

Respiratory Symptoms and Factors Associated with Abnormal Lung Function in Post-Tuberculosis Lung Disease Patients – A Cross Sectional Comparative Study

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Abstract

Patients treated for pulmonary tuberculosis and cured still come down with persistent respiratory symptoms and impaired lung function, this study assessed respiratory symptoms and factors associated with abnormal lung function in post-tuberculosis lung disease patients.

Aim: The study was done to assess respiratory symptoms and factors associated with abnormal lung function in post-tuberculosis lung disease patients.

Methods: This was a hospital based cross sectional comparative study of post pulmonary tuberculosis patients attending Federal Teaching Hospital, Owerri, who completed treatment at the point of treatment completion down/up to 2 years previously. Interviewer based questionnaire was administered to study participant to obtain data regarding socio-demographics. All participants were subjected to spirometry procedure to measure the ventilatory function parameters using spirolab III. Data was analyzed using IBM SPSS statistics version 25.0. Chi-square was used to determine association between categorical variables. The independent student t-test was used to compare continuous data. Logistics regression model was used to assess factors associated with spirometric impairment in post-TB lung disease individuals. A p-value less than 0.05 was considered statistically significant.

Results: Out of the 200 participants recruited, consisting of 100 post-tuberculosis lung disease patients (18 years and above) and 100 age-, sex- and height-matched apparently healthy controls. mean age: 48.0±15.2 for cases and 46.7±13.9 for controls, range 18-90 years with most of the participants between 45-54 years. The most frequent respiratory symptom was cough which was present in 56 (56%) of the cases followed by sputum production in 51 (51%), breathlessness 34 (34%), chest pain 31 (31%), wheezing 13 (13%) and haemoptysis 10 (10%) while none of the controls had respiratory symptoms. Respiratory lung function impairment occurred in 71% of cases and 12% of the control. Only lower body mass index (aOR 0.20, 95% CI: 0.07 to 0.52) was found to be independently associated with impaired lung function in post-TB cases after adjusting for confounders while no significant association was found with age group, sex, educational status, previous TB treatment and presence of respiratory symptoms.

Conclusion: There was significant burden of respiratory symptoms among treated and cured post-tuberculosis lung disease patients. Most of the patients had persistent respiratory symptoms post-tuberculosis treatment and cure, cough was the most common symptom followed by sputum production. There was poor correlation between respiratory symptoms and abnormal lung function, only body mass index showed significant association with abnormal lung function.

Keywords: Respiratory symptoms, Post-tuberculosis, Lung function, Lung Disease Patients, Abnormal Lung Function

Abbreviations:

TB: Tuberculosis
HIV: Human immune deficiency virus
BMI: Body mass index
COPD: Chronic Obstructive Pulmonary Disease
CD: Cluster designation
FEV1: Forced Expiratory Volume in one second
FVC: Forced Vital Capacity
CI: Confidence Interval
WHO: World Health Organisation

1. Introduction

There is a high prevalence of pulmonary tuberculosis in Africa despite current efforts to reduce the incidence and mortality [1]. Tuberculosis has remained one of the leading causes of mortality worldwide. A strong association has been recognised between tuberculosis and chronic respiratory diseases particularly in low and middle income countries [2]. Tuberculosis is preventable, treatable and curable, yet has plagued humankind resulting in adversity and death of millions every year. From the WHO Global report, 2024, tuberculosis caused an estimated 1.25 million deaths in 2023, including 1.09 million among HIV negative people and 161000 among people with HIV. The WHO End TB Strategy and Sustainable Development Goals focus on reducing TB incidence and mortality but no mention of post-tuberculosis lung disease and programmatic intervention [3]. Pulmonary tuberculosis is an important risk factor for chronic respiratory diseases due to residual lung damage [4]. Post-tuberculosis sequelae add substantially to the overall disease burden caused by tuberculosis, post-tuberculosis survivors have a high burden of post-TB lung damage and associated adverse patient outcomes including accelerated lung function decline, respiratory-related persistent chest symptoms after treatment completion [5,6,7].

Tuberculosis is a disease of public health importance because of its high morbidity and mortality and also its communicable nature [8,9]. There is a dearth of information in Nigeria regarding pulmonary function abnormalities among post-TB treatment patients despite the huge disease burden in the country and continuous emerging information on the residual effects of pulmonary TB on pulmonary function. The post-tuberculosis state has not been a major focus on tuberculosis control agenda and at present, has not been given adequate recognition in most national and international guidelines, including the Nigerian national TB guidelines [10]. This study evaluated patients who have completed treatment for pulmonary tuberculosis with spirometry for the detection of persistent respiratory symptoms as well as factors associated with impaired lung function, with a view to identifying individuals who might require further respiratory function evaluation as part of their post treatment monitoring program. Pulmonary tuberculosis can lead to irreversible lung damage visible as scarring, fibrosis, cavitation, or other types of damage on radiological imaging [11,12,13]. This in turn may lead to loss of lung function, long term respiratory symptoms and eventually chronic respiratory disease [14]. Few studies have evaluated the persistence of post-tuberculosis respiratory

symptoms among treated and cured patients. This may manifest as chronic symptoms including cough, sputum production and dyspnoea [15,16].

2. Methods**2.1. Study design**

This was a hospital based cross sectional comparative study that spanned over a period of 7 months. Patients treated and cured for pulmonary tuberculosis were compared with apparently healthy control who have not been previously treated for PTB. Socio-demographic information included age, gender, marital status, occupation, tribe, level of education and religion. Detailed history was obtained from the participants by the researcher about participants' medical history and respiratory symptoms. Physical examination was carried out by the researcher including general and systemic examinations. Spirometry was carried out on the participants by the researcher who is well trained in spirometry using a desk top spirometer (MIR Spirolab III colour version 3.4 ROME ITALY) in an open area with adequate ventilation. Calibration of the spirometer was carried out daily according to ATS/ERS recommendation before the first patient of the day, after every 4 hours, after a temperature change of 2oC and after every 8 to 10th person using a certified 3 litre calibration syringe, the syringe handle was pulled out completely and about 3 litre volume pushed into the spirometer at the correct flow, the calibration check was repeated at least three different times at different flows to ensure the results were within calibration limit.

2.2. Data analysis

Data were analysed using the IBM Statistical Package for Social Science (SPSS) version 25.0. Results were expressed as mean \pm standard deviation at 95% confidence interval (CI). Categorical variables (such as gender, symptoms, etc) were expressed as percentages. The independent Student t-test was used to compare continuous data, logistics regression model as used to assess factors associated with spirometric impairment in post-TB cases and a P value of less than 0.05 was considered statistically significant.

3. Results

One hundred post-TB cases (54 females and 46 males) and 100 controls (56 females and 44 males) were recruited for this study. There was no statistically significant difference in mean age for cases (48.0 \pm 15.2 years) relative to the controls (46.7 \pm 13.9 years, t=0.660; p=0.510). Of the 100 cases, 9 (9%) had no formal education, 39 (39%) had only primary education, 36(36%) had secondary education

while 16 (16%) had up to tertiary education. This was statistically significant ($p < 0.001$) when compared with that of controls. There was no statistically significant difference in the marital status of the cases compared to the controls ($p = 0.432$). The predominant comorbidity was HIV in the cases 19 (19%) compared to the control group 6 (6%) and this was statistically significant ($p = 0.005$) (Table 1). The

most frequent respiratory symptom in the post-TB cases was cough which was present in 56 (56%) of the cases, followed by sputum production in 51 (51%); breathlessness 34 (34%), chest pain 31 (31%), wheezing 13 (13%) and haemoptysis 10 (10%) which was the least reported respiratory symptom. None of the controls reported any respiratory symptoms as summarized in Table 2.

	Cases n = 100, (%)	Control n = 100, (%)	Chi-square (p-value)
Gender			
Female	54 (54.0)	56 (56.0)	0.08 (0.776)
Male	46 (46.0)	44 (44.0)	
Mean age \pm SD (years)	48.0 \pm 15.2	46.7 \pm 13.9	0.660 (0.510) t
Age groups (in years)			
<25	8 (8.0)	6 (6.0)	1.97 (0.894)
25 - 34	11 (11.0)	14 (14.0)	
35 - 44	18 (18.0)	24 (24.0)	
45 - 54	31 (31.0)	28 (28.0)	
55 - 64	18 (18.0)	15 (15.0)	
≥ 65	14 (14.0)	13 (13.0)	
Education			
No formal education	9 (9.0)	0 (0)	39.54 (<0.001)
Primary	39 (39.0)	25 (25.0)	
Secondary	36 (36.0)	19 (19.0)	
Tertiary	16 (16.0)	56 (56.0)	
Marital status			
Single	24 (24.0)	25 (25.0)	3.81 (0.432)
Married	47 (47.0)	49 (49.0)	
Divorced	5 (5.0)	1 (1.0)	
Separated	1 (1.0)	0 (0)	
Widowed	23 (23.0)	25 (25.0)	
Smoking	8 (8.0)	2 (2.0)	3.79 (0.052)
Alcohol	16 (16.0)	0 (0)	17.39 (<0.001)
Comorbidities			
Diabetes	1 (1.0)	1 (1.0)	0 (1.000)
Hypertension	5 (5.0)	1 (1.0)	2.75 (0.097)
HIV	19 (19.0)	6 (6.0)	7.73 (0.005)

Table 1: Distribution of Sociodemographic Characteristics of Study Participants (independent Student-t test)

Greater number of the post-TB cases 27 (53%) had cough productive of whitish sputum followed by those 11 (21%) with cough productive of milky sputum, yellowish sputum in

8 (16%), brownish sputum in 3 (6%), dark brown in 1 (2%) and haemoptysis in 1 (2%), respectively, (Figure 1).

Symptoms	Cases n = 100, (%)	Control n = 100, (%)	Total n = 200, (%)	Odds Ratio (95% CI)	X ² (p-value)
Breathlessness					
Yes	34 (34.0)	0 (0)	34 (17.0)	104.3 (6.3 – 1730.3)	40.96 (<i><0.001</i>)
No	66 (66.0)	100 (100.0)	166 (83.0)		
Chest pain					
Yes	31 (31.0)	0 (0)	31 (15.5)	91.1 (5.5 – 1513.9)	36.69 (<i><0.001</i>)
No	69 (69.0)	100 (100.0)	169 (84.5)		
Cough					
Yes	56 (56.0)	0 (0)	56 (28.0)	255.2 (15.4 – 4223.6)	77.78 (<i><0.001</i>)
No	44 (44.0)	100 (100.0)	144 (72.0)		
Sputum					
Yes	51 (51.0)	0 (0)	51 (25.5)	209.1 (12.6 – 3459.6)	68.46 (<i><0.001</i>)
No	49 (49.0)	100 (100.0)	149 (74.5)		
Haemoptysis					
Yes	10 (10.0)	0 (0)	10 (5.0)	23.3 (1.3 – 403.7)	10.5 (<i>0.001</i>)
No	90 (90.0)	100 (100.0)	190 (95.0)		
Wheezing					
Yes	13 (13.0)	0 (0)	13 (6.5)	31.0 (1.8 – 529.3)	13.9 (<i><0.001</i>)
No	87 (87.0)	100 (100.0)	187 (93.5)		

X² – Chi-square; CI – confidence interval

Table 2: Distribution of Respiratory Symptoms in Study Participants

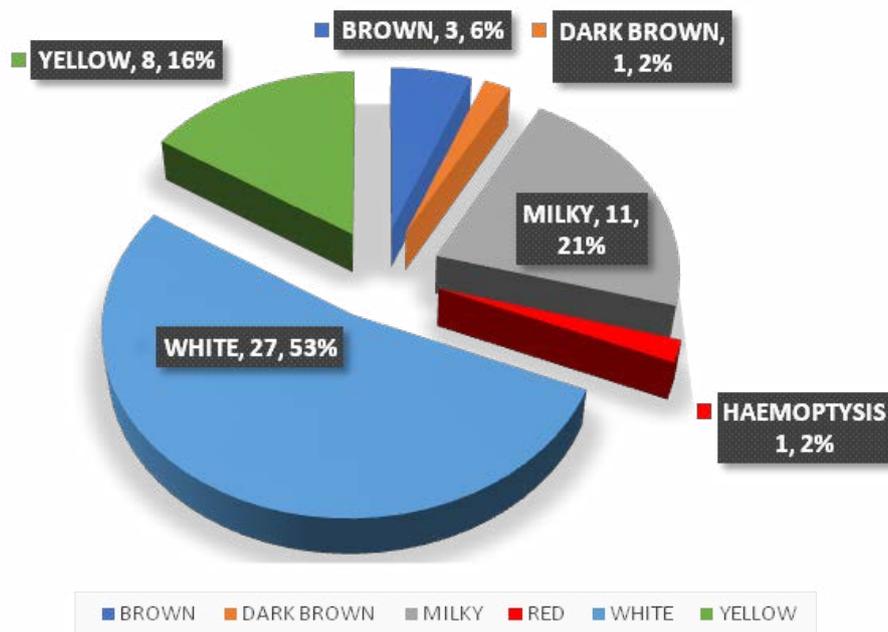


Figure 1: Sputum Characteristics of Study Participants with Productive Cough

The prevalence of lung function impairment was 71% among the post-TB cases compared to 12% in the controls; as shown in figure 2

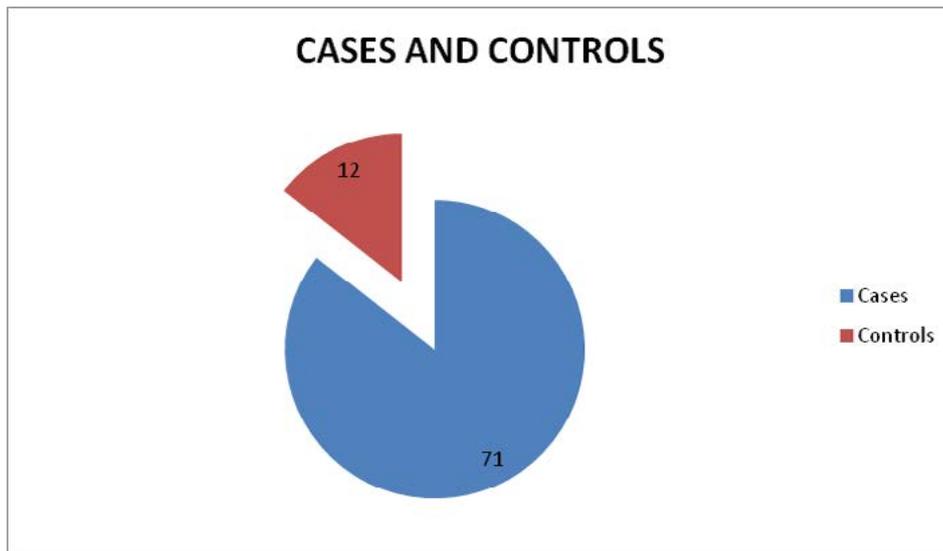


Figure 2: Prevalence of Abnormal Spirometry in Study Participants

The mean FEV1 among the post-TB cases was 1.93 ± 0.73 L (median z-score -2.06) comparatively lower to that of the control group with mean FEV1 of 2.40 ± 0.64 L (median z-score -0.7) and the difference was statistically significant ($t = -4.79, p < 0.001$). Similarly, the mean FVC among the post-TB cases was 2.72 ± 0.87 L (median z-score -2.27) which was lower compared to the control group with mean FVC

of 3.12 ± 0.88 L (median z-score -0.31) and the difference was statistically significant ($t = -3.22, p = 0.001$). Also the mean FEV1/FVC of 69 ± 12.4 among the post-TB cases ($t = -5.62, p < 0.001$), mean FEF₂₅₋₇₅ of 1.57 ± 0.83 ($t = -4.67, p < 0.001$) and mean PEFR of 4.66 ± 1.92 ($t = -5.34, p < 0.001$) were statistically significantly lower in the post-TB cases compared to the control group (Table 3).

	Cases n = 100 mean \pm SD	Control n = 100 mean \pm SD	Student t (p-value)
FEV1 (litres)	1.93 ± 0.73	2.40 ± 0.64	-4.79 (<0.001)
FEV1 z-score	-2.06 (-2.80 – -0.55) †	-0.71 (-0.96 – -0.27) †	2769 (<0.001) ‡
FVC (litres)	2.72 ± 0.87	3.12 ± 0.88	-3.22 (0.001)
FVC z-score	-2.27 (-2.30 – -0.24) †	-0.31 (-0.84 – -0.26) †	3417 (<0.001) ‡
FEV ₁ /FVC (%)	69.5 ± 12.4	77.7 ± 7.9	-5.62 (<0.001)
FEV1/FVC z-score	-1.38 (-2.33 – -0.94) †	-1.34 (-1.38 – -1.21) †	4137 (0.035) ‡
FEF ₂₅₋₇₅ (l/sec)	1.57 ± 0.83	2.09 ± 0.75	-4.67 (<0.001)
PEFR (l/sec)	4.66 ± 1.92	6.16 ± 2.04	-5.34 (<0.001)

† median (interquartile ranges), ‡ Mann-Whitney U test

Table 3: Lung Function Indices of Study Participants with their Z-Scores

Only lower body mass index (aOR 0.20, 95% CI: 0.07 to 0.52) was found to independently predict impaired lung function in post-TB cases after adjusting for confounders while

no significant association was found with age group, sex, educational status, previous TB treatment and presence of respiratory symptoms as shown in Table 4 And Table 5

Variables	Impaired spirometry n = 71, (%)	Normal spirometry n = 29, (%)	Crude Odds Ratio (OR) (95% CI)	p-value	Adjusted Odds Ratio (aOR) (95% CI)	p-value
Gender						
Female	35 (49.3)	19 (65.5)	1	0.143	-	
Male	36 (50.7)	10 (34.5)	1.95 (0.80 – 4.79)		-	
Age group						
≤48 years	34 (47.9)	18 (62.1)	1	0.200	-	
>47 years	37 (52.1)	11 (37.9)	1.78 (0.74 – 4.31)		-	

Educational status						
≤Primary	35 (49.3)	13 (44.8)	1	0.836	-	
≥Secondary	36 (50.7)	16 (55.2)	0.84 (0.35 – 1.99)		-	
Married						
Married	32 (45.1)	15 (51.7)	1	0.546	-	
Not currently married	39 (54.9)	14 (48.3)	1.31 (0.55 – 3.10)		-	
Previous TB treatments						
Once	42 (66.4)	19 (74.1)	1	0.554	-	
More than once	29 (33.6)	10 (25.9)	1.31 (0.53 – 2.23)		-	
BMI						
Normal/underwt	60 (84.5)	15 (51.7)	1	0.001	1	0.014
Overwt/Obese	11 (15.5)	14 (48.3)	0.20 (0.07 – 0.52)		0.20 (0.06 – 0.72)	
Wheezing						
Absent	70 (58.8)	40 (49.4)	1	0.103	-	
Present	49 (41.2)	41 (50.6)	5.70 (0.71 – 46.00)		-	
Difficulty in breathing						
Absent	42 (59.2)	24 (82.8)	1	0.029	1	0.121
Present	29 (40.8)	5 (17.2)	3.31 (1.13 – 9.70)		2.48 (0.79 – 7.83)	
Haemoptysis						
Absent	63 (89.9)	27 (93.1)	1	0.513	-	
Present	8 (10.1)	2 (6.9)	1.71 (0.34 – 8.61)		-	
Sputum production						
Absent	31 (43.7)	18 (62.1)	1	0.098	-	
Present	40 (56.3)	11 (37.9)	2.11 (0.87 – 5.11)		-	

Table 4: Variables Associated with Abnormal Lung Function in Post-Tb Cases.

Variables	Impaired spirometry n = 71, (%)	Normal spirometry n = 29, (%)	Crude Odds Ratio (OR) (95% CI)	p-value	Adjusted Odds Ratio (aOR) (95% CI)	p-value
Cough						
Absent	28 (39.4)	16 (55.2)	1	0.153	-	
Present	43 (60.6)	13 (44.8)	1.89 (0.79 – 4.53)		-	
Alcohol use						
No	11 (15.5)	5 (17.2)	1	0.829	-	
Yes	60 (84.5)	24 (82.8)	0.88 (0.28 – 2.80)		-	
Smoking						
No	64 (90.1)	28 (96.6)	1	0.306	-	
Yes	7 (9.9)	1 (3.4)	3.06 (0.36 – 26.08)		-	
Comorbidities						
Absent	15 (21.1)	9 (31.0)	1	0.295	-	
Present	56 (78.9)	20 (69.0)	0.60 (0.23 – 1.57)		-	
Pulse rate						
Mean ± SD	81.6 ± 12.4	82.9 ± 11.7	0.99 (0.96 – 1.03)	0.620	-	
Systolic Blood Pressure (mmHg)						
Mean ± SD	119.4±15.4	126.6±12.0	0.97 (0.94 – 0.99)	0.031	0.98 (0.94 – 1.01)	0.191
Diastolic Blood pressure (mmHg)						
Mean ± SD	73.4 ± 8.4	76.6 ± 8.1	0.96 (0.91 – 1.01)	0.089	1.00 (0.94 – 1.06)	0.894

Weight (kg)						
Mean ± SD	60.9 ± 10.6	65.1 ± 11.4	0.97 (0.93 – 1.01)	0.087	1.03 (0.97 – 1.09)	0.375
Height (m)						
Mean ± SD	1.68 ± 0.09	1.65 ± 0.13	23.3 (0.21 – 2.6 x 10 ³)	0.190	-	
Oxygen saturation (%)						
Mean ± SD	97.3 ± 1.6	97.7 ± 1.4	0.84 (0.62 – 1.14)	0.272	-	
Respiratory rate						
Mean ± SD	63 (89.9)	27 (93.1)	1.12 (0.88 – 1.43)	0.362	-	

Table 5: Variables Associated with Abnormal Lung Function in Post-Tb Cases (Contd.).

4. Discussion

A greater proportion of the post-TB patients had residual respiratory symptoms with the predominant complaint being cough reported in 56 (56%). Other symptoms in descending order were sputum expectoration in 51 (51%), breathlessness 34 (34%), chest pain 31 (31%), wheezing 13 (13%) with haemoptysis being the least reported symptom in 10 (10%) of post-TB patients. This is similar to the study by Mpagma who reported a similar trend among his study cohorts; The prevalence of cough and sputum production were much higher than the Egyptian study of 38.1% and 24.9%. This could be explained by the predominant obstructive pattern in this study compared to the later that found predominant restriction [17-21]. The predominance of cough and sputum production in this study could be explained by predominant obstruction as the main pathophysiological process which could be linked to greater tissue destruction, evidence of airway dilatation leading to bronchiectasis and formation of cavities. However, these findings were much lower compared to 93.2% with cough and 91.5% with residual sputum production reported among post-TB patients in Lagos [22]. The higher prevalence in the later study could be from possible overcrowding and ambient air pollution in the study region that may further impact on the symptoms; also cough and sputum production are much more perceived symptoms than breathlessness which may be masked by inactivity. Sputum production could occur in association with cough and dyspnoea as corroborated with studies by Nidoi, Ozoh and Patil [23,12,24,25]. Majority of those with sputum production had white mucoid phlegm 27 (53%) followed by milky phlegm in 11 (21%); haemoptysis was seen in only 2% of the cases. The prevalence rate of breathlessness in this study of 34% is close to the rate reported in Ilorin 42%, although they reported it as the predominant symptom but much lower than 79% reported by Pandey in India and 96% reported from Malawi, although like the Ilorin, was found to be the predominant symptom [26, 27, 28]. These findings may be due to the predominant restrictive pattern in the study participants. The predominant restriction could be explained by dysregulation of the mechanism of protease control caused by matrix metalloproteinases leading to lung parenchyma destruction and fibrotic changes. Host immune responses that drive inflammation, cavitation and fibrosis contribute to the variable patterns of lung healing manifesting as breathlessness, cough and sputum production. Fibrogenic cytokines could lead to permanent changes in the lung architecture after tuberculosis leading to aberrant wound

healing processes, excessive collagen deposition and fibrosis. It has been proposed that chronic inflammatory response and long-term anatomic alterations induced by pulmonary tuberculosis are the main pathologic basis of structural damage to large and small airways leading to bronchiolar narrowing and bronchiolitis obliterans manifested as wheezing. This study reported wheezing in 13% of the post-TB patients which was lower than that reported in Brazil [29-34]. Patients with persistent respiratory symptoms post-TB may be misdiagnosed as a case of recurrent tuberculosis or multidrug resistant tuberculosis despite negative laboratory results leading to commencement of re-treatment which are unnecessary and patients may be exposed to unwanted toxicity of the drugs. Persistent residual respiratory symptoms after TB treatment and cure may lead to the erroneous belief that patient is still infectious with resultant stigmatization. The high burden of respiratory symptoms in this study may be due to late presentation to the hospital leading to late diagnosis and extensive lung tissue damage. This study noted significant association between low body mass index and spirometric impairment in post-TB cases similar to a Mozambican study that showed that low body mass index, in addition to low haemoglobin and low CD4 counts as predictors of increased risk of long term lung impairment post-tuberculosis [35]. Nightingale et al in a prospective study similarly demonstrated that low body mass index, negative HIV status and extensive lung parenchymal change predicted lung function decline after 3 years of follow up while higher body mass index at TB treatment completion, duration of illness prior to diagnosis, age and sex were associated with a greater mean FEV1 and FVC scores at 3 years.³⁶ It has been proposed that there is a strong association between low body mass index and tuberculosis across varying incidences of tuberculosis in different countries and across all levels of BMI as opposed to what obtains in non-TB respiratory diseases like COPD and lung cancer where a higher BMI may be associated with higher respiratory mortality indirectly positing that low BMI patients are at increased risk of pulmonary tuberculosis whilst been somewhat protected from other forms of respiratory disease [36,37]. Similarly, a strong association between human immune response and BMI can explain increased risk of tuberculosis in HIV coinfecting patients. Aaron et al had demonstrated that body build may influence susceptibility to tuberculosis because of differences in pulmonary mechanics, it has been proposed that there is an obvious relationship between nutrition and tuberculosis as tuberculosis is associated with poverty which in turn drives

malnutrition [37]. Body build and stature have also been associated with TB; a higher incidence of tuberculosis was found in tall thin American army soldiers compared to short, stout and heavier ones during the first world war [37,38]. This study did not demonstrate any significant association between respiratory symptoms, gender, comorbidities and age with spirometric impairment in post-TB patients; this is in contrast to a study in Ilorin, that showed that patients more than 40 years of age, increasing bacillary load on sputum gene xpert, cases of PTB retreatment and residual respiratory symptoms were positive predictors of lung function abnormalities in post-TB patients as also found by Mikhail et al who demonstrated that having a culture positive tuberculosis in the past, having recurrent tuberculosis, age more than 50 years and lower level of education were associated with increased risk for lung function impairment in post-tuberculosis patients [20,29]. Education is one of the risk factors that influence incidence of pulmonary tuberculosis; low level of education could be associated with TB, arising from the lack of knowledge of the transmission and danger of tuberculosis disease and low socioeconomic standing. In this study, there was no significant relationship between educational status and spirometric impairment post-TB clients which is in contrast to a Russian study that showed significant association between spirometric impairment and a low level of education [29].

5. Conclusion

This study found that residual respiratory symptoms were high in post-TB patients occurring in 10 – 56% of cases in varying combinations. Only body mass index was independently associated with abnormal spirometry while age, previous TB treatment, presence of comorbidities and respiratory symptoms had no significant association with impaired lung function.

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Declarations

Ethics and consent to participate: The research was done in compliance with the Helsinki Declaration. The study was approved by the Ethics committee of the Federal Teaching Hospital, Owerri (FMC/OWR/HREC/VOL11./78). Informed consent to participate was obtained from all of the participants.

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