

# Basic and Descriptive Spectrum of Tuberculosis in a Large Cohort of Hospitalized Patients

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**ABSTRACT:** After 143 years from the discovery of Koch bacillus, the natural history of tuberculosis (TB) is characterized by heterogeneity and gaps of staging defining. The aim of the study consists in assessing the prevalence and characteristics of TB stages, from infection to disease, from acute to chronic disease, among inpatients of Constanta Clinical Pneumophthysiology Hospital. A cross sectional 8-year study, performed, from January 2017 to March 2025, among 630 inpatients, mean aged 58.23 years+/-13.812 std dev, mostly men (n=436; 69.2%) and smokers (n=414; 65.71%), enrolled with a positive diagnosis of TB infection (75 cases, based on positive QuantiFERON TB Gold Plus, 4% progressive forms), or disease (424 infectious, 410 new cases and 178 relapses, 35 multi drug resistant, 17 with mono or poly drug resistance). Subclinical TB was significantly more infectiousness than clinical forms (p=0.000). Active TB disease is characterized by delayed diagnosis (58.57%) and advanced extensive cavitary lesions (73.17%). Post treated lung TB disease (PTLD) occurred in 74.91% of cases, after a mean interval of almost 17 years (205.68 months+/-214.00 std dev), calculating from the first episode of treated TB disease. TB mortality rate was 16.66‰. In conclusion, landscaping tuberculosis' new stages is very complex and challenging. TB infection and subclinical TB are intricated through progressive forms of infection. PTLT must be considered a part of the basic triangle of TB spectrum, standing near infection and active disease, states in a continuous dynamic relation, overlapping through reinfections and relapses, causing PTLT and death.

**KEYWORDS:** Spectrum of tuberculosis, tuberculosis infection, subclinical tuberculosis, clinical tuberculosis, post tuberculosis chronic lung disease.

## Introduction

Tuberculosis (TB) is a timeless symbol of a persistent quiescent and versatile infectious disease, sometimes aggressive and cruel, which continues to surprise and challenge medical world [1].

Natural history of TB described latent and manifest progressive infection, subclinical and clinical stages of disease, with incipient or advanced morphological lesions, pulmonary and/or extrapulmonary involvement, limited or extensive lesions, healed or unresolved, persistent lesions, survival or death.

Important contributors to fatal outcomes of TB disease are delayed diagnosis, the absence or inadequate therapy, non-adherence to anti-TB drugs, and multi resistant strains of Mycobacterium tuberculosis (MTB) along with high risk factors of tuberculosis' occurrence.

Post TB lung disease (PTLD) is the last but not the least piece in the cascade of illness and death.

The substantial heterogeneity of clinical and radiological features of disease requires an increased awareness to the new definition of TB and its spectrum of manifestations, rethinking TB pathogenesis and immunology [2,3].

Latent TB infection (LTBI) means no clinical or radiological manifestations of TB disease, and

a logic debate occurs when there are detected lungs abnormalities by computed tomography (CT). In this context, the binary classification of TB in CT era is no more suitable.

World Health Organization (WHO) proposed the terminology of "TB infection" (TBI) with removal of the word "latent" from the previous used terminology (LTBI) [2,4,5].

New framework for TB states and concepts related to early stage of TB disease require future research for a better understanding of unstable states as TBI and risk of progression to disease.

Early TB, placed beyond LTBI, TBI and TB disease, is highly inconsistent [6].

There are cases more or less symptomatic, without history of treated TB, having imagistic high suggestive lung lesions.

Predisposing conditions as poverty, under nutrition, immunosuppressive agents or corticosteroid prolonged therapy, co-infection with HIV or SARS-CoV-2, diabetes, cancer, end-stage renal disease, silicosis, alcoholism or intravenous drug use are major determinants of progressive TBI towards disease occurrence [7,8].

Romania is still a high burden TB country and, after COVID-19 pandemic, the risk of infection and disease remains underestimated.

This research study proposed to classify, identify and describe different forms of TB

spectrum related to the subsequent stages from infection to active disease and chronic PTLD in a large group of hospitalized patients.

## Patients and Methods

A cross-sectional 8-year observational study was performed, from January 2017 to March 2025, among 676 patients, suspected or diagnosed with pulmonary tuberculosis (PTB), hospitalized in Constanta Clinical Pneumophthisiology Hospital, from South Eastern Region of Romania.

**Collection data** included a complex process of analyzing, retrospectively and/or prospectively, hospital electronic records and Patient Clinical Observation Sheets.

All demographic, behavioral, clinical and paraclinical information related to the diagnosis criteria of TB infection (TBI), TB active disease (TBAD), drug-resistance (DR), were included in data base, as well as the chronologic data about TBI, TBAD, DR, PTLD, deaths.

**The inclusion criteria** consisted in a previous informed consent, respecting privacy and human rights; accessibility to clinical and paraclinical data, including imagistic details, mentioned by chest X-ray and CT reports.

Eligible cases were considered patients confirmed with TBI or TBAD, including cases evolving from infection to disease and from active disease to PTLD.

TBI was assessed by positive QuantiFERON Test (TB Gold Plus) with TB1 and TB2 Antigen  $\geq 0.35$ , representing  $\geq 25\%$  of Nil value (according to manufacturer standards).

TBAD included all cases bacteriologically or clinically confirmed (when criteria for bacteriological confirmation missing), based on clinical and imagistic features (chest X-ray and/or CT), or suggestive histology with TB treatment started.

Notified treated TB cases were classified, by treatment outcome, into new cases and relapses, abandon or failure, death. Cases lost to follow up or transferred were excluded.

We excluded 46 patients with high suspicion of PTB, without history of antiTB therapy or signs of a positive diagnosis of TBI or TBAD.

**Study group** included 630 adults. According to the presence of symptoms, TB active disease cases were divided into subclinical (asymptomatic) and clinical (symptomatic) groups.

Personal medical history was followed till the date of the first episode of TB disease (primary or post primary forms), considered new case, monitoring relapses' occurrence in time, as well as first assessment of PTLD, in previously treated TB patients.

All data about bacteriological methods of smear and cultures' positivity (liquid culture BACTEC MGIT 960 and solid culture Lowenstein Jensen), drug sensitivity test (DST), rapid diagnostic molecular tests [Line Probe Assay (LPA), Xpert MTB/RIF, Xpert MTB/XDR], clinical and imagistic features, histopathologic investigation were assessed.

**Statistical analysis** was performed by SPSS 20th version and Epi Info 7.2.7.0, calculating frequencies, differences between subgroups, t-test for continuous variables, Pearson chi square for comparing categorical variables, variance analysis (ANOVA) of mean values, linearity tests for continuous variables, Spearman correlations, odds ratio (OR) and risk ratio (RR), for a level of significance of  $p < 0.05$ .

## Results

A large group of 630 cases, mean aged 58.23 years+13.812 std dev, with male predominance (n=436; 69.2%; 2.25 M/F ratio), older females (59.91 years+14.199 std dev compare to 57.48 years+13.586 std dev;  $F=4.187$ ;  $p < 0.041$ ).

According to the classic binary classification of TB, firstly, there were analyzed: TB infected patients (n=75; 11.90%) and TB treated patients (n=555; 88.09%) (Figure 1).

Patients with TBI (n=75), positive reactors to QuantiFERON TB Gold Plus, had intermediate mean values of Antigen TB1 and TB2 (5.491+3.225 std dev, respectively 4.9962+3.268), TB1 and TB2 Antigen NIL (4.996+3.122, respectively 5.041+3.134 std dev).

All TBI cases had a high CT suspicion of early TB disease, because of imagistic abnormalities. The follow-up imagistic, bacteriological and molecular investigations revealed 4% rate of progression from infection to TBAD (n=3/75).

According to the new definition of TB spectrum, the TBI group included 72 patients and the rest of ill patients (N=558) were divided into 2 stages of disease: subclinical TB (SC-TB) (n=51), including 3 cases of former TBI, and clinical TB (C-TB) (n=507) (Figures 1 and 2).

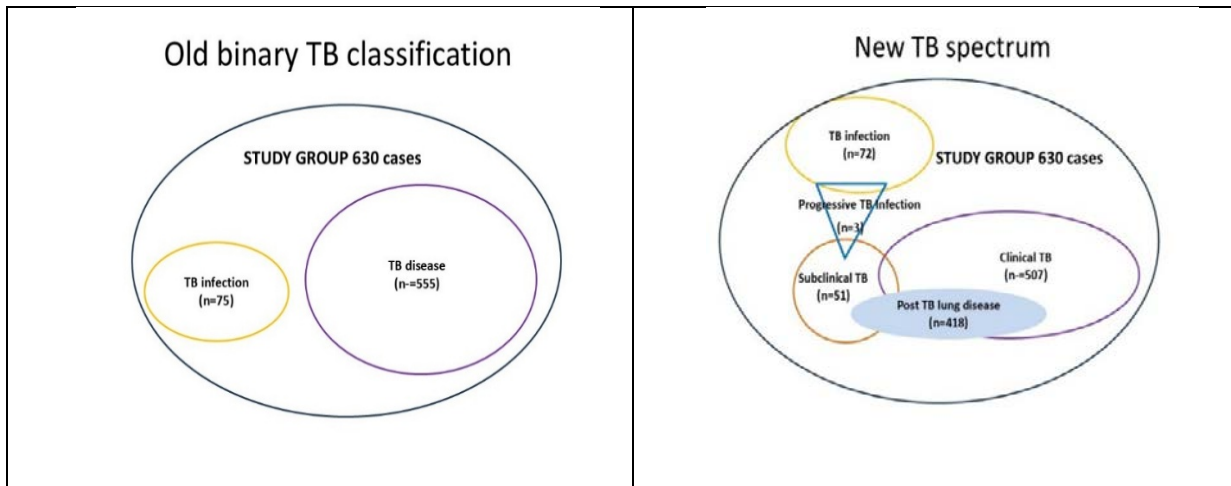


Figure 1. Switching the distribution of study cases into different groups according to old and new definition of TB spectrum.

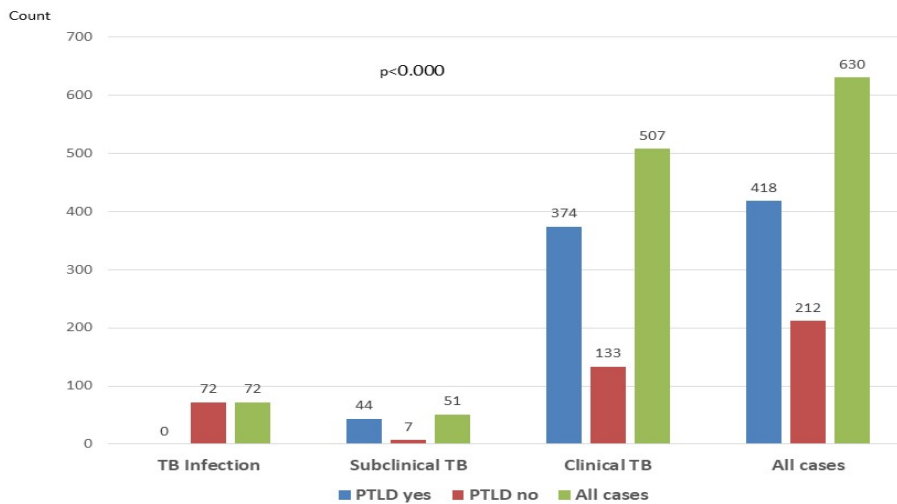


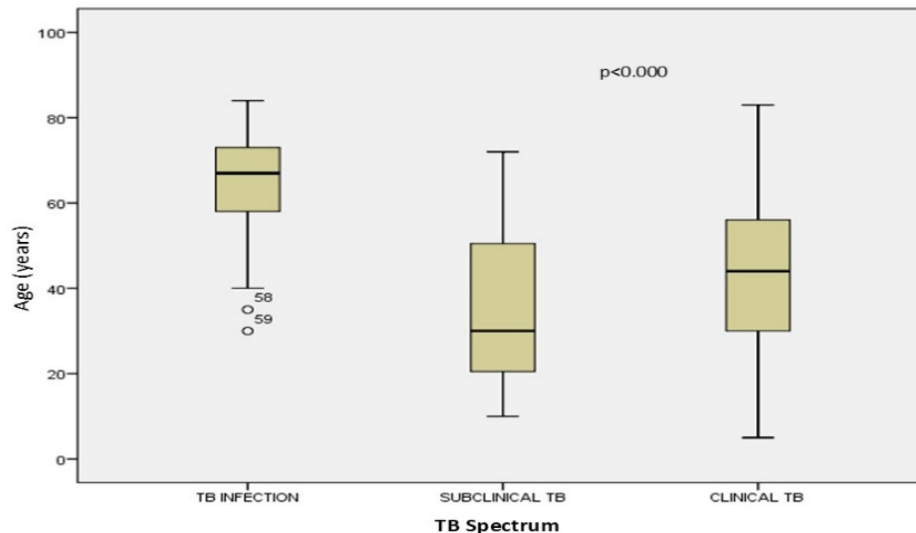
Figure 2. The distribution of post tuberculosis lung disease (PTLD) cases according to TB stages.

The mean age of cases, in the moment of first TB diagnosis, was 45.32 years+17.363 std dev. and the distribution by gender revealed no significant differences by Anova test (44.64+20.151 versus 45.62+15.983; F=0.427, p<0.514).

According to the stage of TB spectrum, mean age of cases was significantly different among groups: the highest value was calculated for TB infected individuals (64.9 years+10.571 std dev), the lower in patients with SC-TB (35.22 years+18.596 std dev) and the intermediate one in patients with C-TB (43.56 years+17.363 std dev) (p<0.001) (Table 1, Figure 3).

Table 1. ANOVA Analysis of patients' mean age according to the stages of TB spectrum.

TB spectrum	Mean age (years)	Cases (number)	Std. Deviation	Mean Square	F	p<
TB infection	64.90	72	10.571	17195.804	69.453	0.001
Subclinical TB	35.22	51	18.596	19053.724	76.957	0.001
Clinical TB	43.56	507	16.029	15337.885	61.949	0.001
Total cases	45.32	630	17.363	247.588		



**Figure 3. The comparison of patients' age according to the stages of TB spectrum.**

Gender and mean age distribution of cases by TB spectrum reveals female predominance ( $n=39/72$ ; 54.16%) in TBI group, with similar older age (63.29 years+13.774 std dev versus 63.73 years+13.345;  $F=0.019$ ;  $p<0.892$ ); almost equal proportions of males and females in SC-TB group (28 men and 23 women), with no difference of age (34.71 years $\pm$ 18.773 std dev

versus 38.68 years+18.385;  $F=0.548$ ;  $p<0.463$ ); and male predominance in C-TB group ( $n=375/507$ ; 73.96%), with significant difference of age between males (44.55 years+14.960) and females (40.43 years+18.547;  $F=6.492$ ;  $p<0.11$ ; Pearson's  $R=-0.217$ ; Spearman correlation=-0.214;  $p<0.001$ ) (Table 2).

**Table 2. The distribution of cases by gender and age according to TB stages.**

TB spectrum	Total cases	Males			Females			F	p<
		Nr	Mean age	Std dev	Nr	Mean age	Std dev		
TB infection	72	33	63.73	13.345	39	63.29	13.774	0.019	0.892
Subclinical TB	51	28	38.68	18.385	23	34.71	18.773	0.548	0.463
Clinical TB	507	375	44.45	14.960	132	40.43	18.547	6.492	0.011
All cases	630	436	45.62	15.983	194	44.64	20.151	0.427	0.514

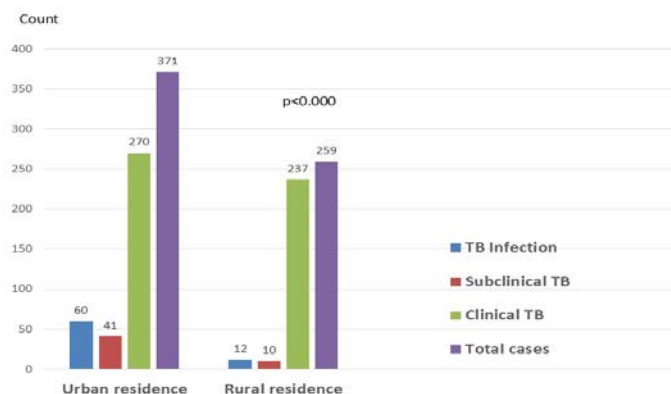
There was a special subgroup of patients ( $n=418/558$ ; 74.91%), previously treated for TBAD, later diagnosed (after 205.68 months+214.00 std dev) with different patterns of pleural, bronchial or lung parenchymal involvement, called PTLD, having roots both in SC-TB ( $n=44$ ) and C-TB group ( $n=374$ ) ( $\chi^2=163.527$ ;  $p<0.001$ ; Spearman correlation=-0.359;  $p<0.001$ ) (Figures 1 and 2).

Jobless, as an expression of poverty, was noticed in a third of cases ( $n=184/630$ ; 29.2%), mostly with advanced forms of PTB (cavitary) ( $n=148/371$ ; 39.89%) compare to noncavitary

PTB disease ( $n=36/259$ ; 13.89%) ( $OR=4.111$ ;  $RR=2.870$ ;  $\chi^2=49.758$ ;  $p<0.001$ ).

The distribution of cases, by residence, reveals urban predominance in the study group ( $n=371/630$ ; 58.88%), with highest frequency in TBI ( $n=60/72$ ; 83.33%) and SC-TB ( $n=41/51$ ; 80.39%), followed by C-TB cases ( $n=270/507$ ; 53.25%) (Pearson  $\chi^2=34.160$ ; Likelihood Ratio=37.284; Linear-by-Linear Association=31.545; Pearson's  $R=-0.224$ ; Spearman Correlation=0.233;  $p<0.001$  for all) (Figure 4).

In PTLD subgroup, 55.98% have urban residence ( $n=234/418$ ).



**Figure 4. The distribution of patients' residence according to the stages of TB spectrum.**

Exposure to TB infection was reported by 84 patients (13.33%) and positive history of intrafamilial contact was noticed in 73 cases (11.58%).

Tobacco smoking was reported by 65.71% of cases (n=414/630), more active (n=279) than former smokers (n=135), with 30.41 mean of cigarettes' pack-year ( $\pm 16.204$  std dev).

The mean BMI was 21.05 kg/m<sup>2</sup>+4.694 std dev. Underweighting, evaluated by BMI $\leq 18.5$ kg/m<sup>2</sup>, was reported in 36.98% of enrolled cases (n=233/630), having a higher prevalence among C-TB group (n=231/507; 45.56%; OR=7.741; RR=4.670;  $\chi^2=53.476$ ; p<0.001), especially in patients with cavitary TB (n=190/371; 51.21% versus n=53/259; 20.46%; OR=4.080; RR=2.502;  $\chi^2=60.769$ ; p<0.001).

Because C-TB was mostly cavitary (n=371/507; 73.17%) and delayed diagnosed (n=369/507; 72.78%), clinical features consisted in predominance of cough (n=505/507; 99.6%), more productive (n=436/507; 85.99%) than dry cough (n=69/507; 11.04%), hemoptysis (n=114/507; 22.48%), dyspnea (n=160/507; 31.55%), fatigability (n=367/507; 72.38%), fever (n=157/507; 30.96%), chest pain (n=147/507; 28.99%), sweats (n=287/507; 56.60%), loss in weight (n=275/507; 54.24%).

The majority of notified TB cases were bacteriologically confirmed (n=424) According to the positive bacteriological smear and/or culture, positive molecular tests (LPA, Xpert MTB/RIF, Xpert MTB/XDR), the prevalence of contagious TB was 67.30% (n=424/630), lower in SC-TB (n=2/51; 3.92%) than in C-TB group (n=422/507; 83.23%) (OR=121.635; RR=22.124;  $\chi^2=159.460$ ; p<0.001; Linear by

linear association=146.255; Pearson's R=-0.512; Spearman correlation=-0.531; p<0.001). Positive histopathologic exam was positive in 3 cases of C-TB, revealing caseation granuloma.

Progressive TBI to SC-TB consisted in 3 cases, but only one had positive bacteriological exam. SC-TB was significantly more infectiousness than clinical forms (2/51; 3.92% vs 423/507; 83.43%; OR=123.375; RR=21.275;  $\chi^2=161.079$ ; p<0.001).

Clinically confirmed cases (n=134) were evaluated after 2 months of antiTB therapy for regressive imagistic lesional dynamic and clinical improvement.

There were 410 new cases (TB-NC) and 178 relapses of TB (TB-R). The rate of positive molecular tests was similar in NC (n= 192/410; 46.82%) and in R (n= 78/178; 43.82%) (OR=1.129; RR=1.068;  $\chi^2=0.451$ ; p<0.6), correlated with positive smear and culture.

Mostly TB-NC and TB-R were significantly associated with DS pattern of MTB strains (n=397/410; 96.36%, respectively n=110/148; 74.82%) (OR=0.094; RR= 0.767;  $\chi^2=66.203$ ; p<0.001). The prevalence of DR-TB, based on rapid positive results of phenotypic (BACTEC MGIT 960, DST) and/or genotypic methods (LPA, Xpert MTB/XDR and/or Xpert MTB/RIF), was 12.26% (n=52/424). The prevalence of acquired (secondary) pattern of DR/MDR-TB, mainly induced by previous incomplete, or incorrect regimens of therapy, was related to relapses (n=21/148; 14.18%), being almost 2 times greater than the prevalence of initial (primary) DR/MDR pattern, diagnosed in TB-NC group (n=30/410; 7.31%) (OR=2.094; RR= 1.939;  $\chi^2=6.173$ ; p<0.012) Tabel 4).

**Table 3. The distribution of drug-resistant TB cases according to spectrum of resistance.**

Drug resistant TB (DR - TB) cases	Mono DR-TB	Poly DR-TB	Rifampicine resistant TB (RR-TB)	Multi drug resistant TB (MDR-TB)	Total cases
Initial (Primary) DR	7	4	8	11	30
Secondary (Acquired) DR	4	2	4	12	21
Total cases	11	6	12	23	52

The spectrum of DR-TB included 17 with mono- or poly drug resistance (3.35%), 35 multi drug resistant (6.9%) strains of MTB, including 12 cases with rifampicin-resistance (RR-TB) (Table 3).

More than a half of acquired DR-TB cases had the pattern of MDR-TB (n=12/21; 57.14%) compare to 36.66% among initial DR-TB cases (n=11/30) (OR=2.303; RR=1.558;  $\chi^2=2.050$ ;  $p<0.15$ ).

The profile of monoresistance against first line antiTB drugs included 10 cases: 8 with resistance against isoniazid (H), 1 against ethambutol (E), 1 against pyrazinamide (Z).

It was a single case with monoresistance against second line antiTB drugs (fluoroquinolone).

Only 3 patients had acquired mono DR against H. Poli-drug-resistance against first line drugs was against HS (3 cases), HSZ (1 case).

Primary resistance against first and second-line drugs (isoniazid and ethionamide) was identified in 2 patients.

MDR-TB included 12 cases with RR pattern, 15 HR, 2 HREZS, 2 HRZS, 1 HRES, 1 HREZ, 2 HRS.

The distribution of comorbidities is extremely heterogenous.

In top three, there were cardiovascular diseases (n=420), anemia (n=249) and COVID-19 infection (n=160).

The absence of comorbidities was reported by 71 patients; 286 patients had one and 273 had  $\geq 2$  comorbidities, associated with both TB infection and disease.

The overall TB mortality rate was 16.66%, increasing progressively from 0% in TBI group, to 4.08% (n=2/49) in SC-TB group and 5 times greater in C-TB group (n=103/507; 20.31%; likelihood ratio=39.182; Pearson  $\chi^2=25.248$ ; linear-by-linear association=24.115;  $p<0.001$ ), significantly correlated with clinical state of TB disease (Pearson's R=0.196;  $p<0.001$ ; Spearman correlation=0.200;  $p<0.001$ ).

The mean survival time after the first TB episode was 110.68 months+179.983 std dev.

## Discussion

After discovery of Koch bacillus, X-rays, regimens of antiTB drugs implementing, the TB natural history is still characterized by heterogeneity and gaps of staging defining [8,9].

Between exposure to infection and the occurrence of disease, there is a complex heterogenous broader spectrum of stages, easily unbalanced by severe comorbidities or even viral respiratory infections, as HIV and COVID-19, which proved, in different period of time, huge impact on TB trends [10-13].

The post pandemic attitude of people pro health contributed to mapping calcified lung and/or pleural lesions, tree in bud, bronchiectasis revealed by CT scan of the chest.

Because TB and COVID-19 are so mimetic, sharing clinical features similarities, TB diagnosis risks to be missed in the favor of long COVID.

So, a precise inventory of imagistic TB lesions became mandatory mainly in patients with normal chest X-ray [15,16].

Positive QuantiFERON TB Gold Plus testing facilitated the diagnosis of a large reservoir of infected individuals, carriers of old healed TB lung lesions, needing to be monitored [14].

Positive IGRA is more than a tool useful for revealing LTBI, can become a red flag of possible incipient TB (if there are no CT abnormalities), or can facilitate the diagnosis of SC-TB in patients with negative X-rays, but positive CT for lung abnormalities.

Our study demonstrated the presence of progressive TBI among IGRA positive reactors.

TBI can progress to disease, depending on the rate of viable MTB' multiplication, causing or not clinical suggestive TB-related symptoms. Imagistic chest abnormalities can be easier detected by CT, and, sometimes, bacteriologically confirmation of TB is noticed [16].

Patients with SC-TB can have mild, intermittent symptoms attributed to smoking, viral infections, air pollution, COPD, lung cancer [17-20] or they have tendency to underestimate or neglect their symptomatology [2,16,21].

In our study, the predominance of males and smokers could be a reason for both neglected symptoms or delayed diagnosis.

It could be a debate if smoking and attributable persistent cough are more neglected by men compare to women among patients with SC-TB. On the other hand, smoking is a risk factor for TB infection or disease [22].

The prevalence of SC-TB, in our study is lower than it was reported by other studies [23].

The burden of people living with SC-TB is raising to higher values (68%), being associated with a negative screening of symptoms and negative chest X-ray [16,18,24].

WHO estimates 7 million people living with subclinical form of TB disease [23].

Increased trends of SC-TB, over time, will allow us to measure this component of TB spectrum, in its full size and composition, improving our understanding of TB groups of vulnerable population [23].

Incipient TB is more likely an infection capable to progress, than an early subclinical TB disease, because of its lack of symptoms and detectable imagistic abnormalities [25].

It is not a type of an early subclinical TB.

The rate of bacteriologically confirmation was significantly greater in clinical TB compare to subclinical TB ( $p < 0.001$ ), being correlated with cavitary advanced active TB disease. The concept of the lack of contagious danger in SC-TB patients is not reflecting the reality. This gray area of TB spectrum mapping is the cover part of the iceberg, remaining silent, but contagious for the community, spreading TB bacilli for years [16,25].

In medical practice, natural TB history is not completely understood regarding the dichotomization of favorable and unfavorable evolution of lesions. Asymptomatic TB is an intermediate stage, moving from infection stage to healed TB lesions or to clinical symptomatic disease. Both movements of reversion or progression are likely to happen, but less is known about these sequences' movement and further implications [26,27].

In the lack of obvious symptoms, or imagistic screening of chest abnormalities, spontaneous resolution of noncavitary TB disease can occur.

Since 2011, molecular tests have revolutionized the framework of rapid TB microbiological diagnostic [27].

In our study of hospitalized patients, the prevalence of TB bacteriologically confirmed cases was high (75.98%). Positive molecular testing was significantly higher in new cases than

in TB relapses ( $p < 0.008$ ), facilitating the rapid diagnosis of primary and acquired DR-TB. The prevalence of MDR-TB (44.23%) highlights the awareness of spreading MDR-TB infection in general population. The high frequency of isoniazid resistance (77.77%), in patients with drug sensitivity to rifampicin, as other studies revealed [28-30] are questioning the rationale of preventive therapy with isoniazid.

The prevalence of PTLD was 66.34%, in our study, is near the upper limit of estimated values by studies (18%- 87%) [31-33].

This last state of TB' spectrum is important to be earlier diagnosed [34,35].

As LTBI is the initial phase of natural TB history, PTLD is the last one, connected with death [36].

The prognostic of death was greater in patients with C-TB than in SC-TB group ( $p < 0.001$ ), but asymptomatic TB cases must not be underestimated. In our study, TB mortality was 16.66%, comparable to other studies [36-38].

## Conclusion

In new classification of TB Spectrum, infection, subclinical disease and PTLD must not be underestimated, or unrecognized.

The hallmark of TB stages is characterized by a continuous dynamic relation, overlapping subclinical and clinical forms, sharing different patterns of DR-TB, through new cases and relapses, inducing frequently PTLD and causing death.

## Author Contributions

Conceptualization, I.A.A.; Methodology, I.A.A., I.I.; Investigation, I.A.A.; Data analysis, I.A.A. and I.T.A.; Manuscript writing and initial draft preparation, I.A.A.; Manuscript review and editing, I.A.A. and I.T.A.; Supervision, I.I. All authors read and approved the final manuscript.

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## Conflicts of interest

The authors declare no competing interests.

## Institutional Review Board

The study was conducted according to the guidelines of the Declaration of Helsinki; the study and the protocols utilised therein were approved by the Institutional Review Board (Ethics Comitee) of Constanta Clinical Pneumophthysiology Hospital (No 745/11.02.2020).

## Consent Statement

All human subjects involved in this study provided a written informed consent prior to participation, including the consent of publishing their anonymized data.

## Data availability

All data presented in the manuscript are available from the authors upon request.

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