmonary tuberculosis in patients with negative smear and negative Xpert MTB/Rif in sputum. In: *European Respiratory Journal.* 2020, 56(64) 530; DOI**:** 10.1183/13993003.congress-2020.530. *ISSN: 0903-1936.*

3.1.20 MUNTEANU, Oxana et al. *Aspergillus*-related diseases: challenges in adults with cystic fibrosis. In: *Al XXVI –lea Congres al Societății de Pneumologie*. 2020, România. CD: ISBN:978-973-0-27977-1.

3.1.21 MUNTEANU, Oxana et al. Haemoptysis - a link symptom between chronic pulmonary aspergillosis and pulmonary embolism. In: *Al XXVI –lea Congres al SRP*. 2020, România. CD:ISBN:978-973-0-27977-1.

3.2 *Abstracts of national scientific conferences proceedings*

3.2.1 VOLOȘCIUC, Irina, MUNTEANU, Oxana, RUSU, Doina. Characteristics of the frequent exacerbator with non-cystic fibrosis bronchiectasis. In: *Abstract book, Congresul consacrat aniversării a 75-a de la fondarea Universității de Stat de Medicină şi Farmacie „Nicolae Testemiţanu”*. Chișinău, 2020, p. 271.

3.2.2 BOTNARU, Victor, MUNTEANU, Oxana. Chronic pulmonary aspergillosis: diagnostic and treatment challenge. In: *Abstract book, Congresul consacrat aniversării a 75-a de la fondarea Universității de Stat de Medicină şi Farmacie „Nicolae Testemiţanu”*. Chișinău, 2020, p. 276.

3.2.3 CEBOTARU, Aurelia et al. Mutilating fungal infection - diagnostic surprise in a patient with post tuberculosis sequelae. In: *Abstract book, Congresul consacrat aniversării a 75-a de la fondarea Universității de Stat de Medicină şi Farmacie „Nicolae Testemiţanu”*. Chișinău, 2020, p. 278.

3.2.4 MUNTEANU, Oxana et al. Assessment of bronchiectasis in adult HIV/AIDS patients: a case series. In: *Abstract book, Congresul consacrat aniversării a 75-a de la fondarea Universității de Stat de Medicină şi Farmacie „Nicolae Testemiţanu”*. Chișinău, 2020, p. 296.

3.2.5 MUNTEANU, O. et al. Non-cystic fibrosis bronchiectasis and calcifications: are IGRAs of any use? In: *Abstract book, Congresul consacrat aniversării a 75-a de la fondarea Universității de Stat de Medicină şi Farmacie „Nicolae Testemiţanu”*. Chișinău, 2020, p. 297.

3.2.6 TAMBALA, Diana, BOTNARU, Victor, MUNTEANU, Oxana. Parathymic syndromes in a young patient with thymoma: bronchiectasis, erythroblastopenia and ulcerative colitis. In: *Abstract book, Congresul consacrat aniversării a 75-a de la fondarea Universității de Stat de Medicină şi Farmacie „Nicolae Testemiţanu”*. Chișinău, 2020, p. 303.

3.2.7 CHESOV, Dumitru et al. Role of the bronchial aspirate samples for the diagnosis of pulmonary tuberculosis. In: *Abstract book, Congresul consacrat aniversării a 75-a de la fondarea Universității de Stat de Medicină şi Farmacie „Nicolae Testemiţanu”*. Chișinău, 2020, p. 279.

4. Scientific studies, documentary editions:

4.1 HORVATH, Ildiko et al. Summer schools of adult and pediatric respiratory medicine: course report. In: *Breathe*. 2016. 12(4): 305-308, DOI:10.1183 /20734735.017016. ISSN 2073-4735.

4.2 CIOBANU, Laura, MUNTEANU, Oxana. Pulmonary rehabilitation. In: *Breathe*. Dec 2017, 13 (4) 275-277; ISSN 2073-4735

5. Textbooks for university education

5.1 BOTNARU, Victor et al. Tuberculoza în cazuri clinice comentate. Chişinău: Tipografia *Balacron*. 2018, 300 p. ISBN 978-9975-3255-4-7.

5.2 BOTNARU, Victor et al. Pneumologia în tabele și cazuri clinice. Chișinău: Tipografia *Balacron*. 2020, 346 p. ISBN 978-9975-66-701-2.

6. Methodological guidelines

6.1 BOTNARU, Victor, MUNTEANU, Oxana. Imagistica toracică în cazuri clinice comentate. Chişinău: Tipografia *Balacron*, 2012, 385 p. ISBN 978-9975-100-75-5.

7. Clinical protocols

7.1 BOTNARU, Victor et al. Bronșiectaziile la adult. Protocolul Clinic Naţional. Chișinău, 2017. 49 p. https://msmps.gov.md /legislatie/ghiduri-protocoale-standarde/ftiziopneumologie.

7.2 BOTNARU, Victor et al. Aspergiloza bronhopulmonară alergică la adult. Protocolul Clinic Național. Chișinău, 2020. 47 p. https://msmps.gov.md /legislatie/ghiduri-protocoale-standarde/ftiziopneumologie.

ADNOTARE
Munteanu Oxana
„Manifestările clinico-imagistice, funcționale și microbiologice în bronșiectazii la adult”
Teză de doctor habilitat în medicină, Chișinău, 2022

Structura tezei: introducere, șase capitole, concluzii, bibliografia din 401 surse, 86 de figuri, 92 de tabele, 1 anexă. Rezultatele studiului au fost publicate în 67 de lucrări științifice.

Cuvinte cheie: bronșiectazii, etiologie, imagistică, Pseudomonas, fenotip, aspergiloză.

Domeniul de studiu: medicina internă, pulmonologie.

Scopul cercetării: evidențierea particularităților etiologice și fenotipice, corelate cu aspectele clinico-imagistice, funcționale și microbiologice, pentru elaborarea strategiei de conduită în bronșiectazii la adulți.

Obiectivele cercetării: determinarea profilului etiologic al bronșiectaziilor la adult; evidențierea spectrului microbiologic în bronșiectazii corelat cu *pattern*-ul funcțional și imagistic; evaluarea semnificației diagnostice și prognostice a metodelor imagistice în bronșiectazii; relevarea rolului abordării multidimensionale în conduita pacienților cu bronșiectazii, inclusiv prin aplicarea unor instrumente de severitate (BSI, FACED, E-FACED) și de evaluare a comorbidităților (BACI, Charlson); evaluarea impactului hipertensiunii pulmonare la pacienții cu bronșiectazii; evaluarea rolului unor markeri inflamatori în estimarea severității exacerbărilor și în evoluția bronșiectaziilor; evidențierea unor fenotipuri de bronșiectazii cu potențial rol în abordarea personalizată a pacientului; evidențierea factorilor pentru o evoluție nefavorabilă a dilatărilor bronșice permanente de severitate diferită.

Noutatea și originalitatea științifică. În baza studiului a fost constatată și sistematizată diversitatea etiologică a bronșiectaziilor la adulți (inclusiv formele rare), cu prezentarea caracteristicilor imagistice și a testelor paraclinice necesare pentru confirmarea. Monitorizarea prin sputoculturi a scos în evidență tipurile și ponderea germenilor patogeni care colonizează căile aeriene, precum și spectrul rezistențelor bacteriene. În premieră a fost demonstrată semnificația testului rapid bazat pe imunocromatografie flux lateral în identificarea aspergilozelor pulmonare printre pacienții cu bronșiectazii. Prin analiza particularităților clinice, radiologice, microbiologice și funcționale au fost evidențiate fenotipuri de bronșiectazii, în vederea abordării personalizate a pacienților cu dilatări bronșice în Republica Moldova. A fost demonstrată valoarea aplicativă și prognostică a scorurilor imagistice și a indicilor multidimensionali în evaluarea severității bolii și impactul asupra calității vieții la pacienții cu bronșiectazii.

Rezultatele noi pentru știință și practică. În baza studiului a fost demonstrată valoarea științifică a diverselor instrumente clinice și paraclinice în evaluarea multidimensională a pacienților cu bronșiectazii, a fost consemnat rolul unor markeri inflamatori în evaluarea severității exacerbărilor și au fost stabiliți predictorii evoluției nefavorabile în bronșiectazii. A fost elucidat spectrul comorbidităților și rolul lor prognostic și a fost demonstrată utilitatea interpretării modificărilor imagistice relevante pentru diagnosticul HTP și pentru leziunile de vase coronariene prin examenul HRCT torace, care vin să completeze implementarea unor strategii moderne de diagnostic și tratament țintit pentru anumite sub-populații de pacienți.

Semnificația teoretică rezidă în elaborarea unui cadru conceptual și metodologic complex în plan analitic de explorare științifică și practică a problematicii heterogenității bronșiectaziilor. Conceptualizarea monitorizării pacientului cu bronșiectazii din perspectivă multidimensională a permis evidențierea unor corelații dintre etiologia bronșiectaziilor, manifestările imagistice, disfuncțiile ventilatorii și infecția cronică a căilor aeriene. Analiza determinantelor responsabile de severitatea bolii, cu identificarea predictorilor pentru evoluția nefavorabilă, a permis elaborarea unui algoritm de diagnostic și de conduită, oferind direcții noi în ameliorarea îngrijirii pacienților cu bronșiectazii.

Valoarea aplicativă. Rezultatele studiului au fost aplicate pentru elaborarea algoritmilor de conduită, de diagnostic diferențial și de tratament al bronșiectaziilor, cu includerea acestora în protocoalele clinice naționale.

Implementarea rezultatelor științifice. Recomandările studiului sunt utilizate în procesul didactic de pregătire a cadrelor medicale la Disciplina de Pneumologie și Alergologie, în secția de ftiziopneumologie a IMSP IFP “Chiril Draganiuc” și secția de terapie generală cu alergologie a IMSP SCR “Timofei Moșneaga”. Au fost înregistrate 3 certificate de inovator și 3 acte de implementare a rezultatelor.

ANNOTATION

Clinical, imaging, functional and microbiological manifestations of bronchiectasis in adults

Munteanu Oxana

Thesis of Habilitated Doctor of Medicine, Chisinau, 2022

Thesis structure: introduction, six chapters, conclusions, 401 bibliographic references, 86 figures, 92 tables. The results were published in 67 scientific papers.

Keywords: bronchiectasis, etiology, imaging, Pseudomonas, phenotype, aspergillosis.

Studied area: internal medicine, pulmonology

Aim of the study: To determine the etiological and phenotypical peculiarities, correlated with the clinical, imaging, functional and microbiological patterns in bronchiectasis for the proposal of the management strategy in adult patients.

Objectives of research: revealing of the etiological profile of bronchiectasis in adults; highlighting the microbiological spectrum in bronchiectasis in correlation with the functional and imaging patterns; assessment of the imaging diagnostic and prognostic significance of bronchiectasis; defining the role of the multidimensional approach in the management of patients with bronchiectasis, including severity (BSI, FACED, E-FACED) and comorbidity assessment tools (BACI, Charlson); estimation of the impact of pulmonary hypertension in patients with bronchiectasis; evaluation of some inflammatory markers in the evolution of bronchiectasis and their role in estimating the severity of exacerbations; revealing phenotypes in bronchiectasis and their potential role in the personalized treatment; highlighting the factors for an unfavorable evolution in different degrees of severity bronchiectasis.

Novelty and originality of the research: Based on the study, the etiological diversity of bronchiectasis in adults was demonstrated, including the rare etiological forms, with the presentation of imaging features and the needed paraclinical tests for their confirmation.

Sputum cultures monitoring revealed the prevalence and the types of pathogenic germs in the airways, as well as the spectrum of bacterial resistances. For the first time, the utility of the immunochromatographic rapid test was demonstrated for the identification of cases of aspergillosis among bronchiectasis patients. Several bronchiectasis phenotypes were revealed based on the analysis of clinical, radiological, microbiological and ventilatory patterns and their role in the personalized approach for patients with bronchiectasis in the Republic of Moldova was shown. The study demonstrated the prognostic value of imaging scores and multidimensional indices in assessing the severity of the disease and the impact on the quality of life of patients with bronchiectasis.

Fundamentally new scientific and practical results. Based on the study, the role of several inflammatory markers in the evaluation of the exacerbation severity, as well as the value of various clinical and paraclinical tools in the multidimensional assessment of bronchiectasis patients was demonstrated, highlighting the predictors. The spectrum of comorbidities and their prognostic role were assessed. The usefulness of imaging signs for the diagnosis of PH and of coronary lesions by using chest HRCT examination was demonstrated, underlying the role of modern diagnostic and treatment strategies in certain bronchiectasis patient sub-populations.

The theoretical significance consists in the proposal of a new complex conceptual framework for scientific and practical evaluation of the bronchiectasis heterogeneity. The long-term monitoring of the bronchiectasis patients from a multidimensional perspective highlighted some correlations according to the etiological, imaging, ventilatory patterns and chronic airway infections in the bronchiectasis patients. The analysis of the determinants responsible for the disease severity and the identification of poor evolution predictors have led to the elaboration of a new diagnostic and treatment algorithm, contributed to improving the management of the disease and the quality of patients care.

The applicative value. The results of the study were applied for the development of diagnostic and treatment algorithms for bronchiectasis, included in national clinical protocols.

Implementation of scientific results. The results of the study are used in undergraduate and postgraduate education at the Division of Pneumology and Allergology, in the Phthisiopulmonology ward of the IFP "Chiril Draganiuc" and General Therapy and Allergology ward of the RCH "Timofei Moșneaga". There were registered 3 certificates of innovations and 3 acts of implementation of the results.

АННОТАЦИЯ

Мунтяну Оксана

Клинико-рентгенологические, функциональные и микробиологические проявления бронхоэктазов у взрослых

Диссертация на соискание ученой степени доктора медицинских наук, Кишинев, 2022

Структура диссертации: введение, 6 глав, выводы, библиография из 401 источников, 86 рисунков, 92 таблиц и 1 приложение. Результаты исследования были опубликованы в 67 научных работах.

Ключевые слова: бронхоэктазы, этиология, рентгенология, *синегнойная палочка*, фенотип, аспергиллез.

Область исследования: внутренние болезни, пульмонология.

Цель исследования: выявление этиологических и фенотипических особенностей, коррелирующих с клинико-рентгенологическими, функциональными и микробиологическими проявлениями, для разработки оптимальной тактики ведения взрослых больных с бронхоэктазами.

Задачи исследования: определить этиологический профиль бронхоэктазов у взрослых; определить микробиологический спектр и возможные корреляции с функциональными и рентгенологическими проявлениями у больных с бронхоэктазами; оценить диагностическую и прогностическую значимость на основе использования современных лучевых методов исследования при бронхоэктазах; определить роль комплексного подхода в ведении пациентов с бронхоэктазами, включая применение инструментов оценки тяжести (BSI, FACED, E-FACED) и инструментов оценки сопутствующих заболеваний (BACI, Charlson); проанализировать прогностическую значимость легочной гипертензии у больных с бронхоэктазами; определить роль воспалительных маркеров в выявлении и в оценке тяжести обострений у больных с бронхоэктазами; выявить фенотипы бронхоэктазов и их роль в персонализированном лечении пациентов с бронхоэктазами; выделить факторы неблагоприятного течения бронхоэктазов различной степени тяжести.

Научная новизна и оригинальность. На основании проведенного исследования определена этиологическая структура бронхоэктазов (в том числе редкие заболевания) у взрослых, с выяснением роли лучевых и других инструментальных методов диагностики. Впервые доказано значимость иммунохроматографического экспресс-теста Aspergillus ICT IgG-IgM в выявлении случаев аспергиллеза среди больных с бронхоэктазами. Анализ клинических, рентгенологических, микробиологических и функциональных проявлений позволил выделить несколько фенотипов бронхоэктазов и определить их роль в персонализированном подходе к лечению пациентов с бронхоэктазами в условиях Республики Молдова. Было продемонстрировано прикладное значение рентгенологических шкал и многомерных индексов для определения тяжести заболевания и оценки влияния на качество жизни больных бронхоэктазами.

Новые научные и практические результаты. На основании проведенного исследования была показана научная ценность различных клинических и параклинических методов обследования в многомерной оценке состояния больных с бронхоэктазами, была определена роль некоторых воспалительных маркеров в оценке тяжести обострений, и были выявлены предикторы неблагоприятного течения болезни. Выявлен спектр сопутствующих заболеваний и их прогностическая роль, а также продемонстрирована значимость рентгенологических признаков для диагностики ЛГ и поражений коронарных сосудов с помощью КТВР грудной клетки, что дополняет внедрение современных диагностических стратегий и целевого лечения определенных подтипов популяции пациентов с бронхоэктазами.

Теоретическая значимость заключается в разработке комплексной концептуальной и методологической основы научно-практического изучения гетерогенной проблемы бронхоэктатической болезни. Анализ факторов, ответственных за тяжесть заболевания, выявил предикторы неблагоприятного течения и позволил предложить усовершенствованные методы ведения больных с бронхоэктазами.

Практическое значимость. Полученные результаты использованы для разработки алгоритмов ведения, дифференциальной диагностики и лечения больных с бронхоэктазами.

Практическое применение. Рекомендации исследования используются в процессе подготовки врачей и постдипломного обучения на кафедре Пневмологии и аллергологии, в отделении фтизиопульмонологии ИФП «Кирил Драганюк» и в отделении общей терапии и аллергологии РКБ «Тимофей Мошняга».

MUNTEANU OXANA

CLINICAL, IMAGING, FUNCTIONAL AND MICROBIOLOGICAL MANIFESTATIONS OF BRONCHIECTASIS IN ADULTS

321.01 – INTERNAL MEDICINE (PNEUMOLOGY)

SUMMARY OF THE HABILITATION THESIS IN MEDICAL SCIENCES

Approved for printing: .....2022 Paper size 60x84 1/16
Offset paper. Digital printing 20 copies
Print runs: 4,0 Order no.

Tipografia PRINT-CARO,
mun. Chișinău, str. Columna 170
tel.: 022-85-33-86