

Spectrum of Post Tuberculosis Chronic Lung Disease in Patients with Previous Bacteriologically Confirmed Pulmonary Tuberculosis

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ABSTRACT: The discovery of anti-tuberculosis (TB) drugs, in the middle of last century, did not resolve the goal of a better healing, and the most important cause is represented by delayed diagnosis of TB disease. We conducted a single-center case control study, from January, 1st, 2017 to December, 31st, 2024, including 400 adult symptomatic inpatients diagnosed with post TB lung disease (PTLD), after a previous episode of treated TB disease. There were excluded 168 patients without pulmonary function testing (PFT), those with significant occupational exposure, and/or diseases autoimmune, COVID-19 or HIV infection, which might interfere lung function assessment. All demographics, behavioral and baseline PTB characteristics (relapses, clinical, imagistic, endoscopic, microbiologic, PFT, evolution) were assessed in order to inventorying sequelae and lung damage, types of lung function impairment. Eligible patients (n=232), mean aged 60.94+/-11.895 years, males (55.17%), were divided into 129 cases with previous bacteriologically confirmed PTB (mean age 58.37+/-11.86 years; 55.81% males) and 103 controls with previous clinically diagnosed PTB (mean age 60.04+/-11.222; 54.37% males). Delayed diagnosis and relapses of PTB had greater impact on PTLT development in cases (p=0.000), as well as previous cavitary PTB (p=0.000). The risk of death, during hospitalization, was greater in cases (p=0.000). Spectrum of PTLT, in cases, was dominated by bronchiectasis (p=0.000), suppurative episodes (p=0.004), open healing cavitation (p=0.000), intracavitary aspergilloma (p=0.002), fibrothorax (p=0.000), lung function impairment (p=0.030). In conclusion, PTLT severity is related to delayed diagnosis of previous contagious PTB, permanent lung damage, impairment of lung function, having a higher risk of death.

KEYWORDS: Spectrum of post TB lung disease, tuberculosis, lung function, delayed diagnosis.

Introduction

Despite the discovery of antituberculosis drugs, with bactericidal or bacteriostatic effect, starting within the XXth century, as well as the molecular epidemiology advances, with consequent significant improvement of the accuracy of diagnostic, in high-prevalence regions of the world, pulmonary tuberculosis (PTB) is still characterized by late detection, high contagious episode, correlating with advanced extensive forms of disease [1-3].

The character of insidious evolution of symptoms makes PTB difficult to identify in its initial, noncontagious stages. The later PTB diagnosis is, the later therapy is started, and more potential sequelae can develop, even in patients with successful completed anti-TB therapy and no relapses. Post-tuberculosis sequelae are associated with persistent symptoms and functional impairment, impacting the income and employment [4].

A successful therapy is not always a successful happy ending story, because in PTB, there is a paradoxical situation in which contagious disease is cured, but the patient can be

not. The concepts of post TB sequelae, lung function impairment or post TB respiratory syndromes were alternatively mentioned soon after the introduction of chemotherapy, in 1945 [5-8].

Initial classification of post TB pathology was based more on pulmonary function testing or anatomical radiological criteria [9].

Romanian school of pneumology reported, in 1979, sequelae of surgical interventions for complicated PTB, and the first Romanian monography about post TB respiratory syndromes was later published, in 1987 [8].

In the last decades, a growing data related to the burden of post TB respiratory sequelae has been published and a new definition was ready to be proposed, in 2019, for this large and various group of long-term complications [10-14].

Considering delayed diagnosis of contagious PTB could be the main cause of subsequent PTLT, this research study proposed, for the first time in Romania, to identify and describe different clinical, imagistic, endoscopic, microbiological and functional patterns of PTLT, correlating spectrum's patterns in relation with

the characteristics of previous treated PTB, among hospitalized patients.

Patients and Methods

A case control study was performed, from January, 1st 2017 to December, 31st 2024, in Clinical Pneumophthiology Hospital, Constanta, Romania, among 400 respiratory symptomatic inpatients, diagnosed with post tuberculosis lung disease (PTLD), after a previous episode of treated pulmonary tuberculosis (PTB) disease.

Data collection from hospital electronic medical records and Patient Clinical Observation Sheets, conducted to a data base including baseline characteristics of patients (clinical, imagistic, endoscopic, microbiologic, lung function, evolution), information related to previous episodes of TB active disease (first episode and relapses), pattern of drug-resistance (DR), date of PTP and PTLD first diagnosis or date of death, as well as estimation of delayed diagnosis from the first PTB episode reported symptoms.

The inclusion criteria referred to a previous ethics approval, respecting the privacy and human rights of patients, and patients favorable informed consent; minimum one episode of treated active PTB disease in their past, complete epidemiological, clinical and paraclinical data, including spirometry, as a mandatory requirement for pulmonary function testing (PFT). In order not to bias the results of PFT, cases and controls were matched to have similar height. We used any “*evidence of chronic respiratory abnormalities with or without symptoms, attributable at least in part to previous pulmonary tuberculosis*” as case-definition of post-tuberculosis lung disease (PTLD), definition proposed in 2019, on the occasion of the first International Post-Tuberculosis Symposium, and used widely by researchers [14].

For a complete hallmark of lung function impairment (LFI), in PTLD patients, some patients succeeded to perform not only spirometry, but also diffusing capacity of the lung for carbon monoxide (DLCO) and impulse oscillometry (IOS). Severity of LFI, evaluated by simple and complex PFT, was based on specific guidelines adequate for the assessment in time, along with the interval of time from 2017 to 2024 [15-21].

The exclusion criteria included significant occupational exposure, and/or any disease (autoimmune, moderate-severe COVID-19, or HIV infection, interstitial lung disease), which

might interfere lung function assessment. There were excluded all patients (n=168) with no assessment of lung function, or any exclusion criteria fulfilment, which can induce bias.

The study group included 232 adults, mean aged 60.94±11.895 years, predominantly males (55.17%). According to the hypothesis of this study, in order to identify how PTB delayed diagnosis and other factors may contribute to PTLD severity, case-control sampling design was based on contagious PTB as criteria for stratifying patients into 129 cases with previous contagious PTB and 103 controls without any episode of contagious PTB.

Details as first time of reporting respiratory symptoms, loss in weight, time of notified PTB diagnosis (new case and relapses), mycobacterial positivity of smears or cultures, molecular testing of sputum samples, drug-resistance, first assessment of PTLD, death outcome, occurred during hospitalization, were recorded, in data base, and intervals of time were calculated.

Statistical analysis, performed by SPSS 20th version, calculated frequencies, median or mean±standard deviation (SD), calculated by ANOVA variance analysis, comparative analyses between cases and controls, differences, for continuous variables, student t-test for normally distributed data or Mann Whitney U-test, Pearson chi square for categorical comparison, linearity tests for continuous variables, Wilcoxon rank test for comparison of continuous variables, Spearman correlations, odds ratio (OR) and risk ratio (RR), for a level of significance of p<0.05.

Results

The eligible enrolled subjects (n=232) diagnosed with post TB lung disease (PTLD) were divided into 129 cases (mean aged 58.37±11.86 years; 55.81% males), with history of minimum one episode of treated contagious PTB (bacteriologically confirmed), and 103 controls (mean aged 60.04±11.22 years; 54.37% males), with previous treated clinically diagnosed disease and no contagious PTB episode. During the interval of time from 2017 to 2024, all baseline demographic and clinic characteristics of cases and controls are summarized and presented in Table 1, along with estimates of associations. There were no differences by gender (p<0.931) between cases and controls. Males were older (62.53±10.985 years) than females (58.97±12.708 years) (F=5.234; p<0.023).

The average interval of time, from the first episode of treated PTB to subsequent PTLD, was

229.95±221.42 months, significantly lower in cases versus controls ($p<0.001$), decreasing abruptly, from PTLD diagnosis till death, to 29.17±35.39 months, greater in cases, but with no significant statistical difference (0.349) (Table 1).

The rate of mortality, during hospitalization, was almost 6 times higher (19.37%) among cases versus controls (3.88%) ($p<0.001$).

Compare to the mean age of cases, in the moment of their first PTB episode, which was significantly lower versus controls (35.00±18.02 years versus 43.65±14.84 years; $F=16.07$; $p<0.001$). In the moment of dying, it was no difference of mean age distribution among deceased PTLD patients ($F=0.155$; $p<0.697$).

Urban residence was predominant in both cases and controls ($p<0.004$). Smoking exposure was reported by most than a half of both cases (66.67%) and controls (61.16%) without significant differences ($p<0.3\%$). The mean number of smoked cigars pack year by controls was significantly higher compare to cases ($F=5.75$; $p<0.018$). Behavior attitude toward alcohol abuse was declared by 20.16% of cases and 14.56% of controls ($p<0.267$) (Table 1).

The median of height was 168 cm both in cases and controls, and mean values were almost equal ($p<0.970$). The mean weight and BMI were lower in cases ($p<0.03$, respectively 0.001), with an increased frequency of clinical cachexia in cases ($p<0.001$) (Table 1).

Table 1. Baseline characteristics of Post Tuberculosis Lung Disease (PTLD) patients.

	Cases	Controls	Total cases	OR (95% CI)	P<
PTLD Patients (n; %)	129 (55.60%)	103 (44.4%)	232 (100%)		
Age (median) (years)	61.00	67.00	63.00		0.002
(mean ± std dev)	58.22±11.84	64.34±11.11	60.94±11.89		
Gender - Male (n; %)	72 (56%)	56 (54.37%)	128(55.17%)	1.06 (0.63-1.78)	0.931
Residence (Urban)(n; %)	67 (52%)	72 (69.90%)	139 (59.91%)	0.46 (0.27-0.80)	0.004
Alcohol abuse	26 (20.16%)	15 (14.56%)	41 (17.67%)	1.48 (0.73- 2.97)	0.267
Smoking Exposure (n; %)	86 (66.67%)	63 (61.16%)	149 (64.22%)		0.3
• Current smokers (CS)	54	25	76		
• Former smokers (FS)	32	38	70		
• Never smokers (NS)	43	40	83		
Cigars pack-year (mean)	30.24±15.10	37.70±22.70	33.41±19.01		0.366
• Current smokers (CS)	31.45±12.31	40.28±21.58	34.28±16.27		
• Former smokers (FS)	28.22±15.10	36.00±25.35	32.44±21.74		
Height (cm) (median)	168	168	168		0.970
(mean)	167.33±8.44	167.38±9.89	167.35±9.09		
Weight (kg) (median)	60	65	62		0.030
(mean)	61.52±14.50	65.57±15.80	64.21±15.36		
Body mass index (kg/m ²) (median) (mean)	21	24	22		0.001
	21.82±5.06	24.19±5.23	22.57±5.26		
Clinical cachexia	47 (36.43%)	17 (16.50%)	64 (27.58%)	2.90(1.54-5.45)	0.001
Delayed diagnosis of previous PTB (n; %)	99 (77%)	7 (6.8%)	116 (50%)	45.25 (18.97-107.94)	0.001
Interval from onset of symptoms to PTB diagnosis (months)	3.55±2.908	2.54±2.601	3.30±2.862		0.027
Previous episode of cavitory PTB (n; %)	106 (82.17%)	4 (3.88%)	146 (62.93%)	114.06 (38.10-341.49)	0.001
Microbiological confirmation of previous PTB (n; %)	129 (100%)	Not applicable (NA)	129 (55.60%)		NA
Positive Smears	115 (89.15%)		115 (49.56%)		
Positive Culture	129 (100%)		129 (55.60%)		
Molecular tests	88 (68.22%)		88 (38%)		
Line Probe Assay (LPA)	18		18		
GeneXpert MTB/RIF	53		53		
Xpert MTB/XDR	17		17		
Drug sensitivity (DS)	114 (88.37%)		114 (88.37%)		
Drug resistant (DR)	5		5		
Rifampicin resistant (RR)	4		4		
Multidrug resistant (MDR)	6		6		
Relapses (n; %)	53 (41.08%)	9 (8.73%)	62 (26.72%)	7.28 (3.37-15.70)	0.001
1 relapse	32	8	40		
2 relapses	15	1	16		
≥3 relapses	6	0	6		
Interval from first PTB diagnosis to PTLD first confirmation (months) (median, mean)	96 136.79±143.87	372	150	-	0.001

		346.62±245.63	229.95±221.42		
Comorbidities (n; %)	120 (93%)	96 (93%)	216 (93.10%)	0.97 (0.34-2.70)	0.956
No one	9	7	16		
One	54	63	117		
Multimorbidity (≥2 comorbidities)	66	33	99		
Deceased (n; %)	25 (19.37%)	4 (3.88%)	29 (12.5%)	0.13 (0.38-0.44)	0.001
Age of deceased (median) (years) (mean +/- std dev)	63 61.32±10.24	64.50 63.50±10.59	63 61.62±10.12	-	0.697
Interval PTLD diagnosis-death (median, mean) (months)	14 31.68±36.97	5.50 13.50±19.46	12 29.17±35.39	-	0.349

The highest frequency of previous cavitary PTB in cases (n=106/129; 82.17%) than in controls (4/103; 3.88%) [OR=114.06 (38.10-341.49); RR=21.158 (8.06-55.48); $\chi^2=140.173$; $p<0.001$] explained the high rate of microbiological confirmation, with smear microscopically positivity (89.15%), relating to delayed diagnosis, which was documented in 77% of cases ($p<0.001$).

The lung damage, which is a pivotal stone for PTLD pathogenesis, was related to relapses. Past recurrent episodes of PTB were significantly increased in cases (n=53/129; 41.08%) versus controls (9/103; 8.74%) [OR= 7.28 (3.37-15.70); RR= 4.7 (2.43-9.07); $\chi^2=30.30$; $p<0.001$].

Drug sensitive TB (n=114) was mentioned 10 times greater than drug resistant forms (n=15).

According to the molecular profile of MTB strains, although 68.22% of subsequent PTLD

cases were investigated by genotypic tests (LPA, Xpert MTB/RIF, Xpert MTB/XDR). The prevalence of previous multidrug resistant-TB was low (n=10; 12.9%), including 4 cases of rifampicin resistant TB).

Clinical features of PTLD are characterized by predominance of cough and dyspnea both in cases and controls ($p=0.262$, respectively $p<0.882$), with no differences on pulse oximetry ($p<0.329$), or Modified Medical Research Council (mMRC) scale of dyspnea ($p<0.129$), or COPD Assessment Test (CAT) score ($p=0.970$) (Figure 1; Table 2).

At admission in hospital, fatigability and fever were reported by most of cases and controls ($p<0.067$, respectively $p<0.292$). Hemoptysis was significantly more frequent attested in a third of cases, during hospitalization ($p<0.001$).

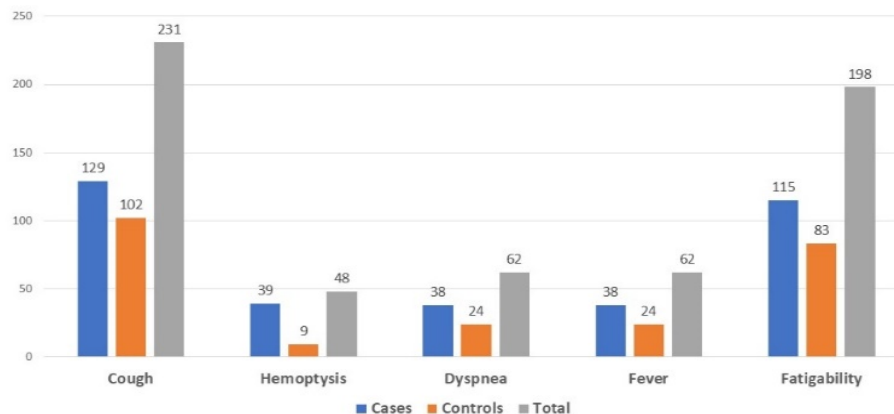


Figure 1. Distribution of admission signs and symptoms in patients with post tuberculosis lung disease.

According to pulmonary function testing (spirometry, DLCO and impulse oscillometry), there were significant differences among cases and controls consisted in lower mean values of percent predicted forced vital capacity (FVC) ($p<0.004$), first second of forced expiration (FEV1) ($p<0.003$), forced expiratory flow

between 25-75% of FVC (FEF25-75%) ($p<0.015$) and forced expiratory flow at 50% of FVC (FEF50%) ($p<0.038$), diffusing capacity of the lungs for carbon monoxide (DLCO) percent (0.010), total lung capacity evaluated through DLCO (TLC) percent ($p<0.002$), and Fres ($p<0.033$) (Figure 2 and Table 2).

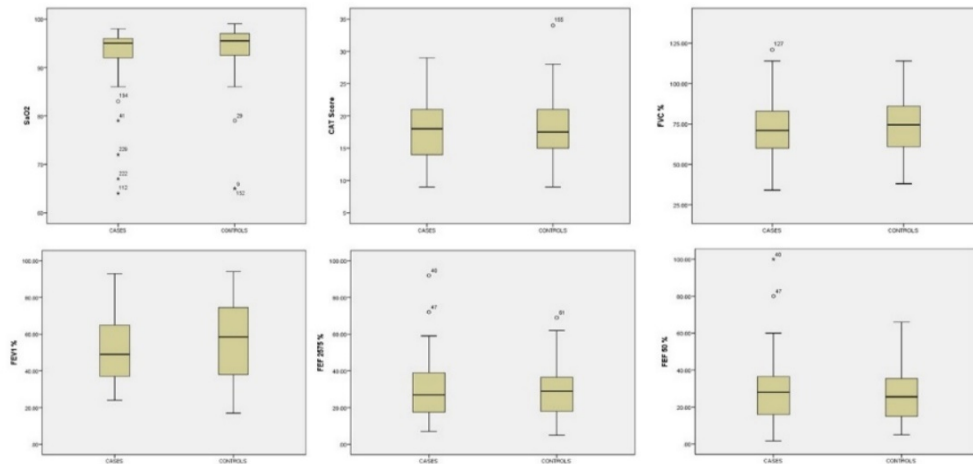


Figure 2. Clustered box plot showing mean values for COPD Assessment Test (CAT) and percentage for pulse oximetric measurements and spirometry results in cases versus controls with post TB lung disease. Abbreviations: SaO2=arterial oxygen saturation; FVC=forced vital capacity (FVC); FEV1=first second of forced expiration; FEF25-75% forced expiratory flow between 25-75% of FVC; FEF50%=forced expiratory flow at 50% of FVC.

Lung Function Impairment was more frequent demonstrated in cases ($p < 0.030$), including restrictive, obstructive and mixed patterns of

ventilatory dysfunction, as well as small airways disease (Figure 3).

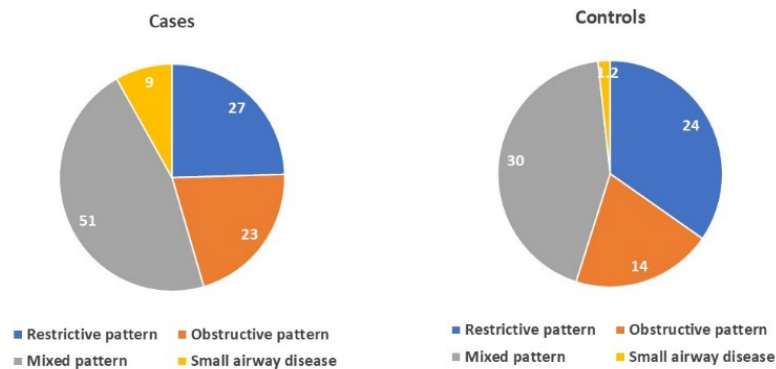


Figure 3. The structure of ventilatory impairment, defined by spirometry, in cases and controls with post TB lung disease.

Chronic obstructive pulmonary disease (COPD), was diagnosed based on spirometry, according to GOLD criteria [16], in 130 patients, highly associated with smoking both in cases ($n = 59/86$; 68.60%) and controls ($n = 42/63$; 66.67%) ($p < 0.804$).

The distribution of COPD in nonsmokers was higher in cases ($n = 19/43$; 44.18%) versus controls ($n = 10/40$; 25%) ($p < 0.7$).

The complex evaluation of PTLD patients based on imagistic abnormalities revealed, among cases compare to controls, a higher proportion of bronchiectasis and open healing ($p < 0.001$), fibrotic scars with loss of volume ($p < 0.002$), or inactive diffuse fibrosis ($p < 0.001$), fibrothorax ($p < 0.001$), pleural thickening ($p = 0.012$), destroyed lung ($p < 0.001$) (Figure 4 and Table 2).

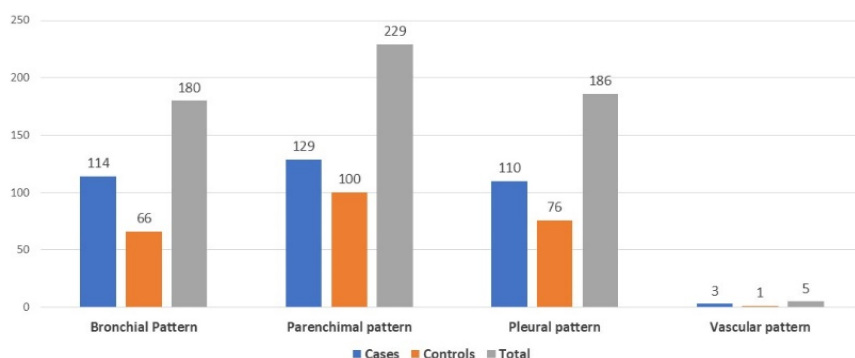


Figure 4. The spectrum of post TB lung disease's patterns among hospitalized patients (cases and controls).

Table 2. Clinical and Functional patterns of Post Tuberculosis Lung Disease (PTLD) Spectrum.

	Cases (n=129)	Controls (n=103)	Total cases (n=232)	OR (95% CI)	P<
Cough (n; %)	129 (100%)	102 (99.02%)	231 (99.57%)	0.44 (0.38-0.51)	0.262
Hemoptysis (n; %)	39 (30.23%)	9 (8.74%)	48 (20.69%)	4.52 (2.07-9.87)	0.001
Fever (n; %)	38 (29.46%)	24 (23.30%)	62 (26.72%)	1.37 (0.75-2.48)	0.292
Fatigability (n; %)	115 (89.15%)	83 (80.58%)	198 (85.34%)	1.97 (0.94-4.14)	0.067
Dyspnea (n; %)	100 (77.52%)	79 (76.69%)	179 (77.15%)	1.04 (0.56-1.94)	0.882
mMRC Scale of dyspnea (mean)	1.50±1.02	1.30±0.98	1.41±1.01		0.129
CAT Score (mean)	18.03±4.74	18.06±5.22	18.04±4.91		0.970
SaO2% at admission	93.23±6.90	94.10±6.41	93.62±6.69		0.329
FVC (L, %) (mean)	2.54±0.81 L 74.45±18.08%	2.71±0.92 L 81.68±19.51 %	2.62±0.86 L 77.68±19.03 %		0.13 0.004
FEV1 (L, %) (mean)	1.66±0.66 L 61.36±21.84%	1.85±0.79 L 70.53±24.01 %	1.73±0.73 L 65.43±23.23 %		0.60 0.003
FEV1/FVC (%) (mean)	65.41±16.42	67.93±15.19	66.26±15.88		0.36
FEF25-75% (L; %) (mean)	1.19±0.71 L 38.53±22.01%	2.77±11.17 L 46.64±28.02	1.89±7.50 L 42.14±25.14 %		0.112 0.015
FEF 50% (L; %) (mean)	2.07±4.86 L 38.14±22.81%	3,14±11.95 L 45.03±27.55 %	2.55±8.74 L 41.20±25.20 %		0.355 0.038
DLCO % (mean)	62.49±16.37	69.21±15.72	65.33±16.39		0.010
KCO % (mean)	94.03±15.45	90.66±12.46	92.61±16.23		0.194
TLC % (mean)	63.89±16.16	71.94±16.19	67.29±16.16		0.002
RV % (mean)	65.50±33.19	75.65±31.78	69.79±32.89		0.053
RV/TLC % (mean)	96.28±40.57	99.94±34.02	97.94±37.86		0.547
R5Hz (kPa; %) (mean)	0.56±0.22kPa 176.48±71.90%	2.09±8.60 kPa 147.61±71.18	1.19±5.51 kPa 164.59±72.50		0.263 0.107
X5Hz (kPa; %) (mean)	-0.51±2.36 kPa 783.88±1234.60 %	- 2.29±6.14kPa 670.14±859.4 3%	- 1.24±4.38kPa 737.04±1089.9 9%		0.100 0.675
R20Hz (kPa; %) (mean)	0.35±0.12 kPa 120.85±36.16%	0.30±0.10 111.46±44.57 %	0.33±0.11 116.99±41.41 %		0.082 0.362
Fres (mean)	24.80±8.09	20.86±6.10	23.18±7.54		0.033
AX (kPa) (mean)	2.54±2.06	1.94±1.94	2.29±2.02		0.233

Di5-20 (kPa) (mean)	6.76±15.71	10.08±71.70	8.13±6.51		0.419
Lung Function Impairment (n; %)	110 (85.27%)	75 (73%)	185 (78%)	2.16 (1.12-4.15)	0.030
Restrictive pattern	27	24	51		
Obstructive pattern	23	14	37		
Mixed pattern	51	30	81		
Small Airway Dysfunction	9	7	16		
COPD in smokers	59	42	101 (43.53)	1.35 (0.57-3.20)	0.493
COPD in nonsmokers	19	10	29 (12.5)		
COPD (n; %)	78 (60.46%)	52 (50.48%)	130 (56.03)	1.50 (0.88-2.53)	0.129
Mild COPD	3	8	11		
Moderate COPD	32	23	55		
Severe COPD	38	18	56		
Very severe COPD	7	5	12		
Bronchial pattern (n; %)	114 (88.37%)	66 (64.08%)	180 (77.58%)	4.26 (2.17-8.34)	0.001
Tree in bud	48	26	74	1.73 (0.97-3.06)	0.058
Bronchiectasis	114	66	180	4.26 (2.17-8.34)	0.000
Cicatrical bronchial stenosis	13	7	20	2.53 (1.32-4.84)	0.005
Suppurative syndrome	41	16	57	2.53 (1.32-4.84)	0.004
Nonobstructive chronic bronchitis	60	56	116	0.73 (0.43-1.22)	0.236
Obstructive Lung Disease	99	78	177	1.05 (0.57-1.94)	0.857
Parenchymal pattern (n; %)	129 (100%)	100 (97.08%)	229 (98.7%)	0.43 (0.37-0.50)	0.510
Open healing cavitation	19	1	20	17.61 (2.31-133.99)	0.001
Destroyed Lung	15	1	16	13.42 (1.74-103.4)	0.001
Fibrothorax	28	1	29	28.27 (3.44-211.79)	0.001
Fibrotic scarring with volume loss (≤1 lobe)	31	9	40	3.30 (1.49-7.31)	0.002
Inactive diffuse fibrosis	110	74	184	2.26 (1.18-4.34)	0.12
Inactive diffuse fibrosis	128	92	210	15.3 (1.94-160.62)	0.001
Fibronodular opacities	124	94	208	2.37 (0.77-7.31)	0.122
Micronodular opacities	75	64	139	0.84 (0.49-1.43)	0.004
Calcified opacities	9	4	13	1.85 (0.55-6.20)	0.310
Lobectomy	2	0	2		
Pneumonectomy	10	0	10		
Intracavitary Aspergiloma (CT)					
Pleural pattern	110 (85.27%)	76 (73.78%)	186 (80.17%)	2.05 (1.06-3.96)	0.029
Pleural thickening	110	74	184	2.26 (1.18-4.34)	0.012
Calcified pleural placards	14	16	30	0.66 (0.30-1.42)	0.291
Pneumothorax	8	2	10	3.33 (0.69-16.07)	0.113
Vascular pattern	3 (2.32%)	1 (0.97%)	4 (1.72%)	2.42 (0.24-23.70)	0.431

Legend: FVC=forced vital capacity (FVC); FEV1=first second of forced expiration; FEF25-75% forced expiratory flow between 25-75% of FVC; FEF50%= forced expiratory flow at 50% of FVC; COPD=chronic obstructive pulmonary disease; CAT=COPD Assessment Testing; SaO2=oxygen saturation of arterial blood; DLCO=diffusing capacity of lungs for carbon monoxide; KCO=carbon monoxide transfer coefficient (ratio DLCO/VA), meaning diffusing capacity for carbon monoxide per unit of alveolar volume); VA=alveolar volume; TLC=total lung capacity; RV=residual volume; R5 Hz=respiratory resistance at 5Hz; predicted-X5=lung reactance; R5-R20 kPa=small airway index (calculated by the difference between resistance at 5 Hz and resistance at 20 Hz), AX=area under reactance curve; Fres=resonant frequency; L=liters; mL=milliliters; Hz=hertz; cycles per second, Kpa=kilopascals; L/s=liters per second; kg=kilograms.

The spectrum of PTLD is extremely heterogenous with various parenchymal, pleural, bronchial and less vascular involvement and significant differences between cases and controls for bronchial and pleural pattern ($p<0.000$; respectively $p<0.029$) (Table 2).

The prevalence of PTLD comorbidities was increased in both cases and controls ($p<0.05$). Cardiovascular diseases and diabetes were more frequent associated in controls ($n=68$; 66%; respectively 30; 39.12%) than in cases (55; 42.64%, respectively 16; 12.40%). The impact of controls' increased number of comorbidities on death outcome is not significant, because there were only 3 deaths

registered, compare to 8 times more ($n=25$) in cases.

Discussion

For a long period of time, TB was resumed to three-act structure composed by infection, primary TB and post-primary TB [22].

Even new spectrum of TB with 5 stages does not include PTLD [23].

Beyond the successful end of treatment, there is a risk of progressive lung damage and functional impairment, which must not be neglected or underestimated [24,25].

There is limited data on the full hallmark of PTLD spectrum. PTLD is an old forgotten entity,

which has been recently rediscovered and definitions revisited.

Post TB health appears a nonsense, because, in most of the cases, TB patients are experienced complications more or less severe after microbiological cure for TB, and sometimes this experience can be a hard one, with chronic lung disease, disability and death [25].

PTLD was revisited and receiving a new identity and family of different patterns which must become a red flag after TB disease resolution [26].

Better research priorities in tuberculosis field are recommended for an efficient algorithm of PTLD diagnosis and a better moment for early detection [27].

Our study offered an approach on the variety of PTLD spectrum, which includes a heterogenous mixture of different morphologic and or functional impairments patterns as airway disease or bronchial pattern (cicatricial bronchial stenosis, bronchiectasis, obstructive lung disease), parenchymal (scars, calcified nodules, limited or extensive fibrosis as fibrothorax, persistent cavitation or open healing, destroyed lung), pleural (chronic pneumothorax, pleural thickening or calcified pleural placards), aspergillus-related PTLD, and pulmonary vascular disease (pulmonary hypertension).

From TB infection and disease till PTLD with lung function impairment and an important ballast of sequelae, can be a shorter way to go if TB patients are monitored [27,28].

PTLD prevalence in Romania is not known. We propose a close monitoring for patients with history of cavitory lesions, underweighting and having persistent respiratory symptoms.

Delayed diagnosis of active contagious PTB is followed by a long window period of clinical denied, both by patients and physicians [29].

Most of our PTLD patients had previous advanced and severe forms of active contagious PTB, caused by delayed diagnosis.

Many post TB patients remain long term carriers of pulmonary abnormalities, heavy symptomatic individuals, others are long term survivors of recurrent episodes of disease, developing structural destroyed lung, extensive fibrosis like fibrothorax, open healing cavitation with or without intracavitary aspergilloma, with consequent lung function impairment, with persistent respiratory symptoms ignored or related to smoking [30-32].

An early pulmonary functional testing (PFT) with reduced FEV1 and/or ratio FEV1/FVC, a

decreased DLCO and or TLC, may anticipate the existence of PTLD.

The ideal time point for PFT seems to be at 6 months after therapy for active disease, but not later than 12 months [33].

Because sometimes PFT can be normal, clinical, morphological and physiological characteristics of PTLD required as well a careful monitoring of TB patients, with initial follow up at 6 months and 12 months after anti-TB therapy, and, then, a long- term management according to the peculiars of PTLD [34-36].

Post TB therapy, some patients may progressively feel worsen and worsen, limiting their physical effort and reducing daily activities. COPD can be a comorbidity or a distinctive phenotype of PTLD, especially in nonsmokers.

Tuberculosis obstructive pulmonary disease (TOPD) is a new entity, which requires more awareness of physicians and researchers [37-39].

There is still much to learn and better understand about TB epidemiology and natural history of TB disease, including post-tuberculosis lung disease, as an end.

A complete inventory of PTB episodes, history of drugs and regimens of therapy, bacteriological status, with an emphasis on imagistic residual chest lesions are recommended to be done systematically.

Along with clinical and imagistic examination, a complete assessment of lung function with spirometry, DLCO is mandatory to be done as soon as possible after anti-TB therapy ending.

There is a close link between delayed diagnosed PTB and the hallmark of PTLD patterns.

In our study, PTLD spectrum was dominated by bronchiectasis ($p<0.001$), suppurative episodes ($p<0.004$), open healing cavitation ($p<0.001$), fibrothorax ($p<0.001$), lung function impairment ($p<0.030$). We highlight the spectrum of PTLD, with massive heterogeneity of patterns and entities.

The evidence and understanding the basic and the peculiar forms of PTLD phenotypes, clinical and imagistic manifestations, must be a priority for researcher, because there are more gaps to be discovered and research. PTLD is more than a stage of TB, it is an attributable consequence of delayed diagnosis of active TB, with subsequent irreversible lung damage and lung function impairment, as our study revealed.

Conclusion

Post tuberculosis lung disease is a last phase in TB Spectrum, having its own spectrum with various patterns, syndromes and diseases, related to previous PTB severity, delayed diagnosis, permanent lung damage, impairment of lung function, having a higher risk of death.

Author Contributions

Conceptualization, I.A.A.; Methodology, I.A.A., I.I. and O.C.A.; Investigation, I.A.A., O.C.A.; Data analysis, I.A.A. and I.T.A.; Manuscript writing and initial draft preparation, I.A.A., O.C.A.; Manuscript review and editing, I.A.A., O.C.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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