“OVIDIUS” UNIVERSITY OF CONSTANTA
DOCTORAL SCHOOL OF MEDICINE
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SUMMARY OF THE DOCTORAL THESIS

SECONDARY PULMONARY TUBERCULOSIS FROM MOLECULAR EPIDEMIOLOGY TO LUNG FUNCTION IMPAIRMENT

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CONTENT

INTRODUCTION

Over the last 143 years in the field of tuberculosis (TB), a progress was noticed from the discovery of Koch's bacillus to the identification of the *Mycobacterium genome tuberculosis* (MTB) , with broadened knowledge and understanding of the evolutionary scenario of mycobacterial strains. Molecular epidemiology and morpho -pathological imaging studies have substantiated the persistence of TB trend of morbidity and mortality, and have explained the favorable conditions for the development of MTB chemoresistance and the extension of TB caseation lesions. The MTB molecular profile, antiTB therapeutic regimens, and monitoring of the contagious pulmonary tuberculosis (PTB) patients have constituted a priority in the field of preventing and achieving control of TB disease. TB must be approached holistically, from the molecular to the morpho-functional profile. The doctoral research aims to address the alternative pathways of TB, from infection to incipient disease, from contagion to chronicity and death, with the identification of molecular, immunological, clinical, imaging, functional ventilatory and evolutionary patterns. The paradigm of MTB strains' molecular epidemiology is being changed with new concepts such as *early detection of incipient forms of TB disease, lacking contagiousness, prediction of forms at risk of severe evolution and death and early optimal identification of post-TB complications*. The validation of PhD research will be brought by algorithmic parameters, specific and easily quantifiable biomarkers, with practical applicability for TB detection in the early phase, alongside with identification of severe PTB, providing an overview of the trajectories and phenotypes of the acute and chronic disease, according to the updated spectrum of TB and post-TB chronic pulmonary disease.

I. CURRENT STATE OF KNOWLEDGE

Part I offers an introduction to theoretical concepts, from *molecular epidemiology to impaired lung function*, an extremely promising topic in the current context of tuberculosis (TB) pathology.

I.1. The molecular epidemiology of tuberculosis (TB) represents the foundation of better understanding the epidemiology and pathology, from the origins of *Mycobacterium tuberculosis* (MTB), to the traditional concepts of contagion, natural history and the TB infection and disease updated definitions. Globally, *we* are *faced with alarming aspects of morbidity and mortality due to TB. In Romania,* the trend of TB endemicity seems favorable, constantly descending in the last 2 decades, registering a slight increase, after the COVID-19 pandemic. In 2023, in the European Union, Romania ranked first in TB morbidity rates reported in the general population and children [1].

I. 2. The spectrum of pulmonary tuberculosis (TBP) suffered change by replacing the classical binary structure infection – disease, with primary and secondary stages [2-5] (Figure 1), with a new scheme, including intermediate reactive stages between latent infection and acute disease, such as TB infection (TBI) and incipient disease [3,6,7], with a new reformulation of TBI concept (with loss of latency status), acute TB disease [8] and postTB chronic lung disease (PTLD) [9-13] (Figure 2).

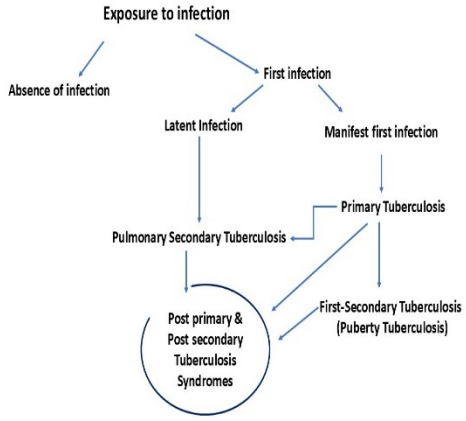


Figure 1. Old spectrum of pulmonary tuberculosis (adapted from [2,4,5,9])

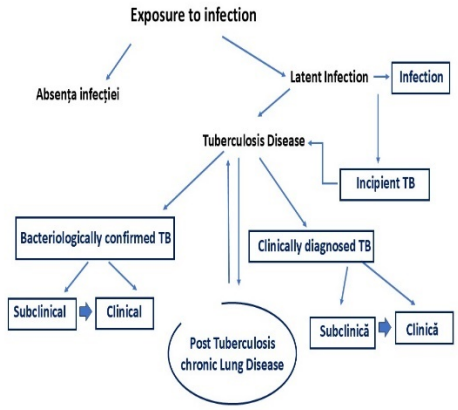


Figure 2. The new spectrum of pulmonary tuberculosis (adapted from [8,10-13])

I.3. Lung Function Impairment. Post-tuberculosis chronic lung disease (PTLD) and its phenotypes are conditions with increasing recognition, but uncertain prevalence (20% - 60%) and underestimated clinical significance [9,11,12]. The global success rate of therapeutic strategies has given rise to an increasing number of survivors who are chronically respiratory ill patients [10]. PTLD patient is generally neglected by the medical system until infectious complications or ventilatory dysfunction become manifest [103-106] and contributes substantially to increased risk of death [14,15]. *Risk factors for lung function impairment* include contagiousness (bacteriological confirmation by microscopy), extensive lung involvement that persists after the acute episode, prolonged duration of anti-TB treatment, delayed diagnosis and initiation of anti-TB therapy [16,17], bacterial superinfections [18], and multidrug resistance [19]. In the absence of guidelines and standards for TB management [20], early detection of post-TB sequelae and, especially, assessment of pulmonary ventilatory function at the end of anti-TB therapy are very important.

II. PERSONAL CONTRIBUTION

II.1. Research premises, general objectives and working hypotheses

In the epidemiological context, in which Romania is the highest tuberculosis (TB) burden European country [1], medical stuff must be concerned with the early detection, identification of the severity and complications of this phenomenon disease, the only one that succeded to resist over the centuries, despite the accessibility of antiTB drugs and improved diagnostic methods. For many years, TB control management has been focused on identifying *the molecular profile of mycobacteria resistance and on combating contagiousness. This doctoral research aims to make the transition from the TB PAST, focused on molecular epidemiology, to the new PRESENT TB algorithm for identifying incipient forms, in contrast to advanced, severe and lethal ones, assessing the FUTURE risk of death and chronicity of TB, with impact on the impaired lung function* .

The main directions of the research are represented by *niche areas*, underestimated in

current Romanian medical practice, which outlined *new valences for evaluating the magnitutude of the current TB problems,* such as:

1. Redefining the entities in acute TB disease spectrum, during 2020-2025, and their interconditioning, from asymptomatic to lethal, from incipient to advanced forms of disease [2,6,7,21,22,23];
2. The magnitude of advanced pulmonary TB, with delayed detected cavitary lesions, bacteriologically confirmed, in microscopy, and poor prognosis, was defined by MacLaren Wallace, at the end of the first decade of 21st century [24], but less studied from the perspective of prognostic biomarkers;
3. The phenotypes within postTB chronic pulmonary disease (PTLD) spectrum have been recently revisited [7,11], although they have been known since the '50s of previous century [2,5,9].

The primary objective of PhD research consisted in a *complex and updated evaluation of the clinical-evolutionary spectrum of secondary TB from infection to disease, from molecular and immuno-inflammatory profile, to morpho-functional patterns of lung structure and ventilatory function deterioration,* with specific presentation of **secondary objectives** for each study.

All **3 studies,** presented in PhD thesis, are non-experimental, non-interventional, and all were approved by *Ethics Committee of Constanta Clinical Pneumophthisiology Hospital (745/February 11, 2020) and Bioethics Committee of Ovidius University, Constanta (UOC 8119/July 22, 2025).*

II.2. Study 1 – The spectrum of pulmonary tuberculosis from infection to disease

II.2.1. Objectives of the study. In order to evaluate *the characteristics of tuberculosis (TB) spectrum, from sequelae to infection and disease, from immuno-inflammatory and epidemiological-molecular perspective to clinical evolution of illness to death,* TB infection and disease were separately analyzed, alongside with the assessment of immunological and molecular profile, clinical and imaging features.

The secondary objectives aimed to identify:

- *prevalence of infection and incipient TB, corresponding to the risk of infection progression;*
- *the risk of TB disease, in an immunosuppressive context and exposure to COVID-19 infection;*
- *predictive factors for distinguishing active pulmonary TB forms from inactive ones,*
- *molecular, clinical and imaging profile of contagious tuberculosis disease,*
- *the risk of death of hospitalized patients with TB disease.*

II.2.2. Study material and methods. The study type was *prospective observational, cohort type, conducted between 01.01.2020-31.05.2025.* There were followed 2 effects over time: the effect of progression of tuberculosis infection in early disease (incipient TB) and the risk of death among patients with pulmonary tuberculosis (PTB). **The study population** included adult patients (≥ 18 years), with TB suspicion, based on with imagistic evidence of lung lesions, hospitalized in Constanta Clinical Pneumophthisiology Hospital, *having previous signed informed consent form*. To evaluate the

components within TB spectrum, from infection to incipient disease, and from advanced disease to death, 2 categories were defined as:

1) **TB suspects -** carriers of lung nodules, detected by chest computed tomography (CT), having uncertain stage of lesional activity, no history of previous treated TB, negative bacteriological smears and cultures, but with mandatory quantitative detection test of serum γ -interferon secretion (IGRA), divided into 2 different types of results: negative IGRA suggestive for TB sequelae and positive IGRA suggestive for TB infection.
2) **TB patients diagnosed with active-evolving lung lesions and administered anti-TB treatment**, classified according to bacteriological confirmation (present or absent).

The inclusion criteria in subcohort 1 consisted in the absence of TB history, quantitative IGRA, routine non-specific inflammatory tests, initial clinical-imaging and bacteriological evaluation, and, in dynamics, after ≥2 and ≤12 months interval, from the first chest CT scan to the progressive imaging shift, supporting the progression of TB infection towards incipient stage of TB disease.

The inclusion criteria in subcohort 2 consisted of TB disease notified cases, regardless of new case or relapse category and bacteriological result (positive or negative), with administered antiTB regimen of therapy, clinical-radiological and bacteriological phenotypic evaluation.

Exclusion criteria in subcohort 1: lack of IGRA test, tuberculin skin testing preceeding IGRA, qualitative or serial IGRA (2 tests with different results; e.g. conversion of IGRA from negative to positive), or indeterminate result (due to the confounding role in TB infection assessment); late bacteriological confirmation by culture positivity, lack of imaging control.

Exclusion criteria in subcohort 2: denial of the initial TB disease diagnosis, after 2 months of anti-TB treatment, in patients without positive bacteriological criterion; absence of phenotypic bacteriological investigation; non-compliance to therapy (therapeutic abandon or failure due to the confounding role in the assessment of death - unfavorable evolution bias); absence of final evaluation (except for death outcome).

The evaluation protocol included basical (demographic, habitual, epidemiological, anthropometric), clinical, imaging, bacteriological, immunological (IGRA QuantiFERON TB Gold Plus-QFT Plus test, and hematological data. Anamnestic evaluation included history of HIV infection, COVID 19 and other diseases possibly aggravating TB. Evaluation of the molecular profile was performed by genotypic tests [GeneXpert MTB/RIF, Line Probe Assay (LPA) and Xpert MTB/XDR], bacteriologically confirmed by phenotypic tests. TB disease definitions of bacteriologically confirmed and clinically diagnosed used World Health Organization classification [25]. Nutritional status assessment included MUST (Malnutrition Universal Screening Tool) score and risk [26].

Suspected TB patients were individuals identified by imaging with apparently stabilized nodular lesions, + calcifications included, fibrotic satellite lesions, in a highly suggestive context, for TB etiology, by specific location (apical segments, apicoposterior upper lobes and apical inferior lower lobes) and included calcifications. Depending on IGRA testing, and imaging progressive changes

detected at the follow-up visit, patients were classified into IGRA negative and sequelae carriers and IGRA positive TB infected. The assessment of early TB disease risk required *the morphometric analysis of pulmonary nodular lesions*, with *measurement of the mean diameter of pulmonary nodular lesions* by calculating the arithmetic mean of all nodules diameters, by using the *Xvision/RAYSCAPE* artificial intelligence computer software program, regardless of IGRA dichotomic results. Patients identified with CT lesions progression were considered eligible of incipient TB.

In PTB patients, the risk of death was assessed till 12 months after enrollment. All patients received anti-TB regimens, or individualized therapy, according to *Mycobacterium tuberculosis* chemoresistance profile, as provided by Romanian guidelines [27,28], and no additional therapeutic interventions were applied, which could be confounding for research.

Statistical analysis was done with *IBM Statistics Package for the Social Sciences version 20 (SPSS Inc., Chicago, Illinois, USA),* the statistical significance threshold was set as a probability of 95%, corresponding to a value of $p < 0.5$. In addition to descriptive statistics of frequencies, analysis of variance, correlations, corresponding to a normal distribution, *Receiver Operational Characteristic (ROC)* analysis was used to establish the risk threshold of TB1-Nil and TB2-Nil antigens, and the mean diameter of the lung nodules. Predictability, for the risk of incipient TB, was corresponding to an area under ROC curve ≥ 0.6 and a significance threshold of $p < 0.05$. *Kaplan Meier survival analysis* assessed life expectancy among TB patients in relation with COVID-19 infection, immunosuppression and multimorbidity (≥ 2 comorbidities) [29]. In assessing the risk of disease and death, *the contingency table was used*, through *the EPI.INFO 7.2.7.0 program.*

II.2.3.Results

II.2.3.1. Descriptive characteristics of the study cohort, according to tuberculosis spectrum

The study cohort included 401 adults, with *a mean age* of 56.50 ± 14.44 years, equal to median value (57 years), predominantly males (n=256; 63.84%). Males were younger (55.30 ±14.08 years) than females (58.63±14.86 years) ($F=4.973$; $p < 0.026$).

Study cohort had 2 subcohorts included 140 TB suspects in subcohort 1, of which 93 were positive IGRA TB infected cases, and 261 patients (subcohort 2) with pulmonary tuberculosis disease (PTB), of which 213 were bacteriologically confirmed. PTB patients had a mean age of 53.60 ± 14.52 years, compared to TB suspects (61.91±12.67 years) ($F= 32.61$; $p <0.001$) and those with incipient TB (58.39±16.07 years). In subcohort 1, women predominated (n=61/140; 43.57%), versus men in subcohort 2 (n=195/261;74.72%).

At baseline, *the prevalence of TB infection* was 23.19% (n=93/401) and the prevalence of TB disease was 53.12% (n=213/401) (Figure 1). *The risk of progression from TB infection to early disease* was 24.73% (n=23//93). It occurred after a mean interval of *4.91 ± 2.87 months* (range 2–12 months). *The prevalence of early TB* in the study cohort was 5.74% (n=23/401). At the final assessment, *the prevalence of TB infection* decreased to 17.46% (n=70/401).

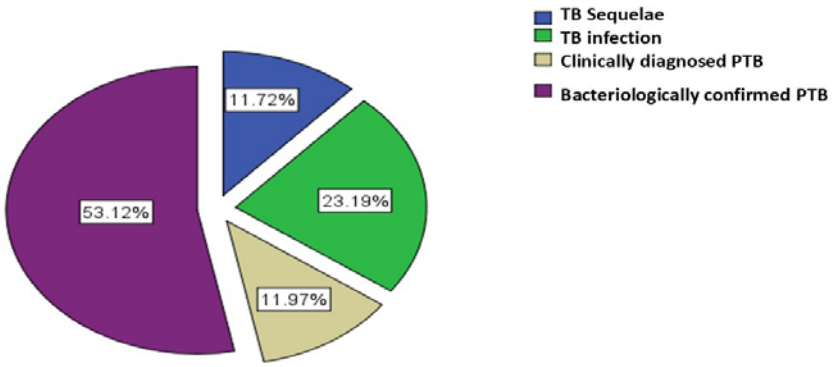


Figure 1. Structure of the study cohort according to pulmonary tuberculosis (PTB) spectrum

The mean body mass index (BMI) recorded low values in bacteriologically confirmed PTB cases (19.67 $\pm$ 4.01 kg/m^2) compared to negative IGRA PTB suspects (25.98 $\pm$ 6.13 kg/m^2) ($F = 53.9$; $p < 0.001$). *The phenomenon of weight loss* (BMI < 18kg/m^2) was evident in PTB patients (n = 136/261; 52.11%) (OR = 20.67; CI95%: 9.30-45.91; RR = 10.42; CI95%: 5.01-21.65; $\chi^2 = 88.13$; $p < 0.001$). Based on the weight loss, the assessment of *MUST* (Malnutrition Universal Screening Tool) *malnutrition score*, using Bapen program [26], recorded (on a scale from 0 to 6) higher values in patients (n=159/213; 74.65%), and lower ones, in suspects. *The risk of MUST malnutrition* was statistically significantly increased, in patients with bacteriologically confirmed PTB ($\chi^2 = 147.266$; $p < 0.001$).

Spearman correlation between BMI and age was moderate and positive ($r_s = 0.408$; $p < 0.001$), *with weight loss was moderate and negative* ($r_s = -0.657$; $p < 0.001$), with *MUST score was high and negative* ($r_s = -0.821$; $p < 0.001$). *BMI < 18.5Kg/m ^{2} and TBP spectrum were negatively and moderate correlated* ($r_s = -0.486$; $p < 0.001$). *Weight loss and MUST score were positively and highly correlated* ($r_s = 0.897$; $p < 0.001$).

II.2.3.2. The molecular profile of pulmonary tuberculosis, *explored through genotypic tests,* revealed 55.87% *positive GeneXpert MTB/RIF results, with a high level of detection of Mycobacterium tuberculosis* (MTB) (n=119/213), genetic mutations of isoniazid resistance, identified by the Line Probe Assay (LPA), revealing *inhA molecular pattern* in 2 patients, and *KatG* in other 5 patients, diagnosed concurrently with *rpoB genetic mutations* for rifampicin.

All positive genotypic tests were confirmed by positive phenotypic tests (MGIT 960 liquid culture method and Lowenstein Jensen solid culture), according to Romanian guideline [27]. *The prevalence of MTB chemoresistance* was reduced in patients with bacteriologically confirmed PTB (n=30/213; 14.09%), increasing to 73.34% in *newly detected cases* (n=22/30). *The prevalence of multidrug-resistant TB* was 9.85% (n=21/213).

II.2.3.3. The clinical-imaging spectrum of tuberculosis was polymorphic. *The prevalence of subclinical (asymptomatic) forms* was 13.03% (n=34/261). The history of cough predominated in both subcohorts (n=395), facilitating lung abnormalities detection by computed tomography. Nodular lung lesions, more frequent in suspects (n=114/140; 81.43%; OR=8.27; CI95%:3.49-19.62; RR=1.19; CI95%:1.10-1.29; χ 2=30.38; $p< 0.001$), had *a highest mean value of diameter (13.16±9.46 mm*) in patients with incipient TB (ITB). According to *linear regression analysis*, there was a statistically significant relationship for a predictive mean diameter value of 9.48±2.10 mm (F= 6.137; $p< 0.016$; t=8.768; $p< 0.001$; CI95%; 6.41-10.22) positively associated with ITB diagnosis (R^2 =0.272; $p< 0.001$).

The prevalence of cavitary TB was increased in the group with bacteriologically confirmed disease (n=187/213; 87.79%). *The Spearman correlation between cavitary TB and bacteriological confirmation was high, negative and statistically significant (r_s =-0.793; p<0.001).*

II.2.3.4. Prognostic biomarkers of early tuberculosis risk of disease included *pulmonary nodule diameter (PND) and immunological biomarkers TB1 and TB2 minus Nil (TB1-Nil and TB2-Nil)* , which stimulate *the secretion of γ-interferon by T-CD4 and T-CD8 lymphocytes. Spearman correlation between TB1- and TB2-Nil was positive and very high (r_s =0.970; p < 0.001).*

Receiver Operator Characteristic (ROC) Analysis identified areas under the curve of:

- 0.722±0.043 (CI95%: 0.637-0.807; p < 0.003), with 0.69 IU/mL cut-off of risk, sensitivity 97% and specificity 57% for TB1-Nil (Figure 2);
- 0.704±0.042 (CI95%: 0.622-0.786; p <0.006), cut-off value of 0.62 IU/mL, with sensitivity 97% and specificity 57% for TB2-Nil (Figure 2);
- 0.653±0.070 (CI95%: 0.515-0.790; p < 0.040), with an increased risk cut-off of 9.5 mm, sensitivity 64% and specificity 59% for lung nodules diameter (LND),
- 0.616±0.058 for lymphocytes, but at the limit of statistical significance ($p < 0.058$).

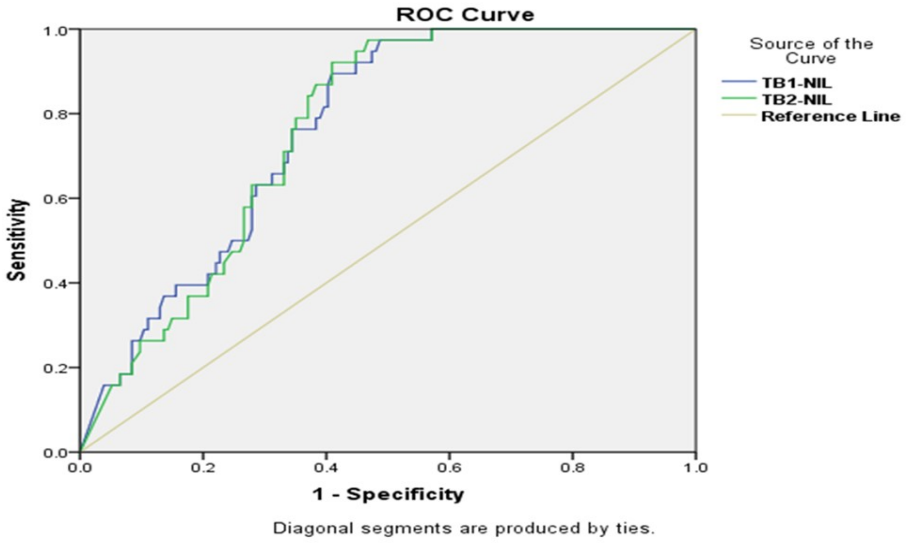


Figure 2. ROC analysis of TB1-Nil and TB2-Nil biomarkers in the incipient TB group

By applying the ROC filter composed of risk values above the identified cut-off (LND ≥ 9.5 mm, TB1-Nil and TB2-Nil ≥ 0.70 IU/mL), in the group of 93 infected subjects, resulted a trimarker risk score with 52.17% sensitivity; 78.57% specificity; having 44.45% positive predictive value and 82.09 negative predictive value; with a likelihood ratio of 1.13 and accuracy of 78.57%.

II.2.3.5. The evolution of tuberculosis spectrum

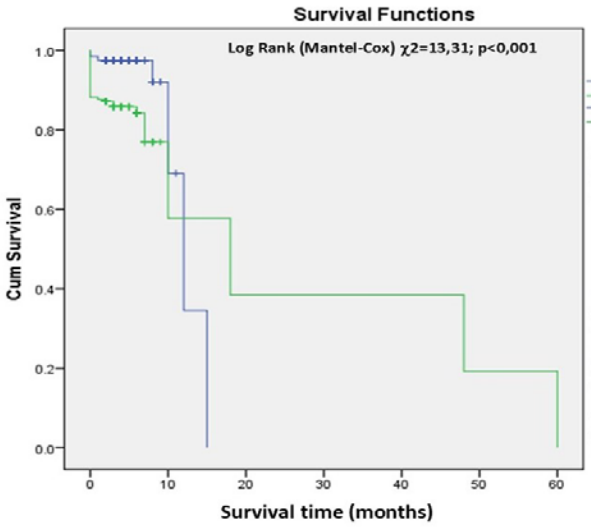
COVID-19 infection preceeded the enrollment in the study, of 228 participants, with a mean interval of 13.19 ± 10.69 months, and a median of 10.50 months, ranging between 17.58 ± 10.85 months in *TB infected subjects* (median of 13 months) and 7.97±9.36 months (median of 6 months) in PTB *bacteriologically confirmed patients* (F= 10.543; $p < 0.001$; R=-0.312; R^2 =0.097; eta = 0.379; eta^2 = 0.143). *The prevalence of COVID-19 infection* was increased in suspects (89.36% in carriers of sequelae, 83.87% in infected subjects, 56.52% in those with incipient TB). *The risk of early TB disease, through the progression of infection, of 24.73%,* was moderately positively correlated with COVID-19 infection (r_s =0.492; $p < 0.001$). *The average interval of time between COVID-19 infection and incipient TB diagnosis* was 15.08±7.9 months (median 14 months), without statistically significant differences compared to the rest of TB infected cases (F = 0.837; $p < 363$; eta = 0.108; eta^2 = 0.012). *The progression of infection in incipient TB was influenced by multimorbidity* (n=19/23; 82.60%; OR=5.97; CI95%: 1.84-19.38; RR=1.86; CI95%: 1.35-2.57; χ 2=10.12; $p < 0.002$).

In subcohort 2, *PTB and COVID-19 infection* developed concurrently in 21 patients, the measure of association of these 2 conditions with highly statistically significance (F=15585.362; $p < 0.001$; R=-0.843; R^2 =0.711; eta = 1.000; eta^2 = 0.99). During the period 30.01-01.02.22, an *outbreak of nosocomial TB- COVID* was identified among 11 patients, of which 3 died.

The overall risk of death in the study cohort was 10.97% (n=44/401), with the highest value (14.56%) in patients with *bacteriologically confirmed TB* (n=38/261; χ^2 =24.52; $p < 0.001$) and the lowest in those with incipient TB (n=1/23; 4.35%). *The mean age of the deceased* was 50.67 ± 14.10 years. *Males* had an increased risk of death (n=37/256; 14%) versus females (n=7/145; 4.8%) (OR=3.33; CI95%:1.44-7.68; RR=2.39; CI95%:1.37-6.54; χ 2 =8.76; $p < 0.003$). There was a male death pattern, with a high negative correlation matrix (-0.967; $p < 0.005$; -2 Log=514.92; Cox & Snell R^2 =0.024; Nagelkerke R^2 =0.033), according to *multinomial logistic regression* .

Kaplan Meier analysis identified, in PTB patients, from subcohort 2, a mean survival time of 22.12±6.62 months (CI95%: 9.14-35.10), a median of 12±2.28 months (CI95%: 7.53-16.47) (Log Rank Mantel-Cox χ 2 = 18.68; p<0.001). *Deaths due to the PTB-COVID-19 association* (n = 9/44; 20.45%) occurred after a mean interval of 2.63 ± 4.86 months from SARS CoV2 infection. The negative impact of COVID-19 infection, according to *Kaplan Meier analysis*, consisted in reducing the survival time (mean of 12.07±1.12 months; CI95%: 9.88-14.25; similar to median value of 12.00±1.53 months; CI95%: 8.99-15.00) (Log Rank Mantel-Cox χ 2 = 13.31; p<0.001) (Figure 3). *Survival life expectancy* was not influenced by potentially immunosuppressive comorbidities of PTB (HIV infection, neoplasia,

diabetes mellitus, chronic hepatitis) (Log Rank Mantel-Cox χ 2 = 0.243; p<0.662), but it was influenced by cavitary lesions, identified in most of the deceased (n = 40/44; 90.90%), and attributed to an increased risk of death (n = 40/194; 20.62%; OR = 5.58; CI95%: 1.93- 16.14; RR = 4.64; CI95%: 1.71-12.57; χ 2 = 12.24; $p < 0.001$). The death occured after a mean survival period of 19.74 $\pm$ 5.59 months (CI95%: 8.77-3.72); a median of 12 $\pm$ 2.49 months (CI95%: 7.11-16.89), according to Kaplan Meier analysis (Log Rank Mantel-Cox χ 2 = 24.37; p<0.001).



Means and Medians for Survival Time

History of COVID	Mean				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Yes (9 deaths)	12.066	1.112	9.885	14.246	12.000	1.532	8.997	15.003
No (35 deaths)	26.817	8.215	10.716	42.918	18.000	8.085	2.154	33.846
Overall	22.050	6.269	9.763	34.336	15.000	3.157	8.813	21.187

Figure 3. Estimation of cumulative survival curves, in the group of TB-COVID co-infected patients, using the Kaplan Meier method

II.2.3. Discussions. The redefined spectrum of tuberculosis (TB) [2,6,7,30,31] addresses latent tuberculosis infection (LTBI) issue, in which latency is difficult to be sustained alongside the obvious imaging-detected lung lesions [32]. In the era of computed tomography, the concept of *TB infection (TBI)* is intertwined by *incipient TB (ITB)*, when the progression of infection to disease can be demonstrated [31,33,34]. TBI provides the framework for therapeutic interventions and opportunities to limit the spread of infection, as patients no longer have time to develop contagious disease [33].

Current conventional bacteriological diagnostic criteria for secondary pulmonary tuberculosis (PTB) have notable limitations in the clinical context of incipient disease. Diagnostic certainty often remains elusive, despite radiological lung abnormalities suggesting an active disease [35,36]. Incipient TB (ITB) was initially defined in *immunocompetent* patients without a history of TB as a *combination of radiological lesions affecting the upper lobes of the lungs exceeding 2 cm2* [31], *but there is no consensus on its definition*. Drain PK et al. (2018) have further elaborated on the stages of TBI and ITB, highlighting the complexity and subtlety of incipient TB, a transient, presymptomatic clinical stage that differs from *subclinical TB*, and it is characterized by the presence of viable, multiplying tuberculous mycobacteria (MTB), with potential progression to disease [33]. In this context, reactivity to MTB antigens, evidenced by positive detection of serum releasing of interferon γ, confirms MTB viability

[32], as 66.43% positive rate in **study 1**. The ITB risk of disease, 12 months monitored, was influenced by COVID-19 infection and multimorbidity, higher than literature data (5-15%, with higher values in the first 2 years after infectious contact) [37].

The RAYSCAPE computerized morphometric investigation of lung nodular lesions, in dynamics, represented a *strong point of the doctoral research, demonstrating that the mean diameter of lung nodules can have a role of incipient TB diagnostic biomarker*.

In opposition to the incipient forms, there are the advanced, cavitary ones, in which positive smears and cultures provide certainty of TB etiology and allow the identification of *chemoresistant molecular profile, with a low frequency* (14.08%), in **study 1**. Multidrug resistant pattern, although reduced (9.85%), is increasing compared to the previous years 2013-2017, when, in the same hospital, it was 1.95% [38]. The most accessible molecular test performed, in **study 1**, was *GeneXpert MTB/RIF* (59.82%), similar to 2013-2017 interval (53.57%) [39], but with an *increased rate of detection of Mycobacterium tuberculosis (MTB) DNA (82%) and a low (3.98%) rate of rifampicin resistance* versus 15.43%, in Marius Nasta Institute of Pulmonology, from Bucharest [40].

The phenotype of severe weight loss was identified in the early and advanced stages of confirmed bacteriologically disease. *The malnutrition score MUST (Malnutrition Universal Screening Tool)* [26], applied in **study 1**, best reflects the precarious nutritional status of patients with confirmed bacteriologically PTB. *MUST is an element of originality of the research* , being little studied in the field of TB [41], although the malnutrition-TB interrelation is known [42].

During the first 2 years of the pandemic, despite of transient intersection between *MTB* and *SARS CoV2*, severe and lethal PTB forms were revealed [43]. In **study 1**, *the risk of death* was 10.97%, increased in males, and cavitary TB patients. The association between TB and COVID-19 represented an epidemiological peculiarity of PhD research, influencing the early illness risk and reduced life expectancy.

II.3. Study 2 – Prognostic biomarkers of tuberculosis disease′ severity

II.3.1. Research premises and objectives. Starting from the desire to achieve a better control of tuberculosis (TB) endemic, despite involved strategic plans [44], there is a paradox related to the apparent decline trend of TB cases in contrast to severe, advanced, extensive, late-detected, cavitary phase forms, capable to induce death even in young adults.

In this context, early detection and prediction of severe evolution become important objectives, and **the premise of the research,** in study 2, for *identifying rapid, inexpensive diagnostic tests that are predictive of TB disease severity and risk of death, such as serum adenosine deaminase (sADA),* a relevant biomarker of cellular immunity in TB pathology [45,46], studied in diagnosed and treated pulmonary tuberculosis (PTB) [47,48], *but not in advanced forms of disease* [49]; and *systemic immune inflammatory index (SII), a neutrophil surrogate biomarker* [50], studied in

autoimmune diseases [51], neoplasia [50,52], sarcoidosis [53], COVID-19 infection [54,55], *but not in advanced forms of TB disease* [49].

The primary objective was to identify *immuno-inflammatory biomarkers, easily accessible, with clinical applicability, in the early severity prediction of advanced forms of pulmonary tuberculosis (*$_A$ *PTB), and* **the secondary objectives** aimed *to identify the prevalence of advanced forms of PTB disease, and its phenotype causing severe evolution to death.*

II.3.2. Study material and methods

The type of study was *prospective observational, conducted between 01.01.2020-31.03.2025.*

The study population included adult patients (≥ 18 years old), hospitalized in Constanta Clinical Pneumophthisiology Hospital, and diagnosed with pulmonary tuberculosis (TB), new case or relapse, *having a previous signed informed consent form (ICF).*

Inclusion criteria were serum adenosine deaminase (sADA) dosing prior to initiating antiTB treatment; hematological investigations: complete blood count (leukocytes, lymphocytes, neutrophils, platelets); imaging evaluation to confirm cavitary lesions; assessment of malnutrition score and risk by Malnutrion Universal Screening Tool (MUST) Bapen calculator [26]; bacteriological phenotypic screening for TB mycobacteria; and **exclusion criteria** consisted of lack of informed consent , clinically diagnosed and refuted TBP case, after 2 months of initiating antiTB regimen; any disease with potential to disrupt the results provided by ADA test (pleural empyema, HIV coinfection, concomitant COVID-19 infection, neoplasia, autoimmune diseases, liver diseases, to avoid sADA growth bias); case of abandon or therapeutic failure (to avoid unfavorable evolution bias). According to the definition and TB diagnostic criteria, established by the World Health Organization [25] , the **study group** was divided into 2 groups: group 1 consisting of cases with bacteriologically confirmed TB, and group 2 with clinically diagnosed TB. In this study, a special subcategory was included, called **advanced pulmonary tuberculosis (**$_A$**TBP)**, firstly defined, in 2009, by MacLaren Wallace *et al*. [24], as *disease with cavitary lesions, identified by chest radiography, positive sputum microscopy, by Ziehl Nielsen staining, reflecting TB delayed diagnosis and contributing to the severe evolution towards relapses or death, as poor outcomes*. Delayed diagnosis was considered to exceed the time interval ≥ 2 weeks from the onset of symptoms to the initiation of antiTB treatment [56].

The evaluation protocol included standard evaluation with anamnesis, medical history, clinical and radio-imaging examination, bacteriological (microscopy, liquid culture, solid, molecular tests GeneXpert MTB/RIF, Line Probe Assay), with nutritional status assessment by MUST (Malnutrition Universal Screening Tool) score and risk [26], calculation of *the systemic immuno-inflammatory index (SII)* according to the formula: (neutrophil count x platelet count)/lymphocyte count. According to the kinetic method of determining serum adenosine deaminase (ADA), in the biochemistry lab of Constanta Clinical Pneumophthisiology Hospital, values >19 IU/L were considered

elevated. Biomarkers with potential predictability of severe evolution were evaluated, considering, ab initio, advanced TBP as a severe form of the disease, with a poor prognosis.

Statistical analysis, done with *IBM Statistics Package for the Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, Illinois, USA)* included, in addition to descriptive statistics of frequencies, analysis of variance, correlations, corresponding to a normal distribution. *Receiver Operational Characteristic (ROC) analysis* was performed in order to establish the threshold between negative and positive serum results of adenosine deaminase (sADA), systemic immunoinflammatory index (SII) and MUST malnutrition score. To evaluate the discriminative power of sADA and SII, the optimal high risk cut-off values for an area under the curve (AUC) ≥0.6 and p <0.05 were applied; and sensitivity and specificity were determined. A value of p <0.05 was considered statistically significant.

II.3.3. Results

II.3.3.1. Demographic, epidemiological and nutritional characteristics of the study group

Study group included 208 adults, mean aged 54.40 ± 14.40 years, 74% men (n=154), 75% smokers (n=156). *The mean age* was almost equal distributed by gender (54.61 ± 16.53 years, men, compared with 54.29 ± 15.83 years, women; F=0.02; $p < 0.887$).

The study group structure included 156 bacteriologically confirmed patients (group 1) and 52 clinically diagnosed (group 2), 75% new cases. *The prevalence of advanced pulmonary tuberculosis* ($_A$PTB) was 88.46% (n=138/156). *Late diagnosis* was frequent in group 1 (n=138/156) versus group 2 (n=10/52) (OR=32.2; CI95%:13.81-75.08; RR=4.6; CI95%: 2.63-8.05; χ^2 =90.63; $p < 0.001$). *The mean interval between the onset of symptoms and $_A$PTB diagnosis* was 3.30±2.86 months, in the study group, and 3.53±2.636 months in patients with $_A$PTB (p <0.001). Early detection was determined by hemoptysis and fever, but cavitary lesions confirmed $_A$PTB.

The prevalence of chemoresistance was 8.17% in the study group, 11.50% in group 1. *Multidrug-resistant forms* (n=11) included 4 rifampicin-resistant (RR) cases.

The prevalence of underweighting with BMI < 18.5 kg/m^2 appears increased in patients with *bacteriologically confirmed PTB* (n= 70/156; 44.87%) versus clinically diagnosed ones (n=10/52; 19.23%) OR= 3.41; CI95%: 1.60- 7.29; RR= 2.33; CI95%: 1.30- 4.18; χ 2= 10.78; p< 0.001). *The average malnutrition score MUST (Malnutrition Universal Screening Tool) by Bapen* [26], ranged from 3.80±2.31, in patients with advanced TB, (eta =0.370; eta ^{2} =0.137; F=36.60; p< 0.001) to 4.38 ±2.30, in deceased (eta =0.180; eta ^{2} =0.032; F = 6.89; p< 0.009). MUST score 6 was detected in 33.33% of bacteriologically confirmed TB cases (33.33%) (eta =0.328; χ^2= 27.801; p< 0.001).

Severe malnutrition risk was identified in:

- 73.01% of bacteriologically confirmed TB cases (n=114/156; eta =0.306; χ 2= 23.347; p< 0.001),
- 73.65% of patients diagnosed late (n=109/148; 73.65%; eta =0.300; χ 2= 21.234; p< 0.001),
- 79.16% of deceased (n=19/24; eta =0.099; χ 2 =3.289; p< 0.2).

II.3.3.2. The clinical-imaging and evolutionary characteristics of the study group were represented by extensive cavitary lesions (n=145), severe forms of hematogenous dissemination (n=9), bronchopneumonia (n=18), late detection (n=148), attributes of the severity of tuberculosis disease, with an increased impact on the fatality rate in the study group (n=24/208; 11.53%), especially in group 1 (n=22/156; 14.10%) (OR= 4.10; CI95%: 0.93-18.09; RR= 3.67; CI95%:089-15.06; χ^2=4, p < 0.046).

II.3.3.3.Biomarkers with predictive potential for the prognosis of TB disease severity

Serum adenosine deaminase (sADA) recorded average values:

- 34.06 ± 9.27UI/L, in *bacteriologically confirmed cases* (p <0.002),
- 34.04 ± 9.01UI/L in those with *advanced pulmonary tuberculosis (ATBP)* (p <0.016),
- 37.17 ± 9.94 IU/L, in the *deceased* (p < 0.016), with no influence by age (p < 0.345), patient gender (p < 0.165), residence (p < 0.964), weight loss (p < 0.091), but *increased proportionally with MUST malnutrition score* (F=2.49; p < 0.024; R= 0.154; R^2 = 0.024; eta=0.263; eta ^{2} =0.069) and *severity of malnutrition risk. MUST* from 28.91 ± 6.44 IU/L, to 34.11 ± 9.43 IU/L (F=3.38; p < 0.036; R= 0.153; R^2 = 0.024; eta=0.179; eta ^{2} =0.032) (Figure 4).

The systemic immuno-inflammatory index (SII) recorded average values:

- 2006.47 ± 3028.18 in *cases with bacteriologically confirmed TB* (F=5.64; p< 0.018);
- 2126.23 ± 3110.14 in patients with *cavitary TB* (F=9.53; p< 0.002);
- 2077.67 ± 3131.46 in patients with *advanced TB,* compared to the rest of the patients (1110.63 ± 1355.68) (F=6.085, p< 0.014; age = 0.169; eta² = 0.029);
- 3308.16 ± 3023.07 in *deceased* (F=9.34; p< 0.003);
- 3251.13 ± 4477.43 in *malnutrited patients* with a MUST score of 6 (F= 4.908; p< 0.001; R= 0.306; R^2 = 0.093; eta=0.357; eta ^{2} =0.128).

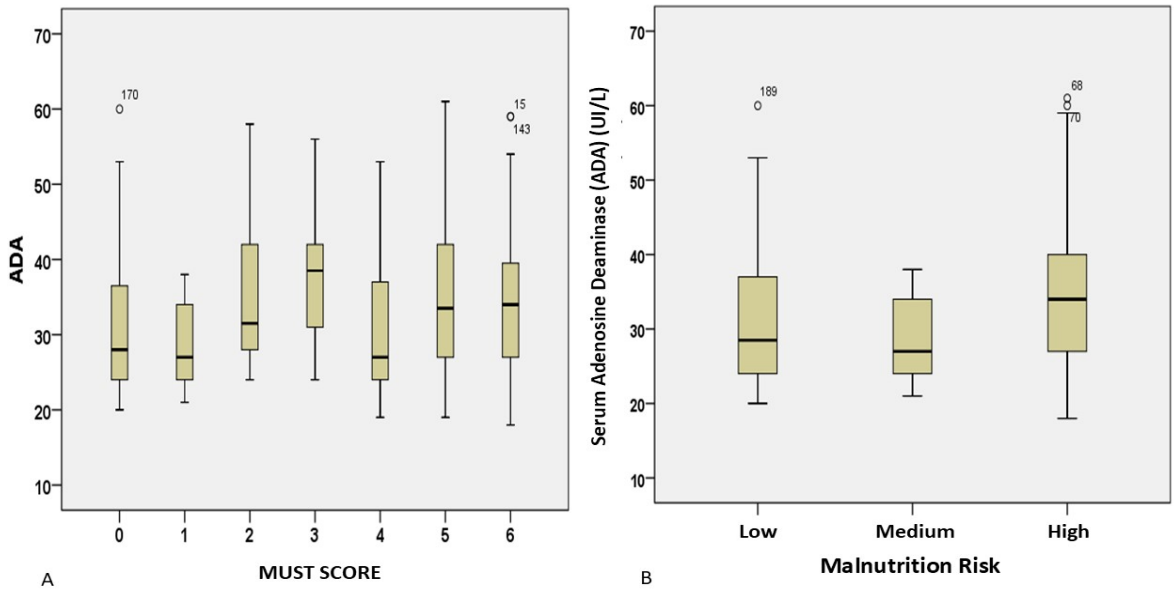
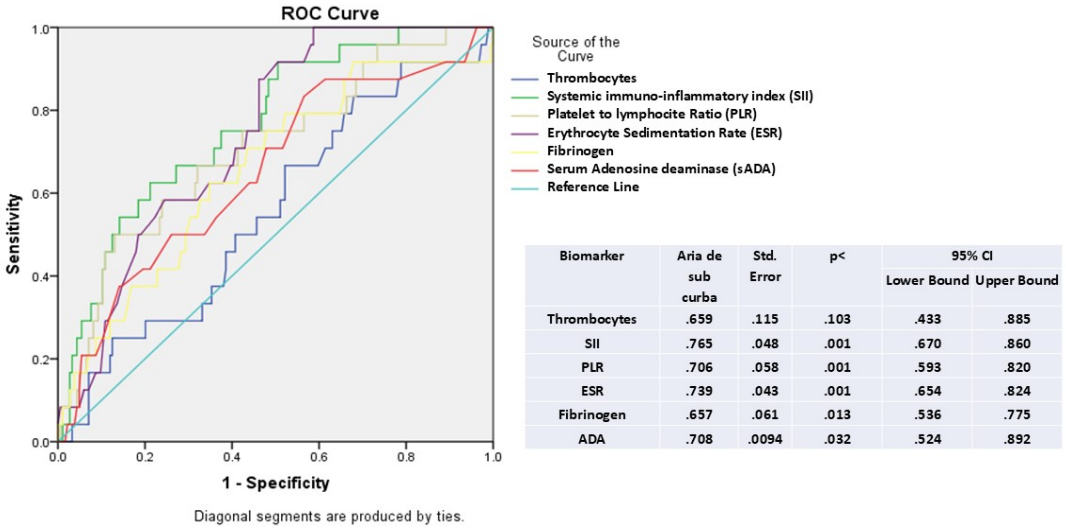


Figure 4. Mean serum adenosine deaminase (ADA) values according to MUST (Malnutrition Universal Screening Tool Bapen [26]) score (A) and malnutrition risk (B)

Receiver Operational Characteristic (ROC) analysis revealed a predictive area under the curve (AUC) of 0.708 ± 0.09 ($p < 0.032$) for sADA and 0.765 ± 0.05 ($p < 0.001$) for SII (Figure 5), identifying the sADA risk threshold of 30.50 IU/L, with sensitivity (Sn) of 75%; specificity (Sp) of 78%; and the SII threshold of *902*, with 50% Sn and 84% Sp.



Biomarker	Aria de sub curba	Std. Error	p<	95% CI	
				Lower Bound	Upper Bound
Thrombocytes	.659	.115	.103	.433	.885
SII	.765	.048	.001	.670	.860
PLR	.706	.058	.001	.593	.820
ESR	.739	.043	.001	.654	.824
Fibrinogen	.657	.061	.013	.536	.775
ADA	.708	.0094	.032	.524	.892

Figure 5. Evaluation of inflammatory biomarkers by Receiver Operating Characteristic (ROC) analysis, in study group (adapted from[49])

Applying the sADA ≥ 30.50 IU/L filter, the ADA risk cohort (n=116) was identified, representing

- 61.54% of PTB bacteriologically confirmed cases (n=96/156) (OR= 4.16; CI95%: 2.26-7.64; RR= 2.21; CI95%: 1.49-3.28; χ^2 =22.36, $p < 0.001$),
- 66.67% of advanced pulmonary tuberculosis ($_A$TBP) cases (n=92/138),
- 75% of total deaths (n=18/24), 15.52% risk of death (n=18/116) (OR=2.63; CI95%: 0.99-6.93; RR= 2.387; CI95%: 0.98-5.75; χ^2 = 4.05, $p < 0.045$).

In $_A$PTB assessment, sADA threshold had a positive predictive value of 83.62% a negative predictive value of 55.43% and a 75% sensitivity and 46.74% specificity in death risk prediction.

By applying *the SII ≥ 902 filter,* resulted *a SII risk cohort of 110 patients*, representing

- 60.26% in bacteriologically confirmed PTB group (n=94/156) (OR=5.22; CI95%: 1.71-15.87; RR= 4.45; CI95%: 1.57-12.58; χ^2 = 10.05, $p < 0.002$),
- 81.82% of $_A$PTB cases (n=90/110),
- 83.84% of total deaths (n=20/24), inducing a death risk of 18.18% (n=20/110) (OR= 5.22; CI95%: 1.71-15.87; RR= 4.45; CI95%: 1.57-12.58; χ^2 =10.05, $p < 0.002$).

SII risk had a sensibility (Sn) of 65.22% and 71.43% specificity (Sp) in predicting the risk of $_A$PTB; with 83.33% Sn and 51.08% Sp in predicting the risk of death.

The mean interval from TB diagnosis to death was 54.32 ± 76.61 days, reduced to 43.10 ± 74.41 days in patients with $_{A}$PTB and 21.50 ± 21.89 days in sADA+SII risk cohort, with statistically significant *multinomial multiple regression* (χ^2 =16.529; $p < 0.036$), log odds for the fitting model (-2Log likelihood) of 28.359, and pseudoR ^{2} Cox and Snell of 0.952 and Nagelkerke of 0.976.

ROC analysis for MUST score and body mass index (BMI) revealed predictive AUC only for MUST (0.71 in $_{A}$PTB cases and 0.67 in deceased) (Figure 6). The cut-off value of MUST score 3 had, in patients with $_{A}$PTB, a 74% Sn and 66% Sp, and, for deceased, a cut-off value of 4 had a Sn of 71% and a Sp of 51%.

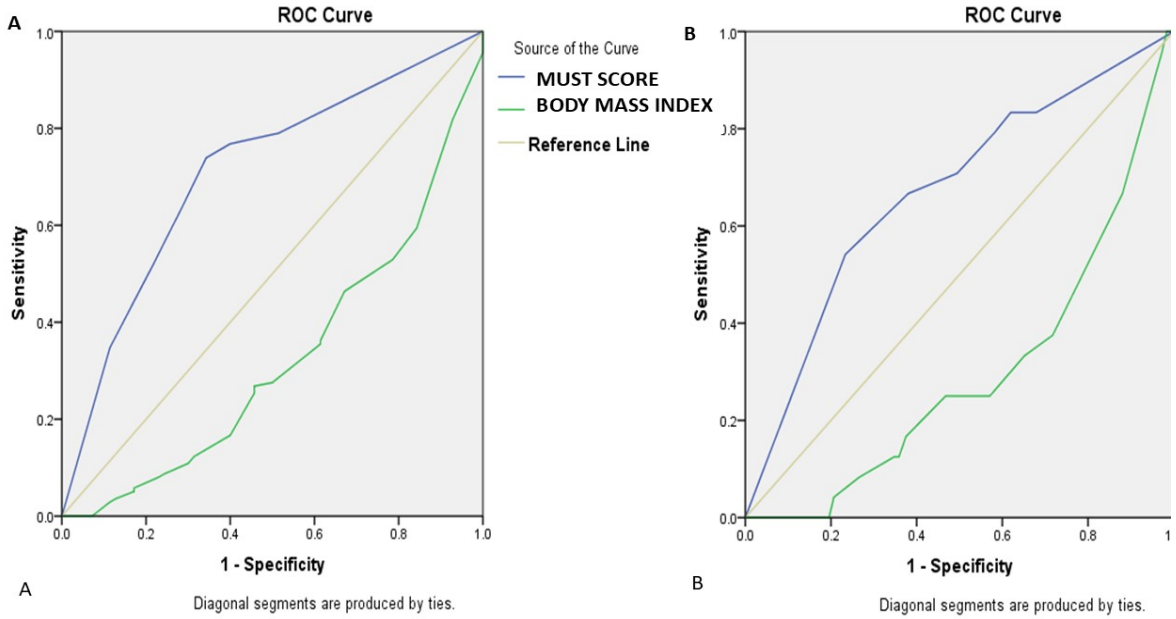


Figure 6. Evaluation of nutritional status′ biomarkers (MUST score and BMI) by Receiver Operating Characteristic (ROC) analysis, in patients with advanced pulmonary tuberculosis (A) and in deceased patients (B)

The prevalence of malnutrition, corresponding to a MUST score ≥ 4 , was 51.92% in the study group (n=108/208), 63.77% in *the $_{A}$PTB group* (n=88/138), 87.50% in the $_{A}$PTB cohort with sADA+SII risk filter (n=49/56), and 70.83% in *the deceased group* (n=17/24). Using this filter of *biomarker threshold values prognostic factors ADA, SII, MUST.*

The prevalence of PTB with severe evolution was identified in half of $_{A}$PTB patients (n=63/138; 45.65%) (OR= 5.04; CI95%: 2.88-10.65; RR= 3.19; CI95%: 1.75-5.83; χ^2 = 19.16, $p < 0.001$).

II.3.4. Discussion. The partial results of **study 2** were published in June 2025 [49]. The delayed diagnosis of pulmonary tuberculosis (PTB) justifies, morphologically, the extensive caseation, lesional extension and bilateralization, and, epidemiologically, the contagion, since the majority of enrolled inpatients had cavitary lesions and positive smears, determinants of *advanced forms of PTB ($_{A}$PTB)* [24]. In order not to influence *the prediction of death*, in **study 2**, *aggravating comorbidities with the potential to increase serum adenosin deaminase (sADA) and systemic immuno-inflammatory index (SII)*

levels were excluded, independent of TB-dependent immuno-inflammatory activation way. In general, studies have explored the diagnostic role of sADA in PTB patients [48,57-62]. There is a notable lack of information regarding the value of sADA as a *prognostic biomarker* in $_{A}$PTB [47,57]. Some researchers have proposed it to be considered a diagnostic biomarker when bacteriological confirmation of TB is lacking [58,59], with *critical threshold values* between 21-34 IU/L [47,60,61,63].

There is a complex bidirectional relationship between inflammation-cachexia-anorexia-malnutrition [42]. *Malnutrition may be a surrogate biomarker of $_{A}$PTB*, as demonstrated by MUST score ≥ 4, comparable to 3.5 value identified by Miyata [64,65]. The association of MUST score with sADA-SII prognostic biomarkers duet [49] constitutes a *trimarker with a strong imprint in the prediction of severity and death in $_{A}$PTB. The phenotype of the PTB patient at risk of severe progression and death, identified in study 2, is male, aged < 60 years, diagnosed late with cavitary lesions, with positive bacteriology in microscopy, ADAs ≥ 30.50UI/L, SII ≥ 902 and MUST score ≥ 4*.

II.4. Study 3- Impaired lung function, phenotype of post-tuberculosis chronic lung disease

II.4.1. Research premises and objectives. The success of antituberculosis chemotherapy has turned into a real chance of survival with post-tuberculosis (TB) sequelae and lung function impairment (LFI) [66], since completed antiTB therapy has not always been associated with healing [2,9,67-69]. After revisited post-TB chronic lung disease (PTLD) [11], new definition and spectrum phenotypes have emerged [13,70,71]. In the context of a true *extremely complex and heterogeneous phenotypic cluster,* the magnitude of PTLD prevalence and LFI are topics that have not been addressed in Romania [69]. Starting from the hypothesis that *the passive, late detection of advanced forms of PTLD is the main cause of impaired lung function*, this study aims, as **its main objective**, *to identify the impaired lung function, a PTLD phenotype,* with **secondary objectives** to assess the *ventilatory defects patterns, related to PTLD phenotypes, including chronic obstructive pulmonary disease (COPD),* and *subsequent risk of death in PTLD, LFI, COPD patients.*

II.4.2. Study material and methods

The study type was an ambispective, longitudinal cohort, conducted between 01.01.2017 and 31.05.2025, in order to cover a longer period of time, retrospectively (2017-2019) and prospectively.

The study population was represented by adult patients (≥18 years), with a history of pulmonary tuberculosis (PTB) and completed anti-TB treatment, diagnosed with chronic post-TB lung disease (PTLD), in whom lung function impairment (LFI) and PTLD phenotypes were monitored.

Inclusion criteria consisted in history of at least one episode of treated PTB, PTLD diagnosis, clinical, imaging and lung function evaluation, at least mandatory validated spirometry.

Exclusion criteria included lack of informed consent, cognitive deficit, lack of cooperation when performing spirometry, conditions that are contraindications to spirometry (severe cardiovascular disease, severe chronic respiratory failure, thromboembolism, hemoptysis in the last 30 days), diseases (such as bronchiectasis, chronic bronchitis, pulmonary fibrosis, asthma, chronic obstructive pulmonary

disease (COPD), pleural pathology), that preceded PTB first treated episode, or comorbidities responsible for lung parenchyma damage and LFI (severe forms of COVID-19 infection, HIV, neoplasms, autoimmune diseases, extreme obesity) in order to avoid bias.

The evaluation protocol included retrospective data collection from the hospital's electronic database and clinical observation records of patients with acute-evolving PTB, prior to 2020, alongside to prospective evaluation of PTLD cases diagnosed after January 2020. The evaluation of eligible cases included demographic, anthropometric, clinical, imaging, nutritional data. Assessment of dyspnea, exercise tolerance and quantification of exercise desaturation according to the covered distance were performed by *the 6-minute walk test (6MWT)* [72], pulse oximetry, mMRC (modified Medical Research Council) dyspnea scale [73], standardized CAT questionnaire (COPD- Assessment Test- COPD assessment test) [74]. *Pulmonary function testing* by spirometry was mandatory for all enrolled patients. Ventilatory dysfunction patterns (obstructive, restrictive, mixed) and LFI severity assessment by spirometry and complex lung function tests as diffusing capacity of the lungs for carbon monoxide (DLCO) and impulse oscillometry (IOS), were defined according to guidelines [75-81]:

- *obstructive ventilatory dysfunction (OVD)* by the ratio between maximum expiratory volume in the first second (FEV1) and forced vital capacity (FVC) < 70%, normal or lower FEV1 < 80%,
- *restrictive ventilatory dysfunction (RVD)* by total lung capacity (TLC) (determined by DLCO technique) below 80%; normal or increased FEV1/FVC ratio (above 70%), low FVC;
- *mixed ventilatory dysfunction (MVD)* by low FEV1/FVC ratio < 70%, FVC and FEV1 < 80%, in association with low DLCO (mild between 61-75%, moderate between 41-60% and severe ≤40 %);
- *chronic obstructive pulmonary disease (COPD)* by bronchial obstruction syndrome, identified by the ratio FEV1/ FVC <0.70; absence of reversibility ≥12% in the bronchodilator test; with the *4 stages of severity* depending on the FEV1 value: I- mild (FEV1 ≥ 80%), II- moderate (50%-79%), III- severe (30%-49%), IV- very severe (FEV1 < 30%)], corresponding to the COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification [82].

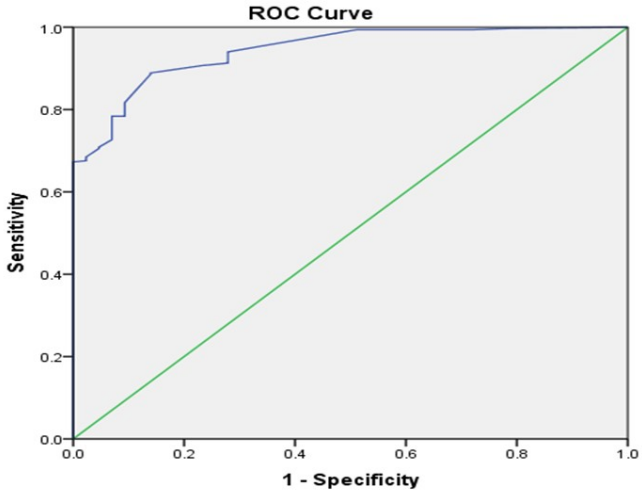
Statistical analysis done with *IBM Statistics Package for the Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, Illinois, USA),* included descriptive statistics of frequencies, analysis of variance, correlations, corresponding to a normal distribution, *Receiver Operational Characteristic analysis,* to assess the risk threshold of time interval between ended antiTB treatment and LFI occurrence. The chi ^{2} test was used to measure *the association between PTLD and LFI, COPD, the risk of death, at a statistical significance threshold* of $p < 0.05$ corresponding to a confidence level of 95%.

II.4.3. Results

II.4.3.1. Descriptive characteristics of the study cohort

The study cohort included 376 adult patients, mean aged 60.30 ± 12.61 years, predominantly males (n=253) and smokers (n=239). *The prevalence of lung function impairment (LFI)* was 86.17% (n=324/376). *The predictive time interval for LFI detection after a first treated episode of pulmonary*

tuberculosis (PTB), identified by *the Receiver Operating Characteristic (ROC) method*, according to the predictive area under the curve (AUC) of 0.944 ± 0.015 (CI95%:0.91-0.97; p < 0.001) was *6.50 months, with 94% sensitivity and 78% specificity* (Figure 7).



Variable	Area under the curve	Std Error	p<	CI 95%	
				Lower Limit	Upper Limit
Interval of time PTB- PTLD (mpnths)	.944	.015	.001	.915	.972

Figure 7. Receiver Operating Characteristic (ROC) analysis of the time interval between the diagnosis of pulmonary tuberculosis (PTB) and post-tuberculous chronic lung disease (PTLD)

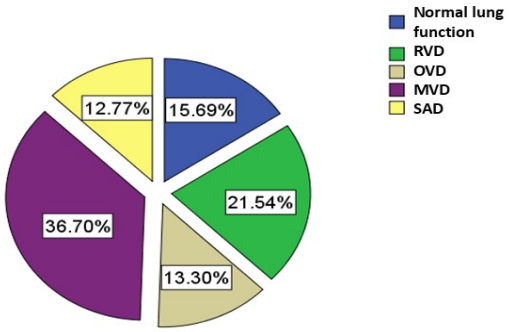
The mean age of patients with LFI was 60.43 ± 12.16 years, (median of 62 years; limits: 21- 89 years) ($p < 0.624$). *Males dominated LFI cohort* (57.41%) (OR=2.56; CI95%: 1.41-4.64; RR=1.46; CI95%: 1.09-1.96; $\chi^2 = 10.09$; $p < 0.002$).

The prevalence of smoking exposure in the PTLD cohort was 63.56% (n=239/376), and 68.20% in the LFI subcohort (n=221/324). *The risk of LFI in PTLD smokers* was 92.46% (n=221/239) versus 75.18% in *non-smokers* (n=103/137) (OR=4.05; CI95%: 2.18-7.51; RR=1.23; CI95%:1.11-1.36; $\chi^2 = 21.77$; p < *0.001*).

II.4.3.2. The phenotypes of post-tuberculosis chronic lung disease (PTLD), by concerned anatomical compartment, were classified into *subgroup 1* with lung fibrotic sequelae, or missed lung tissue (postsurgery), with 93.88% prevalence; *subgroup 2* with destroyed lung by persistent cavities ± intracavitary aspergillomas, with 16.65% prevalence; *subgroup 3* with bronchial sequelae and 81.38% prevalence; *subgroup 4* with pleural sequelae, and highest prevalence (93.88%). PTLD patients with lung function impairment (LFI) had more fibrosis in subgroup 1 ($p<0.001$), bronchial lesions in subgroup 3 ($p<0.005$) and pleural lesions in subgroup 4 ($p<0.001$). Bronchiectasis was a frequent phenotype regardless of LFI association (n=265/376; 70.48%) (p<0.129). The suppurative bronchiectasis phenotype was associated with bacterial spectrum dominated by *Pseudomonas*

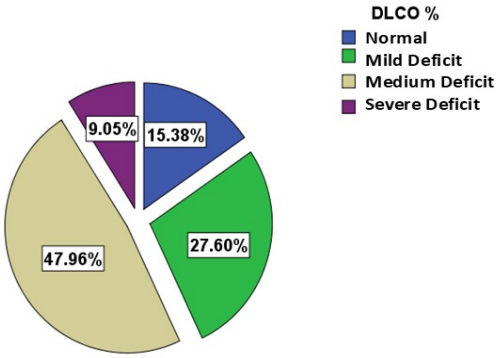
aeruginosa and *Klebsiella pneumoniae* and extended antibiotic resistance spectrum to β lactams and cephalosporins (n=27/43; 62.79%).

II.4.3.3. Classification of lung function impairment (LFI) patterns included mixed ventilatory deficit (n=138; 36.70%), obstructive (n=105; 13.30%), restrictive (n=81; 21.54%), and small airway disease (12.77%). Ventilatory deficit was classified into mild (FEV1 > 70%) in 33.02% of patients; moderate (FEV1 between 50-60%) in 30.56%; severe (FEV1 between 35-49%) in 27.78%, and very severe (FEV1 < 35%) in other 8.02% of patients (Figure 8). The diffusing capacity of the lungs for carbon monoxide (DLCO%) was <75% in 69.13% of investigated PTLD LFI cases (n=168/243), with an increased prevalence of moderate deficit (47.96%) (Figure 9).



Legend:
RVD= Restrictive Ventilatory Defect;
OVD= Obstructive Ventilatory Defect;
MVD=Mixed Ventilatory Defect;
SAD= Small Airway Disease

Figure 8. Structure of ventilatory deficits in patients with post-tuberculosis chronic pulmonary disease



Legend: DLCO = Diffusing Capacity of the Lung for Carbon Monoxide

Figure 9. Structure of DLCO deficits in percentage in patients with post-tuberculosis chronic lung disease

II.4.3.4. Evaluation of chronic obstructive pulmonary disease in the context of smoking exposure.

Chronic obstructive pulmonary disease (COPD), *a phenotype of postTB lung disease (PTLD)*, was diagnosed in 214 patients with impaired ventilatory function, corresponding to a *prevalence* of 56.91% (n=214/376), higher in smokers (n=162/221; 73.30%) versus non-smokers (n=52/103; 50.48%) (OR= 2.69; CI95%: 1.65-4.38; RR= 1.45; CI95%: 1.18- 1.78; $\chi^2 = 16.26$; $p < 0.001$). *The TB associated COPD cohort* included 2 groups: 52 non-smokers (NS) NS-TB-COPD; and 162 smokers (S) S-TB-COPD, in whom *the average number of pack/years* was 33.78±16.21.

The age of COPD patients at the time of PTB first diagnosis was not different between groups (42.31 ± 18.28 years versus 42.48±15.62 years; $p < 0.949$), but subsequently, at the time of COPD diagnosis, it was increased in NS (64.98±11.35 years) versus S (60.44±10.26 years) ($p < 0.007$).

The gender distribution of patients with TB-COPD highlights an increased male proportion in smokers (n=130/162; 80.24%) versus nonsmokers (n=27/52; 51.92%) (OR= 3.46; CI95%: 1.76-6.81;

RR= 1.48; CI95%: 1.14- 1.94; $\chi^2 = 13.63$; $p < 0.001$). *Non-smoking women had an increased prevalence of COPD* (n=25/52; 48.07%) compared to smoking women (n=32/162; 19.75%) (OR=3.76; CI95%: 1.93-7.33; RR=2.43; CI95%: 1.59-3.70; $\chi 2 = 16.08$; $p < 0.001$).

Clinical evaluation of TB-COPD patients highlights statistically significant differences in the sensation of chest tightness ($p < 0.001$) and fatigue ($p < 0.031$) in non-smokers. *Imaging evaluation of TB-COPD patients* reveals differences in the distribution of scar lung fibrosis ($p < 0.021$), bronchiectasis ($p < 0.009$), fibrothorax ($p < 0.003$), more frequent in non-smokers, compared to emphysema, more frequent in smokers ($p < 0.037$) (Table 1).

Table 1. Imaging phenotypes of TB-COPD, depending on smoking exposure

Variable	NS-TB-COPD (N=52)	S-TB-COPD (N=162)	Total N=214	OR CI95%,	$\chi 2$	$p<$
Emphysema	18	83	101	0.50 (0.26-0.96)	4.36	0.037
Scar fibrosis	47	122	169	3.08 (1.14-8.28)	5.36	0.021
Fibrothorax	11	11	22	3.68 (1.49-9.09)	8.76	0.003
Bronchiectasis	43	102	146	2.81 (1.28-6.17)	6.98	0.009
Destroyed lung	11	27	38	1.34 (0.61-2.93)	0.54	0.463
Missing lobe / missing lung*	5	9	14	1.8 (0.57-5.66)	1.06	0.303

Legend: COPD= chronic obstructive pulmonary disease; TB=tuberculosis; NF=non-smokers; F=smokers; * post-surgical intervention

Lung function assessment, by spirometry, reveals reduced mean values of forced vital capacity (FVC) in non-smokers ($p < 0.001$) and decreased bronchial permeability index (BPI) in smokers ($p < 0.002$). *COPD severity* classified in the 4 GOLD stages does not appear to be influenced by smoking exposure ($\chi^2 = 6.21$; $p < 0.400$). *The diffusing capacity of the lungs for carbon monoxide (DLCO%)* was lower in smokers ($p < 0.002$). *Impulse oscillometry (IOS)* revealed the small airways stiffness syndrome, with fibrosis and a greatly increased resonance frequency (Fres) > 20 Hz in both subgroups, but without statistically significant differences ($p < 0.733$).

Isolated TB-COPD phenotypes such as chronic bronchitis and pulmonary cachexia were similarly distributed in non-smokers (NS) and smokers (S). Emphysema occurred more frequently in S (*$p< 0.038$), in contrast to NS, in which the phenotypes of scar lung fibrosis* ($p<$ 0.021), fibrothorax ($p<$ 0.003) and bronchiectasis ($p<$ 0.009) were more frequent. *The phenotypic cluster* of bronchiectasis, lung fibrosis and COPD had an increased prevalence in NS (n= 36/52; 69.23%) versus S (n= 33/162; 20.37%) (OR= 8.79; CI95%: 4.36- 17.75; RR= 3.39; CI95%= 2.38- 4.84; $\chi 2=42.81$; $p< 0.001$).

II.4.3.3. Assessment of death risk

The risk of death in the study cohort with post-tuberculous chronic lung disease (PTLD) was 11.43% (n=43/376), increasing to 17.52 in *patients with lung function impairment* (*LFI*) (n=41/234). Over ½ of the deaths in the PTLD+LFI cohort were due to TB-COPD phenotype, regardless of smoking

exposure (n=25/41; 60.97%). *The mortality prevalence in the TB-COPD cohort, regardless of smoking exposure and comorbidities*, was 11.68% (n=25/214). *The death risk of TB-COPD patients due to severe and very severe forms of COPD* (stages III and IV GOLD) was 16.10% (n=19/118), higher in NS (n=9/28; 32.14%) compared to S (n=10/90; 9%) OR=3.43; CI95%: 1.23-9.51; RR=2.70; CI95%: 1.21-6.01; $\chi^2 = 5.97$; $p < 0.015$). Non-smoking TB-COPD males had a 4-fold increased risk of death (27.58%) compared to smoker ones (8.46%) (OR= 4.12; CI95%: 1.48- 11.45; RR= 3.39; CI95%= 2.38- 4.84; RR=3.26; CI95%: 1.44-7.38; χ 2=8.19; $p< 0.005$).

5.4. Discussion. In the final stage of tuberculosis (TB) cycle, the extent of chronic posttuberculous lung disease (PTLD), with distinct phenotypes, converging with lung function impairment (LFI), which may be greater than estimates in the literature. This study is *the first cohort study that approaches the issue and phenotypes of PTLD, from the perspective of redefined disease and spectrum* [10-13], *and developing assessment standards* [20], after Anastasatu and Didilescu prior research [9]. PTLD is a generic, umbrella terminology for a series of complications, classified into *phenotypes*, that can occur months or years after the completion of antituberculosis therapy, requiring early identification and a multidisciplinary approach [2,5,7,9,10-13]. In **study 3**, *the critical interval from PTB diagnosis to PTLD occurrence*, identified by Receiver Operational Characteristic analysis, was *6.50 months, with high sensitivity (94%) and specificity (78%),* in contrast to the threshold of 24 months stipulated in the 1980s [9]. The PTLD prevalence and phenotypes have not been yet a research topic in Romania since the 1980s [9,69]. *The phenotypes identified in the cohort of* 376 hospitalized PTLD patients included scar lung fibrosis, bronchiectasis, chronic obstructive pulmonary disease (COPD) and fibrothorax, a pathology less studied, which had a low prevalence, but highly associated with COPD in non-smokers, resulting in a distinct PTLD phenotype, with an increased risk of death. There is a great heterogeneity in the prevalence of LFI, investigated by spirometry, with limits between 18 and 87% [83]. Impaired pulmonary function is a frequent phenotype of PTLD (86.17%), in the study cohort, being at the upper limit of the values mentioned in recent years, in the literature [84,85]. In **study 3**, spirometry identified all types of ventilatory dysfunctions, with predominant mixed deficit (36.7%), followed by restrictive (21.54%) and obstructive (13.30%) dysfunction. In the literature, the prevalence of ventilatory dysfunction differs, depending on the history of *Mycobacterium tuberculosis* chemoresistance, with oscillations between 15% for restrictive deficit and 43% for mixed [86]. In other studies, obstructive deficit predominates (23-61%) [87,88].

As a particularity of **study 3**, there was an increased share of mixed dysfunction in non-smoking TB-COPD patients, in contrast to the predominant obstructive dysfunction in smokers. Severe and very severe ventilatory deficit, in the PTLD-LFI study cohort, had a prevalence of 35.8%, higher than the 26.3% identified in an African multicenter study [84]. *The reduction in gas diffusion (DLCO)* was significant in the cohort of S-TB-COPD, being attributable, on the one hand, to pulmonary emphysema [89], frequently encountered in smoker group, and, on the other hand, to the combined

phenotype of COPD with post-TB lung scaring fibrosis, since the rest of pathologies, which could have interfered the results, constituted *ab initio* exclusion criteria. In contrast to the classic phenotype of *emphysema, smoking and COPD*, which occurs predominantly in men over 40 years [90], COPD also occurs in 25–30% of nonsmokers, somewhat equally distributed by gender, more prevalent in young individuals, associated with small airway dysfunction, preserved DLCO, and a slow rate of decline in lung function [89]. TB-COPD is both a phenotype of TB, but itself has a wide spectrum of phenotypes [91–93]. *The combined phenotypes identified in the TB-COPD cohort* included scaring lung fibrosis, fibrothorax and bronchiectasis in nonsmokers; emphysema and bronchiectasis in smokers ($p < 0.031$).

According to literature data, post-TB sequelae with residual pleuro - broncho -pulmonary structural alterations are responsible for 18-80% risk of death, and LFI increases this risk [14,94]. Progressive decline in lung function leads to increased hospitalizations and risk of death [95-98]. Between 28 and 68% of patients with inactive TB lung lesions are at risk of developing COPD [99], and patients with TB-COPD have an increased risk of death even in the first year after diagnosis [100]. The risk of death highlighted in **study 3**, in TB-COPD cohort, was 11.68%, being influenced by male gender ($p< 0.005$), COPD severity (stages III and IV GOLD) and multimorbidity ($p< 0.001$). A limitation of the study in generalizing the data may be the unicentric nature and the inclusion of hospitalized patients. Given the endemicity of TB in Romania, patients suspected of developing TB are in any geographical or administrative area of our country.

6. General conclusions

1. The PhD research approaches, for the first time in Romania, pulmonary tuberculosis (PTB), at the interface of its newly defined spectrum, identifying the course of infection and disease from incipient to advanced forms, from acute to chronic phase of disease, with polymorphic structural alterations and deterioration of lung ventilatory function.
2. The discrepancy between incipient, subclinical and advanced forms of TB disease is justified by the increased severity profile, specific to inhospital morbidity, with an increased rate of bacteriological confirmation, in the context of late detection of TB.
3. The screening of interferon γ serum releasing in TB suspects, in conjunction with dinamic imaging evaluation, within a maximum of 12 months, provides, through the RAYSCAPE software program, and arguments he transition of infection into incipient disease. Thus, the multimarker composite score of mean diameter of lung nodules ≥ 9.5 mm, TB1- and TB2-Nil antigens ≥ 0.70 IU/L can anticipate and facilitate, in TB infected patients, the detection of TB disease at an early stage.
4. In the context of the COVID-19 pandemic retrospective, there is an accelerated transition from TB infection to disease and from disease to death, with reduced survival time.
5. Cavitary lesions, late detection, multimorbidity, age under 60 years, and male gender have a negative impact on the risk of death in patients with advanced PTB.

6. The severe evolution of PTB can be estimated, from the first week of hospitalization, by determining serum adenosine deaminase, systemic immuno-inflammatory index and MUST malnutrition score, prognostic biomarkers of PTB disease severity, that are easily accessible, inexpensive, and studied, for the first time, together in human pathology and in the context of advanced TBP disease.
7. The screening of postTB sequelae by complete clinical-imaging, endoscopic evaluation and functional testing should be performed early, at an optimal interval of 6 months, after the completion of anti-TB treatment.
8. The heterogeneity of isolated and combined PTLD phenotypes reveals the high prevalence of LFI, regardless of PTLD phenotype. The most common phenotype of impaired pulmonary function was mixed ventilatory dysfunction justified by the extent of fibrotic lesions, which can coexist and interact with chronic obstructive pulmonary disease (COPD), in the absence of smoking exposure.
9. This study identified antibiotic resistance of microbial flora associated with post-TB bronchiectasis exacerbations, and rare PTLD phenotypes such as tracheobronchial stenosis syndrome with cartilaginous spurs, and post-TB fibrotorax and COPD cluster phenotype, in non-smokers, with an increased risk of death (a phenotype that has not been yet reported in the literature).
10. Pulmonary function testing in PTLD patients should be performed by both spirometry and gas diffusion method, not neglecting the importance of impulse oscillometry method, capable to early revealling of small airway disease. Impulse oscillometry was used for the first time in Romania, within a doctoral research, in the evaluation of a cohort of COPD patients.

7. Originality and innovative contributions of the thesis

The doctoral research confirms that tuberculosis (TB) is a complex entity, transcending the importance of classical paradigm consisting in molecular epidemiology, acute disease notification and curability of the infectious episode. The results obtained from the three studies show that pulmonary tuberculosis (PTB) is a process with various evolutions, from exposure and latent infection, to active disease and, subsequently, to chronic post-tuberculous lung disease (PTLD), with structural and functional sequelae. **The first 2 studies** approaches the TB spectrum components in suspects and ill patients, from inactive lung sequelae and infection, to early forms of the disease, in contrast to advanced pulmonary tuberculosis (PTB), with favorable or unfavorable, lethal prognosis. **Study 1** highlighted TB spectrum distinct clinical forms, transition to incipient PTB. Low-dose computed tomography (CT) imaging monitoring, digitally assisted by RAYSCAPE software program, allows the morphometric evaluation of nodular lung lesional dynamics in patients with suspected TB. The multimarker composite score, consisting of mean diameter of lung nodules ≥9.5 mm and TB1 and TB2-Nil antigens ≥0.70 IU/L, represents a simple and extremely accessible tool in detecting incipient TB disease. **Study 2** introduced the concepts of advanced PTB [24] and delayed diagnosis [56], demonstrated the value of serum adenosine deaminase (sADA) and systemic immunoinflammatory index (SII) as prognostic biomarkers in the early definition of severe evolution [49]. The immunoinflammatory pattern, nutritional status,

clinical examination, imaging, bacteriological and molecular investigation, facilitated diagnosis and prognosis of advanced PTB by prognostic biomarkers. The assessment of nutritional status by MUST (Malnutrition Universal Screening Test) malnutrition score, using the Bapen computer [26], was used, for the first time, in a large cohort of TB patients, in Romania, and represents an original contribution of doctoral research. The use of the ADAs+SII duet, in **study 2**, to identify the critical threshold in the prognosis of advanced PTB represents, again, a premiere of Romanian research in the field of phthisiology [49], and the association of the third pillar, the MUST malnutrition score, enhances the predictability of ADAs-SII duet in the early anticipation of death risk, in the first week of hospitalization. It is the first research that propose 3 biomarkers with predictive value of advanced TBP severe evolution and risk of death.

The 3rd study explored the topic of classical post-tuberculosis respiratory syndromes, almost 40 years after the research conducted by C. Anasatastu and C. Didilescu [9] , from the perspective of modern imaging and functional-ventilatory complex exploration. The era of molecular epidemiology is overshadowed by the ballast of chronic survivors of prior treated PTB. The doctoral thesis confirms the theory that the microbiological success of clearing the contagiousness does not coincide with the restoration of pulmonary integrity and does not ensure a normal ventilatory function. The complex evaluation of lung function, by gas diffusion through the alveolar-capillary membrane (DLCO) and impulse oscillometry (IOS), represents a special contribution of the PhD research, being used, for the first time, in Romania, for evaluating a large cohort of PTLD patients.

Study 3 showed that PTLD is not a uniform and static picture, it is a dynamic expression of a great variety of imaging and functional phenotypes. The combinations between imaging phenotypes (lung fibrosis, cavities, bronchiectasis) and functional defects (obstruction, restriction, mixed) have outlined distinct clinical profiles, with variable impact on exercise capacity and quality of life. Among these particular PTLD phenotypes, described in **study 3**, *there is one not yet described in literature, post-TB COPD and fibrothorax phenotypic cluster* in non-smoking males, correlated with an increased risk of death. Also, TB associated COPD phenotype with tracheobronchial stenosis, cartilaginous spurs, retractile fibrous upper lobitis identified in doctoral research and reported at an international congress [101].

Taken together, the three studies, part of the doctoral research, demonstrate that there is not a single pattern of evolution, but a diversity of paths, determined by the interaction between the pathogen, the host's immuno-reactivity and the epidemiological context. *Innovative contributions of the doctoral research and the applicability of doctoral research results in medical practice include:*

- *the phenotype of the adult patient with incipient TB (ITB), identified predominantly in women aged <60 years, with moderate malnutrition risk, predominance of multimorbidity and COVID history;*
- *paucisymptomatic stage of ITB revealed by multimarker risk score of TB1- and TB2-Nil antigens plus the average diameter of pulmonary nodules, with progressive lesion dynamics,*

- *ITB diagnostic algorithm included digitally assisted chest CT screening using the RAYSCAPE program in dynamics to detect progressive nodular lesional progression in suspects with pulmonary nodules, positive quantitative IGRA test and multimarker risk score,*
- *the phenotype of the adult patient with a risk of severe evolution and risk of death was identified predominantly in men <60 years old, delayed diagnosed with cavitary lesions, with positive bacteriology in microscopy, detected by serum adenosine deaminase (sADA) ≥ 30.50UI/L, systemic immuno-inflammatory index (SII) ≥ 902 and MUST score ≥ 4;*
- *the algorithm for evaluating patients with advanced PTB* by *assessing nutritional status with estimation of kilograms lost, weight before and after weight loss; use of the Bapen calculator [26] for calculating the score and risk of malnutrition using the universal malnutrition screening tool (MUST); determination of sADA and complete blood count with leukocyte formula for calculating SII by the calculation formula (neutrophils x platelets)/ lymphocytes.*
- *the algorithm for early evaluation of PTLD, 6 months after the completion of anti-TB therapy,* through *clinical -imaging methods and exploration of lung ventilatory function through spirometry + DLCO and IOS*;
- *TB-COPD phenotype in non-smokers (NS) identified in elderly women, characterized by the severity of COPD, with an increased risk of death in men, phenotype to be suspected in patients with PTLD and clinical pattern dominated by thoracic constriction, functional pattern of mixed ventilatory dysfunction and DLCO% < 75%, distinct fibrotic imaging pattern, in which fibrothorax and bronchiectasis are particular components of the overlap with COPD.*

For an early identification and complex approach of PTB and PTLD phenotypes, optimized diagnostic and therapeutic protocols to prevent chronicity are necessary, protocols integrated in a molecular, clinical and morpho-functional epidemiological context.

Bibliography

1. ECDC Surveillance Report 2025. Tuberculosis Surveillance and Monitoring in Europe, 2025. https://www.ecdc.europa.eu/sites/default/files/documents/TB-2025-Surveillance-report.pdf
2. Nasta M, Brill A. Tuberculoza. Vol I, Ed Medicală, București, 1957.
3. Esmail H, Macpherson L, Coussens AK, Houben RMGJ. Mind the gap - Managing tuberculosis across the disease spectrum. EBioMedicine. 2022; 78:103928.
4. Arghir OC, Popescu GG, Marica C. Tuberculoza- Curs . Ed.Bucuresti, 2015.
5. Marica C, Didilescu C, Murgoci G, Tănăsescu M, Arghir O. Compendiu de tuberculoză. Ed.Curtea Veche, București, 2011.
6. Migliori GB, Ong CWM, Petrone L, D'Ambrosio L, Centis R, Goletti D. The definition of tuberculosis infection based on the spectrum of tuberculosis disease. Breathe (Sheff). 2021; 17(3):210079.
7. Yadav S, Rawal G. Understanding the Spectrum and Management of Post-Tuberculosis Lung Disease: A Comprehensive Review. Cureus. 2024; 16(6):e63420.

8. Xpert MTB/RIF Implementation Manual: Technical and Operational ‘How-To’; Practical Considerations. Geneva: World Health Organization; 2014. 6, Case definitions and patient registration. https://www.ncbi.nlm.nih.gov/books/NBK254327/
9. Anastasatu C, Didilescu C. Sindroamele respiratorii post-tuberculoase. Ed Medicală, București, 1987, 3-251.
10. Chakaya J., Kirenga B. & Getahun H., Long term complications after completion of pulmonary tuberculosis treatment: A quest for a public health approach. J Clin Tuberc Other Mycobact Dis. 2016; 3:10–12.
11. Allwood BW, van der Zalm MM, Amaral AFS, Byrne A, Datta S, Egere U, Evans CA, Evans D, Gray DM, Hoddinott G, Ivanova O, Jones R, Makanda G, Marx FM, Meghji J, Mpagama S, Pasipanodya JG, Rachow A, Schoeman I, Shaw J, Stek C, van Kampen S, von Delft D, Walker NF, Wallis RS, Mortimer K. Post-tuberculosis lung health: perspectives from the First International Symposium. Int J Tuberc Lung Dis. 2020; 24(8):820-828.
12. Mpagama SG, Msaji KS, Kaswaga O, Zurba LJ, Mbelele PM, Allwood BW, Ngungwa BS, Kisonga RM, Lesosky M, Rylance J, Mortimer K. The burden and determinants of post-TB lung disease. Int J Tuberc Lung Dis. 2021; 25(10):846-853.
13. Visca D, Centis R, Munoz-Torrico M, Pontali E. Post-tuberculosis sequelae: the need to look beyond treatment outcome. Int J Tuberc Lung Dis. 2020; 24(8):761-762.
14. Ranzani OT, Rodrigues LC, Bombarda S, Minto CM, Waldman EA, Carvalho CRR. Long-term survival and cause-specific mortality of patients newly diagnosed with tuberculosis in São Paulo state, Brazil, 2010-15: a population-based, longitudinal study. Lancet Infect Dis. 2020; 20(1):123-132.
15. Reis-Santos B, Rocha MS. Tuberculosis: an instrument of early mortality in life course. Lancet Infect Dis. 2020; 20(1):11-12.
16. Chung KP, Chen JY, Lee CH, Wu HD, Wang JY, Lee LN, Yu CJ, Yang PC; TAMI Group. Trends and predictors of changes in pulmonary function after treatment for pulmonary tuberculosis. Clinics (Sao Paulo). 2011; 66(4):549-556.
17. Gandhi K, Gupta S, Singla R. Risk factors associated with development of pulmonary impairment after tuberculosis. Indian J Tuberc. 2016; 63(1):34-38.
18. Cupido G, Günther G. Post tuberculosis lung disease and tuberculosis sequelae: A narrative review. Indian J Tuberc. 2024; 71(1):64-72.
19. Singla R, Mallick M, Mrigpuri P, Singla N, Gupta A. Sequelae of pulmonary multidrug-resistant tuberculosis at the completion of treatment. Lung India. 2018; 35(1):4-8.
20. Migliori GB, Marx FM, Ambrosino N, Zampogna E, Schaaf HS, van der Zalm MM, Allwood B, Byrne AL, Mortimer K, Wallis RS, Fox GJ, Leung CC, Chakaya JM, Seaworth B, Rachow A, Marais BJ, Furin J, Akkerman OW, Al Yaquobi F, Amaral AFS, Borisov S, Caminero JA, Carvalho ACC, Chesov D, Codecasa LR, Teixeira RC, Dalcolmo MP, Datta S, Dinh-Xuan AT, Duarte R, Evans CA, García-García JM, Günther G, Hoddinott G, Huddart S, Ivanova O, Laniado-Laborín R, Manga S, Manika K, Mariandyshev A, Mello FCQ, Mpagama SG, Muñoz-Torrico M, Nahid P, Ong CWM, Palmero DJ, Piubello A, Pontali E, Silva DR, Singla R, Spanevello A, Tiberi S, Udwadia ZF, Vitacca M, Centis R, D Ambrosio L, Sotgiu G, Lange C, Visca D. Clinical standards for the assessment, management and rehabilitation of post-TB lung disease. Int J Tuberc Lung Dis. 2021; 25(10):797-813.
21. Barry CE 3rd, Boshoff HI, Dartois V, Dick T, Ehrt S, Flynn J, Schnappinger D, Wilkinson RJ, Young D. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat Rev Microbiol. 2009; 7(12):845-855.
22. Dheda K, Migliori GB. New framework to define the spectrum of tuberculosis. Lancet Respir Med. 2024; 12(6):426-428.

23. Buonsenso D, Sali M, Focarelli B, Onesimo R, Palucci I, Delogu G, Valentini P. The tuberculosis spectrum: Translating basic research into pediatric clinical practice. Med Hypotheses. 2020; 141:108091.
24. Wallace RM, Kammerer JS, Iademarco MF, Althomsons SP, Winston CA, Navin TR. Increasing proportions of advanced pulmonary tuberculosis reported in the United States: are delays in diagnosis on the rise? Am J Respir Crit Care Med. 2009; 180(10):1016-1022.
25. World Health Organization WHO. Definitions and reporting framework for tuberculosis - 2013 revision. Geneva: World Health Organization; 2013. https://iris.who.int/bitstream/handle/10665/79199/9789241505345_eng.pdf?sequence=1
26. Elia M. The "MUST" Report. Nutritional Screening of Adults: A Multidisciplinary Responsibility. Development and Use of the "Malnutrition Universal Screening Tool" ('MUST') for Adults. BAPEN; Redditch, UK: 2003. Chairman of MAG and Editor Advancing Clinical Nutrition, a Standing Committee of BAPEN.
27. Ghid Metodologic din 31 martie 2022 de implementare a programului național de prevenire, supraveghere și control al tuberculozei și altor micobacterioze. Publ Monitorul Oficial nr 326 bis din 4 aprilie 2022. [online]. https://legislatie.just.ro/Public/DetaliiDocument/297973
28. Ghid Național Managementul tuberculozei drog rezistente. Societatea Română de Pneumologie. 2023. https://srp.ro/ghiduri/GHID%20MDR%202023.pdf
29. Skou FS, Fortin M, Guthrie B, Nunes BP, Miranda JJ, Boyd CM, Pati S, Mtenga S, Smith SM. Multimorbidity. Nat Rev Dis Primers. 2022; 8(14):48.
30. Kiazyk S, Ball TB. Latent tuberculosis infection: An overview. Can Commun Dis Rep. 2017; 43(3-4):62-66.
31. Achkar JM, Jenny-Avital ER. Incipient and subclinical tuberculosis: defining early disease states in the context of host immune response. J Infect Dis. 2011; 204(Suppl 4):S1179-1186.
32. Behr MA, Kaufmann E, Duffin J, Edelstein PH, Ramakrishnan L. Latent Tuberculosis: Two Centuries of Confusion. Am J Respir Crit Care Med. 2021; 204(2):142-148.
33. Drain PK, Bajema KL, Dowdy D, Dheda K, Naidoo K, Schumacher SG, Ma S, Meermeier E, Lefwinsohn DM, Sherman DR. Incipient and Subclinical Tuberculosis: a Clinical Review of Early Stages and Progression of Infection. Clin Microbiol Rev. 2018; 31(4):e00021-18.
34. Zaidi SMA, Coussens AK, Seddon JA, Kredo T, Warner D, Houben RMGJ, Esmail H. Beyond latent and active tuberculosis: a scoping review of conceptual frameworks. The Lancet, 2023; 66:102332.
35. Mnyambwa NP, Philbert D, Kimaro G, Wandiga S, Kirenga B, Mmbaga BT, Muttamba W, Najjingo I, Walusimbi S, Nuwarinda R, Okelloh D, Semvua H, Ngocho J, Senkoro M, Stephen O, Castelnuovo B, Wilfred A, Mgina E, Sanga C, Aman F, Kahwa A, Mfinanga S, Ngadaya E. Gaps related to screening and diagnosis of tuberculosis in care cascade in selected health facilities in East Africa countries: A retrospective study. J Clin Tuberc Other Mycobact Dis. 2021; 25:100278.
36. Shah HD, Nazli Khatib M, Syed ZQ, Gaidhane AM, Yasobant S, Narkhede K, Bhavsar P, Patel J, Sinha A, Puwar T, Saha S, Saxena D. Gaps and Interventions across the Diagnostic Care Cascade of TB Patients at the Level of Patient, Community and Health System: A Qualitative Review of the Literature. Trop Med Infect Dis. 2022; 7(7):136.
37. World Health Organization. WHO Global tuberculosis report 2024 https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/tb-reports/global-tuberculosis-report-2024
38. Fildan AP, **Arghir IA**, Popescu GG, Matei C, Nemes RM, Tofolean D, Dantes E, Pop CS, Cambrea SC. The Prevalence and Spectrum of Mycobacterium Tuberculosis Chemoresistance among TB Patients. Farmacia. 2020; 68(1):129-134.

39. Ding C, Hu M, Guo W, Hu W, Li X, Wang S, Shangguan Y, Zhang Y, Yang S, Xu K. Prevalence trends of latent tuberculosis infection at the global, regional, and country levels from 1990-2019. Int J Infect Dis. 2022; 122:46-62.
40. Popescu GG, Moisoiu A, Fildan AP, Tofolean DE, **Arghir IA**, Ion I, Arghir OC. Genexpert rapid detection of rifampicin resistance among patients with pulmonary tuberculosis. Rom Biotechnol Lett. 2021; 26(1): 2283-2288.
41. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, Compher C, Correia I, Higashiguchi T, Holst M, Jensen GL, Malone A, Muscaritoli M, Nyulasi I, Pirlich M, Rothenberg E, Schindler K, Schneider SM, de van der Schueren MA, Sieber C, Valentini L, Yu JC, Van Gossum A, Singer P. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr. 2017; 36(1):49-64.
42. Ockenga J, Fuhse K, Chatterjee S, Malykh R, Rippin H, Pirlich M, Yedilbayev A, Wickramasinghe K, Barazzoni R. Tuberculosis and malnutrition: The European perspective. Clin Nutr. 2023; 42(4):486-492.
43. **Arghir I**, Ion I, Dantes E, Fildan Ap, Tofolean D, Cambrea S, Babu L, Arghir OC. Severe COVID-19 Associated with Advanced Forms of Pulmonary TB Disease in an Endemic Area of Romania. Chest. 2022; 161(6):A342.
44. Lönnroth K, Migliori GB, Abubakar I, D'Ambrosio L, de Vries G, Diel R, Douglas P, Falzon D, Gaudreau MA, Goletti D, González Ochoa ER, LoBue P, Matteelli A, Njoo H, Solovic I, Story A, Tayeb T, van der Werf MJ, Weil D, Zellweger JP, Abdel Aziz M, Al Lawati MR, Aliberti S, Arrazola de Oñate W, Barreira D, Bhatia V, Blasi F, Bloom A, Bruchfeld J, Castelli F, Centis R, Chemtob D, Cirillo DM, Colorado A, Dadu A, Dahle UR, De Paoli L, Dias HM, Duarte R, Fattorini L, Gaga M, Getahun H, Glaziou P, Goguadze L, Del Granado M, Haas W, Järvinen A, Kwon GY, Mosca D, Nahid P, Nishikiori N, Noguer I, O'Donnell J, Pace-Asciak A, Pompa MG, Popescu GG, Robalo Cordeiro C, Rønning K, Ruhwald M, Sculier JP, Simunović A, Smith-Palmer A, Sotgiu G, Sulis G, Torres-Duque CA, Umeki K, Uplekar M, van Weezenbeek C, Vasankari T, Vitillo RJ, Voniatis C, Wanlin M, Raviglione MC. Towards tuberculosis elimination: an action framework for low-incidence countries. Eur Respir J. 2015; 45(4):928-952.
45. Conlon BA, Law WR. Macrophages are a source of extracellular adenosine deaminase-2 during inflammatory responses. Clin Exp Immunol. 2004; 138(1):14-20.
46. Zhuang L, Yang L, Li L, Ye Z, Gong W. Mycobacterium tuberculosis: immune response, biomarkers, and therapeutic intervention. MedComm (2020). 2024; 5(1):e419.
47. Soedarsono S, Prinasetyo KWAI, Tanzilia M, Nugraha J. Changes of serum adenosine deaminase level in new cases of pulmonary tuberculosis before and after intensive phase treatment. Lung India. 2020; 37(2):126-129.
48. Binesh F, Jalali H, Zare MR, Behravan F, Tafti AD, Behnaz F, Tabatabaee M, Shahcheraghi SH. Diagnostic value of sputum adenosine deaminase (ADA) level in pulmonary tuberculosis. Germs. 2016; 6(2):60-5.
49. **Arghir IA**, Arghir OC, Otelea MR, Andronache IT, Ion I. Adenosine Deaminase and Systemic Immune Inflammatory Index-A Biomarker Duet Signature of Pulmonary Tuberculosis Severity. Medicina (Kaunas). 2025; 61(6):1096.
50. Liu J, Li S, Zhang S, Liu Y, Ma L, Zhu J, Xin Y, Wang Y, Yang C, Cheng Y. Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio can predict clinical outcomes in patients with metastatic non-small-cell lung cancer treated with nivolumab. J Clin Lab Anal. 2019; 33(8):e22964.

51. Mangoni AA, Zinellu A. The diagnostic role of the systemic inflammation index in patients with immunological diseases: a systematic review and meta-analysis. Clin Exp Med. 2024; 24(1):27.
52. Zhong JH, Huang DH, Chen ZY. Prognostic role of systemic immune-inflammation index in solid tumors: a systematic review and meta-analysis. Oncotarget. 2017; 8(43):75381-75388.
53. Kerget B, Afşin DE, Aksakal A. The role of systemic immune-inflammation index (SII) in the differential diagnosis of granulomatous and reactive LAP diagnosed by endobronchial ultrasonography. Sarcoidosis Vasc Diffuse Lung Dis. 2023; 40(3):e2023038.
54. Fois AG, Paliogiannis P, Scano V, Cau S, Babudieri S, Perra R, Ruzzittu G, Zinellu E, Pirina P, Carru C, Arru LB, Fancellu A, Mondoni M, Mangoni AA, Zinellu A. The Systemic Inflammation Index on Admission Predicts In-Hospital Mortality in COVID-19 Patients. Molecules. 2020; 25(23):5725.
55. Karaaslan, T.; Karaaslan, E. Predictive Value of Systemic Immune-inflammation Index in Determining Mortality in COVID-19 Patients. J Crit Care Med (Targu Mures). 2022, 8(3):156-164.
56. Ahmad Z, Zubair I, Ahmad S, Zuber N, Salar W. Reasons and extent of delay in the diagnosis of pulmonary tuberculosis after the appearance of symptoms. J Family Med Prim Care. 2024 May;13(5):1683-1687.
57. Salmanzadeh S, Tavakkol H, Bavieh K, Alavi SM. Diagnostic Value of Serum Adenosine Deaminase (ADA) Level for Pulmonary Tuberculosis. Jundishapur J Microbiol. 2015; 8(3):e21760.
58. Barua R, Hossain M. Adenosine Deaminase in Diagnosis of Tuberculosis: A Review. Anwer Khan Mod Med Coll J.2014; 5(2), 43–48.
59. Verma M, Narang S, Moonat A, Verma A. Study of adenosine deaminase activity in pulmonary tuberculosis and other common respiratory diseases. Indian J Clin Biochem.2004;19(1):129-131.
60. Saini V, Lokhande B, Jaswal S, Aggarwal D, Garg K, Kaur J. Role of serum adenosine deaminase in pulmonary tuberculosis. Indian J Tuberc. 2018; 65(1):30-34.
61. Pandey R, Tamrakar D, Jaiswal S, Sharma A, Koju S, Duwal S. R, Sharma I, Jayaswal R. P, Pankaj P. P. Serum Adenosine Deaminase: A Novel Biomarker Tool For The Diagnosis Of Tuberculosis. Biosci Biotechnol Res Asia, 2016; 13(1).
62. Jadhav AA, Kumar A, Khurana AK, Kanwar JR, Kotnis A, Lokhande SL. Diagnostic Accuracy of Adenosine Deaminase Levels in Peripheral Blood Lymphocyte of Patients with Pulmonary Tuberculosis. Ann Afr Med. 2025. French, English. doi: 10.4103/aam.aam_212_24.
63. Rokayan SA. Serum adenosine deaminase activity and its isoenzyme in patients treated for tuberculosis. J Coll Physicians Surg Pak. 2003; 13(1):11-4.
64. Miyata S, Tanaka M, Ihaku D. The prognostic significance of nutritional status using malnutrition universal screening tool in patients with pulmonary tuberculosis. Nutr J. 2013; 12:42.
65. Miyata S, Tanaka M, Ihaku D. Usefulness of the Malnutrition Screening Tool in patients with pulmonary tuberculosis. Nutrition. 2012; 28(3):271-274.
66. Maleche-Obimbo E, Odhiambo MA, Njeri L, Mburu M, Jaoko W, Were F, Graham SM. Magnitude and factors associated with post-tuberculosis lung disease in low- and middle-income countries: A systematic review and meta-analysis. PLOS Glob Public Health. 2022; 2(12):e0000805.
67. Anno H, Tomashefski JF. Studies on the impairment of respiratory function in pulmonary tuberculosis. Am Rev Tuberc. 1955; 71(3, Part 1):333-348.

68. Gaensler EA, Lindgren I. Chronic bronchitis as an etiologic factor in obstructive emphysema; preliminary report. Am Rev Respir Dis. 1959; 80(1, Part 2):185-93.
69. **Arghir IA**, Arghir OC, Andronache IT, Ion I. Spectrum of Post Tuberculosis Chronic Lung Disease in Patients with Previous Bacteriologically Confirmed Pulmonary Tuberculosis. Curr Health Sci J. 2025; 51(2): 279-288; DOI: 10.12865/CHSJ.51.02.13.
70. Allwood B, van der Zalm M, Makanda G, Mortimer K; Steering Committee of the First International Post-Tuberculosis Symposium. The long shadow post-tuberculosis. Lancet Infect Dis. 2019; 19(11):1170-1171.
71. Allwood BW, Byrne A, Meghji J, Rachow A, van der Zalm MM, Schoch OD. Post-Tuberculosis Lung Disease: Clinical Review of an Under-Recognised Global Challenge. Respiration. 2021; 100(8):751-763.
72. American Thoracic Society Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002; 166(1):111-117. Erratum in: Am J Respir Crit Care Med. 2016;193(10):1185.
73. Sunjaya A, Poulos L, Reddel H, Jenkins C. Qualitative validation of the modified Medical Research Council (mMRC) dyspnoea scale as a patient-reported measure of breathlessness severity. Respir Med. 2022; 203:106984.
74. Jones P, Harding G, Wiklund I, Berry P, Leidy N. Improving the process and outcome of care in COPD: development of a standardised assessment tool. Prim Care Respir J. 2009; 18(3):208-215.
75. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J. 2005; 26(2):319-338.
76. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, Kaminsky DA, McCarthy K, McCormack MC, Oropez CE, Rosenfeld M, Stanojevic S, Swanney MP, Thompson BR. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019; 200(8):e70-e88.
77. Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, MacIntyre NR, Thompson BR, Wanger J. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J. 2017; 49(1):1600016. Erratum in: Eur Respir J. 2018;52(5):1650016.
78. King GG, Bates J, Berger KI, Calverley P, de Melo PL, Dellacà RL, Farré R, Hall GL, Ioan I, Irvin CG, Kaczka DW, Kaminsky DA, Kurosawa H, Lombardi E, Maksym GN, Marchal F, Oppenheimer BW, Simpson SJ, Thamrin C, van den Berge M, Oostveen E. Technical standards for respiratory oscillometry. Eur Respir J. 2020; 55(2):1900753.
79. Kaminsky DA, Simpson SJ, Berger KI, Calverley P, de Melo PL, Dandurand R, Dellacà RL, Farah CS, Farré R, Hall GL, Ioan I, Irvin CG, Kaczka DW, King GG, Kurosawa H, Lombardi E, Maksym GN, Marchal F, Oostveen E, Oppenheimer BW, Robinson PD, van den Berge M, Thamrin C. Clinical significance and applications of oscillometry. Eur Respir Rev. 2022; 31(163):210208.
80. Danteș E, Andrei DG, **Arghir IA**, Ciociodei SL, Cioroiu I, Cîrjaliu RE, Gherca S, Ghițulescu I, Lupșa S, Pîslan V, Pohrib I, Stanciu IV, Ștefan CA, Ștefănescu F. Explorarea paraclinică a aparatului respirator. Note de curs. Ed Pro Universitaria, 2021; Capitolul 4:171-192.
81. Budin CE, Nemeș RM, Ianoși ES. Explorările funcționale aplicații practice, cazuri clinice. Ed Pro Universitaria, 2023:11-27.
82. Lin JS, Webber EM, Thomas RG. Screening for Chronic Obstructive Pulmonary Disease: A Targeted Evidence Update for the U.S. Preventive Services Task Force [Internet]. Rockville

(MD): Agency for Healthcare Research and Quality (US); 2022 May. (Evidence Synthesis, No. 215.) Table 1, Classification of COPD as Defined by Global Initiative for Chronic Obstructive Lung Disease (GOLD) https://www.ncbi.nlm.nih.gov/books/NBK580644/table/ch1.tab1/

83. Taylor J, Bastos ML, Lachapelle-Chisholm S, Mayo NE, Johnston J, Menzies D. Residual respiratory disability after successful treatment of pulmonary tuberculosis: a systematic review and meta-analysis. EClinicalMedicine. 2023; 59:101979.
84. Mkoko P, Naidoo S, Mbanga LC, Nomvete F, Muloiwa R, Dlamini S. Chronic lung disease and a history of tuberculosis (post-tuberculosis lung disease): Clinical features and in-hospital outcomes in a resource-limited setting with a high HIV burden. S Afr Med J. 2019; 109(3):169-173.
85. Rachow A, Ivanova O, Bakuli A, Khosa C, Nhassengo P, Owolabi O, Jayasooriya S, Ntinginya NE, Sabi I, Rassool M, Bennet J, Niemann S, Mekota AM, Allwood BW, Wallis RS, Charalambous S, Hoelscher M, Churchyard G. Performance of spirometry assessment at TB diagnosis. Int J Tuberc Lung Dis. 2023; 27(11):850-857.
86. Ivanova O, Hoffmann VS, Lange C, Hoelscher M, Rachow A. Post-tuberculosis lung impairment: systematic review and meta-analysis of spirometry data from 14 621 people. Eur Respir Rev. 2023 Apr 19;32(168):220221.
87. Gaensler EA, Lindgren I. Chronic bronchitis as an etiologic factor in obstructive emphysema; preliminary report. Am Rev Respir Dis. 1959; 80(1, Part 2):185-93.
88. Sinder GL, Doctor L, Demas TA. Obstructive airway disease in patients with treated pulmonary tuberculosis. Am Rev Resp Dis. 1971; 103: 625- 640.
89. Salzman SH. Which pulmonary function tests best differentiate between COPD phenotypes? Respir Care. 2012; 57(1):50-57;
90. Friedlander AL., Lynch D, Dyar LA, Bowler RP. Phenotypes of Chronic Obstructive Pulmonary Disease. COPD: J Chron Obstr Pulm Dis. 2007; 4 (4): 355–84.
91. Kakavas S, Kotsiou OS, Perlikos F, Mermiri M, Mavrovounis G, Gourgoulianis K, Pantazopoulos I. Pulmonary function testing in COPD: looking beyond the curtain of FEV1. NPJ Prim Care Respir Med. 2021; 31(1):23.
92. Byrne A, Al-Hindawi Y, Plit M, Yeung L, Rigava S, King M, Ng K, Mungovan SF. The prevalence and pattern of post tuberculosis lung disease including pulmonary hypertension from an Australian TB service; a single-centre, retrospective cohort study. BMC Pulm Med.2025; 25:84
93. Fortis S, Georgopoulos D, Tzanakis N, Sciurba F, Zabner J, Comellas AP. Chronic obstructive pulmonary disease (COPD) and COPD-like phenotypes. Front Med (Lausanne). 2024; 11:1375457.
94. Ratnakumar S, Hayward SE, Denneny EK, Goldsmith LP, Evans R, Checkley W, Goletti D, Ong CWM, Gotowiec M, Zhu J, Friedland JS, Porter JC. Post-pulmonary tuberculosis lung function: a systematic review and meta-analysis. Lancet Glob Health. 2025; 13(6):e1020-e1029.
95. Ranzani OT, Rodrigues LC, Bombarda S, Minto CM, Waldman EA, Carvalho CRR. Long-term survival and cause-specific mortality of patients newly diagnosed with tuberculosis in São Paulo state, Brazil, 2010-15: a population-based, longitudinal study. Lancet Infect Dis. 2020; 20(1):123-132.
96. Choi JY. Pathophysiology, clinical manifestation, and treatment of tuberculosis-associated chronic obstructive pulmonary disease: a narrative review. Ewha Med J. 2025; 48(2):e24.
97. Jiang Z, Dai Y, Chang J, Xiang P, Liang Z, Yin Y, Shen Y, Wang R, Qiongda B, Chu H, Li N, Gai X, Liang Y, Sun Y. The Clinical Characteristics, Treatment and Prognosis of Tuberculosis-Associated Chronic Obstructive Pulmonary Disease: A Protocol for a Multicenter Prospective Cohort Study in China. Int J Chron Obstruct Pulmon Dis. 2024; 19:2097-2107.

98. Choi H, Han K, Jung JH, Park SH, Kim SH, Kang HK, Sohn JW, Shin DW, Lee H. Long-Term Mortality of Tuberculosis Survivors in Korea: A Population-based Longitudinal Study. Clin Infect Dis. 2023; 76(3):e973-e981.
99. Fan H, Wu F, Liu J, Zeng W, Zheng S, Tian H, Li H, Yang H, Wang Z, Deng Z, Peng J, Zheng Y, Xiao S, Hu G, Zhou Y, Ran P. Pulmonary tuberculosis as a risk factor for chronic obstructive pulmonary disease: a systematic review and meta-analysis. Ann Transl Med. 2021; 9(5):390.
100. Sershen CL, Salim T, May EE. Investigating the comorbidity of COPD and tuberculosis, a computational study. Front Syst Biol. 2023; 3:940097.
101. **Arghir I**, Ion I, Cioti C, Fildan A, Arghir O. Heterogenous Chronic Postuberculosis Lung Disease Associated a Rare Cartilaginous Endobronchial Involvement. Case Report**.** European Journal of Case Reports in Internal Medicine Abstract Book ECIM 2023; 1056; Submission 2151: 488; DOI: 10.12890/2023_V10Sup1.