NIGERIAN INFECTIOUS DISEASES SOCIETY

Original Article

Ventilatory Function Phenotypes in Patients with Pulmonary Tuberculosis

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ABSTRACT

Background: Ventilatory function abnormalities following pulmonary TB has now emerged as a distinct clinical entity, yet the prevalence of these abnormalities in Nigeria remains unknown. This study aimed at determining the prevalence of these abnormalities and investigating its associated factors.

Methods: The design was prospective comparative study whereby ventilatory function of 88-consecutive patients aged 18-years and above (57 males and 31 females) who completed 6-months of treatment for pulmonary TB was compared with that of equal number of age, sex and height-matched controls. Both groups underwent spirometry at recruitment and after 3-months follow-up. Their lung functions were classified as normal or abnormal (obstructive, restrictive or mixed). Chest x-rays of the cases at end of 5-months of treatment were also reviewed. Data obtained were analyzed using SPSS version 20.

Results: The prevalence of abnormal ventilatory function of was 77.3%, with restrictive pattern being the most common 65 (73.9%), followed by obstructive pattern 2 (2.3%). Ventilatory function improved after 3-months post-treatment. The control group had an overall prevalence of ventilatory function abnormality of 22.6% at recruitment with 15 (17.0%) having restrictive abnormality, 4 (4.5%) having obstructive abnormality. After 3-months follow-up however, abnormal ventilatory function among the control group was seen in 8 (9.0%) subjects, 6 (6.8%) of whom were restrictive and 1 (1.1%) each with obstructive and mixed disorders.

Conclusions: More than two-third of the cases studied had ventilatory function abnormalities after 6 months of completed treatment. This underscores the need for ventilatory function assessment after treatment for pulmonary TB.

Key words: Tuberculosis, pulmonary, function, Nigeria.

INTRODUCTION

Tuberculosis (TB) is a chronic granulomatous disease caused by the acid-fast bacillus (AFB) Mycobacterium tuberculosis or its closely related species. The disease most commonly affects the lung, pulmonary TB (PTB), but can affect extra pulmonary sites (EPTB). It is transmitted from person to person by inhalation of droplet nuclei aerosolized by patients with infectious TB. It is one of the top 10 causes of death worldwide[1].

Tuberculosis remains one of the leading causes of death worldwide and the leading cause from a single infectious agent. Pulmonary tuberculosis can result in lung parenchymal destruction by up-regulation of several proteases and deregulations of protease control[2]. It is often characterized by the formation of caseating granuloma, tissue liquefaction, and cavity formation[3].

These lead to bronchial and parenchymal structural changes, including bronchiectasis, bronchovascular disruption, emphysematous changes, and pulmonary fibrosis.

This entity is major public health concern due to its potential to add to the burden of chronic obstructive airway disease[4].

Previous studies have reported a wide variation in the prevalence of post-TB ventilator dysfunction (PTBVD). There is heterogeneity in the prevalence of PTBVD, with a reported prevalence as low as 22.7%[5], and as high as 74%[6]. Demographic population differences and varying airway remodeling risk factors perhaps may account for the wide spectrum. Earlier studies revealed obstructive defects as the predominant abnormality, however, abnormalities could be obstructive, restrictive, or mixed patterns. Accordingly, severity of the impairment varies from mild to severe presentations[7,8]. Despite permanent pulmonary structural changes, further evaluation of pulmonary function at the completion of therapy is not routinely performed[9].

While the burden and spectrum of TB has been well characterized, associated ventilatory abnormalities has not been fully elucidated. We intend to identify and characterize pulmonary functional changes following infection with Tuberculosis (PTB) and to determine their short-term trend.

METHODS

Study Population

We studied persons aged 18-years and above with smear positive or negative pulmonary tuberculosis with or without extra-pulmonary tuberculosis who have completed 6 months of therapy. Patients were recruited consecutively over a period of 14-months between June, 2017 and July, 2018. Informed written consent was obtained from all participating patients. Study cases were recruited from TB cases from Aminu Kano Teaching Hospital and Infectious Diseases Hospital Kano. Persons attending the two hospitals' general out-patient department for non-respiratory ailments were recruited as controls.

Study design

This was a hospital -based prospective comparative study where ventilatory function of patients treated for pulmonary TB was compared with that of apparently healthy controls at the end of treatment, and at 3 months post treatment. We determined that with 176 samples (88 cases and 88 controls), a difference of 10 percent in ventilatory functional biomarkers could be determined between study cases and controls. Study cases were matched with controls for age, sex and height.

Study area

The study was conducted at Aminu Kano Teaching Hospital, Kano (AKTH). AKTH is a 700-bed tertiary health institution serving as referral center for patients from neighboring states like Jigawa, Katsina, Bauchi and Zamfara, as well as the neighboring Niger republic. Kano has an estimated population of 9.4 million people according to the last national population census figures in 2006. It is located on latitude 120 3I N, and longitude 80 32I E. The Directly Observed Therapy Short-course (DOTS) clinic of the hospital was the site from where patients were recruited. The DOTS clinic operates daily from Monday to Friday attending to both new and follow-up cases. On the average 20 patients are seen daily out of which 3-5 are new cases while 2-3 have completed 6 months of treatment.

Inclusion criteria for cases

All consenting Patients aged 18 years and above who had completed 6-months of anti-TB treatment irrespective of sputum AFB smear status.

Exclusion criteria for cases

We excluded persons with pulmonary co-morbidities, including doctor diagnosed Bronchial Asthma, Chronic Obstructive Pulmonary Disease (COPD) confirmed by spirometry, history of respiratory failure requiring mechanical ventilation, lung cancer, active chest infection (bacterial, viral or fungal), skeletal abnormalities like kyphosis, scoliosis and previous history of lung resection. We also excluded persons with clinical evidence of congestive cardiac failure (New York Heart Association class >2) after examining the patient; Human immunodeficiency virus (HIV) infection; Doctor diagnosed autoimmune disease; pregnant women.; and patients with current or past history of cigarette smoking. Other exclusion reasons where patients with treatment failure or drug resistant TB. Equally, patients with current hemoptysis and those who were unable to perform spirometry were excluded from the study.

Study tools/Instruments

We used a pre-tested questionnaire (adapted from ATS - DLD-78)[10]

Weighing scale with standing height measuring rod (ZT-160, MEDFRIEND ENGLAND, Supplementary IV)

Spirometer (Spirolab III colour, Ver 2.1, FCC ID: TUK MIR009, Supplementary V)

Study protocol

Patients that presented to DOTS clinic after completing 6-months of treatment were recruited into the study and followed up for 3 months with a repeat spirometry.

Anthropometric indices were recorded using a weighing scale with standing height measuring rod (ZT-160 MEDFRIEND ENGLAND). Body weight was measured in kilograms (kg) with subject in erect position, wearing only light clothing and without shoes. Standing height was measured in centimeters using meter rod without shoes or cap. A full clinical examination was conducted on each subject to ascertain clinical evidence of any of the exclusion criteria above.

A pretested questionnaire (adapted from ATS-DLD-78)[10], was used to abstract data on demographic and occupational information, as well as history of current pulmonary TB.

Spirometric Measurement

Spirometry was conducted in a well-ventilated room between the hours of 9:00 am -1:00 pm. Recommendations of the American Thoracic Society[11] for subject manoeuver, techniques, and quality control were adhered to. The spirometer device used for this study was Spirolab III colour, Ver 2.1, FCC ID: TUK MIR009. The device was calibrated regularly before use. Disposable mouthpiece was used for each participant.

Pre-test instructions on how to perform the procedure were given to each subject followed by a demonstration to enhance understanding. These include correct posture i.e., seated on a chair with back erect and head slightly elevated. Attaching nose clip and placing mouthpiece in the mouth making a seal round it with the lips. This was followed by taking in a deep inhalation to fill his/her lungs to total lung capacity. Subjects then quickly exhale through the mouthpiece as fast, as forcefully and as completely as possible, until no more air can be expelled, while maintaining the same posture. Instructions and couching were repeated as necessary to ensure good quality result at the end of the test.

Three tests with values within 5% were accepted, and the best of three values was used. When variation was > 5%, the best three results from eight tests were selected. Forced expiratory volume in the 1st second (FEV_1), FVC, FEV_1/ FVC ratio, and their respective percent predicted values were obtained.

Predicted values were determined for each subject based on their age, gender, height, and race for FEV_1, FVC, and the ratio of FEV_1 to FVC (FEV_1/FVC) using the built-in Global Lung Initiative (GLI) equation[12] in the spirometer. Abnormal results for FEV_1, FVC and FEV_1/FVC were determined by comparison to their lower limits of normal (LLN).

Airway obstruction was defined as an FEV1/FVC ratio of < 0.7 and an FVC of > 80% predicted, restrictive defects as an FEV1/FVC ratio of > 0.7 with an FVC of < 80% predicted, and mixed defects as an FEV1/FVC ratio of < 0.7 and an FVC of < 80% predicted[13,14]. A follow-up spirometry was performed for each participant at 3 months post recruitment. This was to find out whether changes seen at enrolment were due to TB or due to chance variation and equally to determine the trend over time, at least on a short-term.

Equal number of age, height and gender-matched subjects where enrolled as control group. They differ from the cases only in that they have never suffered pulmonary TB. They also underwent spirometry at enrolment and a repeat spirometry after a 3-month follow-up using the same steps outlined above.

Radiographic scoring and grading

Chest x-rays at end of 5 months of treatment were reviewed to determine presence of residual radiographic abnormalities. Poor record keeping and mishandling of the initial CXR by many of the participants hindered review of the pre-treatment CXR which could have enabled comparison of ventilatory function with both pre and post-treatment CXRs.

A simplified and validated CXR reporting method 15 was employed to grade the percentage of lung affected. Each lung was divided into 3 zones (upper, middle and lower) and each zone was scored separately. Visual estimation of the extent of opacification, cavitation or other pathology as a percentage of visible lung was made; dense opacification of a zone was graded as 100% of that zone, while patchy opacification within a zone attracted scores <100% depending on the extent of opacification. The radiological score for each patient was obtained by the sum of the scores of the 6 zones, i.e. for both lungs. The total score is then divided by 6. Presence of cavitation(s) attracts an additional score of 40% as shown below:

CXR score = proportion of lung affected (%) + 40 if cavitation present.

The overall score is graded in to 5 based on severity of the CXR abnormalities as shown in the table 1 below:

Table 1: Grading of Chest X-ray abnormalities based of fibro cavitatory changes.

Radiographic score (%)	Grade	Interpretation of CXR abnormalities
0	0	Normal CXR
1-19	1	Mild CXR abnormalities
20-39	2	Moderate CXR abnormalities
40-59	3	Severe CXR abnormalities
≥ 60	4	Very severe CXR abnormalities

An example of a patient having right sided upper zone fibrosis with cavitation (100% for that zone) and infiltrates in the remaining middle (30%) and lower zones (10%), but a normal left lung with 0% score in all zones.

The total score for the 6 zones of both lungs = 100+30+10+0 +0+0 = 140, dividing it by 6 gives a net score of 23 .3%. Presence of cavities attracts additional score of 40, giving him an overall score of 23.3 + 40 = 63.3% (Grade 4 or very severe).

Findings were corroborated by a qualified radiologist and overall radiographic scores were assigned to each subject.

Data analysis

Data discrepancies were queried and corrected. Data analysis was performed using statistical software package (IBM SPSS statistics, version 20 for Windows; SPSS Inc; Chicago, IL).

Parametric data summary was with means with standard deviations (SD) and non -parametric with median and interquartile range. For the analysis of parametric variables student t-test was used to compare inter group differences while Mann Whitney test was used for non-parametric data. Association between categorical variables was assessed using chi-square test or Fisher 's exact test as appropriate. Binary logistic regression models were used to determine the predictors of ventilatory function abnormalities. In all iterations, P-value of <0.05 was considered statistically significant.

Ethical Approval

Ethical approval for the study was obtained from the medical and research ethics committee of AKTH, Kano. Written informed consent was also obtained from all participants.

RESULTS

Socio-demographic characteristics of the cases and controls

A total of 88 subjects who completed treatment for PTB and 88 controls were recruited in to the study. The socio-demographic characteristics of the cases and controls are summarized in Table 2. The mean age was 33 .3 + 10 .8 years, while that of the control group was 34 .1 + 11 .4 years, (P = 0.57). The mean height was 167 .0 + 8.8 cm, while that of the control group was 166.5 + 8.8 cm, (P = 0. 92). There were 57 (64.8%) males and 31 (35.2%) females among the cases while 44 (50%) each among the control group, (P = 0.05). More than a third of the cases 33 (37.5%) had at least secondary education, while in the control group majority 62 (70.5%) had tertiary education. Majority of the cases 77 (87 .5%) and the controls 87 (98 .9%) resides within Kano metropolis. None of the participant had workplace exposure to dust irritant gases or chemical fumes. They were predominantly civil servants, petty traders and undergraduate students. None of the participants has current or previous history of tobacco smoking.

Table 2: Socio-demographic characteristics of the cases and controls

Characteristics		**Cases n=88**	**Controls n=88**	**p-value**
Age(years) mean ± SD		33.3 ± 10.8	34.1 ± 11.4	0.57#
Height (cm) mean ± SD		167.0 ± 8.8	166.5 ± 8.8	0.92#
Sex		**n (%)**	**n (%)**	
Male		57 (64.8)	44 (50)	
Female		31 (35.2)	44 (50)	0.05*
Marital status		**n (%)**	**n (%)**	0.60**
Single		41 (46.6)	32 (36.4)	
Divorced		1 (1.1)	1 (1.1)	
Married		43 (48.9)	52 (59.1)	
Widowed		3 (3.4)	3 (3.4)	
Level of education		**n (%)**	**n (%)**	
Informal		15 (17.0)	5 (5.7)	**<0.001***
Primary		15 (17.0)	3 (3.4)	
Secondary		33 (37.5)	18 (20.5)	
Tertiary		25 (28.4)	62 (70.5)	

- student t test, * - Chi square test, ** - Fisher exact test

Clinical characteristics of the cases

The clinical characteristics of the cases are summarized in Table 2 Cough was by far the most common presentation of PTB in the study population seen in 87 (98 .9%) cases, frequently productive of sputum 85 (96.6%), followed by weight loss 77 (87.5%) and fever in 68 (77.3%) cases. Night sweats was also seen in close to two-third of patients 58 (65. 9%), followed by breathlessness 53 (60.2%) and chest pain 51 (58 .0%). Bloody sputum was the least common manifestation of PTB in the cases studied 32 (36.4%).

The mean duration of symptoms before diagnosis was 65.7 + 55.2 (238) days. Complete resolution of symptoms was seen in majority of the cases 77 (87 .5%) following treatment, while residual symptoms were still present in 11 (12.5%) cases. Breathlessness was the most common residual symptom seen in 7 (8.0%) cases, followed by chest pain in 3 (3.4%) cases and 2 (2.3%) patients still had productive cough but none of them was producing bloody sputum after completing treatment.

Out of the 88 cases studied only 1 (1.1%) interrupted his treatment for a period of 5 weeks and his treatment was extended by 2 months because of non-compliance. Treatment was extended in a total of 6 (6.8%) cases for various reasons. The two most common reasons were persistent CXR abnormalities in 2 (2.3%) cases and coexistent radiographic evidence of tuberculous spondylitis without clinical signs in 2 (2.3%) cases.

Their treatment was extended by 2 months and 6 months respectively. Twelve (13.6%) of the 88 cases studied had one previous PTB treatment. Patients with other comorbid conditions like HIV were excluded as highlighted in the exclusion criteria.

Laboratory characteristics of the cases

Majority of the cases 77 (87.5%) had smear positive PTB. Eleven (12.5%), were treated as smear and GeneXpert negative based on physician diagnosed TB.

Radiographic characteristics of the cases.

The radiographic characteristics of the cases are presented in Table 3. Although for most cases pre-treatment CXRs were not available for review, more than two-third of the cases 62 (70.5%) had residual CXR abnormalities that were presumed to be from the recent pulmonary TB, while the rest, 26 (29.5%) had resolved CXR abnormalities.

Fibrosis was the most common CXR abnormality seen in more than a fifth, 20 (22.7%) of cases, followed by patchy/ nodular infiltrates in 14 (15.9%), mixture of infiltrate and fibrosis or fibro-cavitatory lesions in 12 (13 .9%) and cavitation in 4 (4.5%) cases. Radiographic abnormalities were mostly involving the upper zones but some cases had widespread abnormalities . None of the cases had emphysematous changes, segmental or lobar collapse. All the subjects with residual CXR abnormalities had a radiographic score of at least 20 % (grade 2/moderate) except 8 (9.1%), who had a score of 1-19% (grade 1/mild).

Table 3: Chest x-ray features after 5-months of treatment

Chest x ray status	**Frequency (n=88)**	**Percentages**
Residual CXR abnormalities	62	70.5
No Residual abnormalities	26	29.5
Types of CXR abnormalities:		
Fibrosis	20	22.7
Patchy/nodular infiltrates	14	15.9
Cavitation & fibrosis	12	13.6
Fibrosis & infiltrates	12	13.6
Cavitation	4	4.5

Radiographic score (%) **(Grade of CXR abnormalities)**		
0 (Grade 0/Normal)	26	29.5
1-19 (Grade 1/Mild)	8	9.1
20-39 (Grade 2/Moderate)	20	22.7
40-59 (Grade 3/Severe)	28	31.8
≥60 (Grade 4/Very severe)	6	6.8

Ventilatory abnormalities in the cases

At the time of recruitment (end of 6-months of treatment), more than two-third of the cases, 68 (77.3%) had abnormal ventilatory function, Restrictive ventilatory abnormality was commonest, was seen in 65 (73.9%) cases, followed by obstructive in 2 (2.3%) cases and mixed pattern of abnormality in 1 (1.1%) case.

Twenty-four (27.3%) patients who had abnormal spirometry at recruitment reversed to normal after 3 months of follow-up. The prevalence of ventilatory function abnormality therefore dropped, as 44 (50%) of the cases had normal ventilatory function while 44 (50%) still had abnormal ventilatory function. The pattern of spirometry abnormality was still predominantly restrictive, seen in 43 (48.9%) cases with only 1 (1.1%) case having obstructive ventilatory abnormality. Therefore, there was statistically significant improvement in ventilatory function after 3 months follow-up (P <0.001). Table 4

Table 4: Comparison between spirometry result at completion of treatment and after 3 months of follow-up among cases

Ventilatory function	**Spirometry 1** **n (%)**	**Spirometry 2** **n (%)**	**Test Statistic**	**p-value**
Normal	20 (22.7%)	44 (50.0%)	45.812**	**<0.001**
Restrictive	65 (73.9%)	43 (48.9%)		
Obstructive	2 (2.3%)	1 (1.1%)		
Mixed	1 (1.1%)	0 (0.0%)		
Total (n=88)	88 (100%)	88 (100%)		

Spirometry 1-At recruitment, Spirometry 2-After 3 months follow-up, ** - Fisher exact test

Relationship between socio-demographic characteristics of the cases and ventilatory function after 6 months of treatment

The socio-demographic characteristics of the cases i.e., gender, age, level of education and place of residence did not show statistically significant relationship with ventilatory function assessed at the end of treatment as shown in Table 5.

Table 5: Relationship between socio-demographic characteristics of the cases and ventilatory function after 6 months of treatment

Characteristic	Spirometry		Total (n=88)	Test Statistic	p-value
	Normal	Abnormal			
Sex				1.186*	0.28
Male	15 (17.0%)	42 (47.7%)	57 (64.8%)		
Female	5 (5.7%)	26 (29.5%)	31 (35.2%)		
Age group (years)				0.092*	0.99
18-24	5 (5.7%)	16 (18.2%)	21 (23.9%)		
25-34	7 (8.0%)	24 (27.3%)	31 (35.2%)		
35-44	5 (5.7%)	16 (18.2%)	21 (23.9%)		
≥45	3 (3.4%)	12 (13.6%)	15 (17.0%)		
Level of education				3.351**	0.34
Informal	2 (2.3%)	13 (14.8%)	15 (17.0%)		
Primary	3 (3.4%)	12 (13.6%)	15 (17.0%)		
Secondary	6 (6.8%)	27(30.7%)	33 (37.5%)		
Tertiary	9 (10.2%)	16 (18.2%)	25 (28.4%)		
Place of residence				0.148*	0.70
Urban	18 (20.5%)	59 (67.0%)	77 (87.5%)		
Rural	2 (2.3%)	9 (10.2%)	11 (12.5%)		

* - Chi square test, ** - Fisher exact test

Relationship between clinical characteristics of the cases and ventilatory function after 6 months of treatment

The relationship between clinical characteristics of the cases and ventilatory function assessed after 6 months of treatment is not statistically significant as shown in Supplementary Table 1.

Ventilatory abnormalities in the control group

The prevalence of various forms of ventilatory function abnormalities among the controls are summarized in Supplementary Table 2. Significantly higher prevalence of ventilatory function abnormalities was observed among the cases than the control group at recruitment ($p<0.001$) as shown in Table 7. Out of the 88 apparently healthy controls studied only about a fifth, 20 (22 .6%) had an abnormal ventilatory function at the time of recruitment. Amongst them 15 (17.0 %) had restrictive ventilatory defect, obstructive defect in 4 (4.5%) and mixed disorder in 1 (1.1%) subject

Relationship between radiographic scores of the cases and ventilatory function after 6 months of treatment

Relationship between radiographic scores and ventilatory function abnormalities is depicted on Supplementary Table 3, Extent of residual radiographic abnormalities (grade of CXR abnormalities) is significantly associated with ventilatory function abnormalities ($p=0.001$)

On multivariate modeling Radiographic score was a significant predictor of respiratory dysfunction even after controlling for a number of variables Supplementary table 4

DISCUSSION

Pulmonary TB is becoming increasingly recognized as an important contributor to the pool of large number of patients living with various forms of lung function impairment, early recognition of lung function impairment will serve as a bold step in reducing long-term sequelae of PTB.

This study therefore, assessed the ventilatory function of treated pulmonary TB patients using spirometry at end of 6-months of treatment and after 3 months follow-up, with the aim of finding the different types of abnormalities and their risk factors. The study found a high rate of abnormal ventilatory function at the end of 6 months of treatment, restrictive pattern being commonest. The occurrence was also significantly higher than in controls.

The prevalence of abnormal ventilatory function obtained in this study is consistent with findings from several other studies, although, one study reported a relatively low prevalence of 22.7%,[16] Furthermore, a number of other studies also found restrictive disorder as the predominant pattern with various proportions[17,18].

Nevertheless, other studies found that airflow obstruction was the most common defect[19,20]. Varying degrees of lung parenchymal destruction with reduction in lung volume that frequently follows pulmonary TB has been postulated to be responsible for restrictive ventilatory function abnormalities[21]. Several other reasons have been postulated to explain post tuberculous obstructive impairment[22,23]. Consequently, there is no consensus as to the predominant ventilatory impairment phenotype in pulmonary TB.

[24]Overall it appears the resultant ventilatory disorder is an interplay between host immune response and pathogen factors that in concert with environmental exposures establish which abnormality a particular patient develops[25].

It was noted that after three months of follow-up there was a significant reduction in overall prevalence of ventilatory function impairment; with restrictive ventilatory impairment still remaining the predominant phenotype. These finding suggest resolution of ventilatory function impairment following pulmonary TB over time. However, further studies would be needed to determine at what point on a temporal scale this switch occurs. Equally to be determined is whether all impairments ultimately return to normal.

A number of studies found similar improvement in lung function with time[26]. It is likely that healing process continue even after completing TB treatment, resulting in further improvement in lung parenchymal structure and function[27,28,29]. Conversely one study[30] revealed that ventilatory function abnormality discovered after 5 months of treatment did not significantly differ from that seen after an additional 4 months of follow-up, implying that impairment, when present, may be permanent. In this study, extent of residual CXR abnormalities at the end of treatment is the most important factor that determines whether or not ventilatory function abnormalities improves.

There was significantly higher ventilatory dysfunction in cases compared to controls at recruitment. This may suggest ventilatory function abnormalities observed in the cases were most likely a consequence of the pulmonary TB. Lung function usually reaches a peak at about the age of 25 years, thereafter it begins to decline steadily. Therefore, test results need to be compared to predicted values for age, and lower and upper limits of normal (LLN and ULN), respectively that are appropriate for the individual being tested. This enables discrimination of truly abnormal lung function from the usual age-related decline[12].

Prolong duration of symptoms before diagnosis and treatment could result from patient-level delays in seeking health care and/or clinician -level delays in diagnosis and treatment. Lack of effective case detection strategies also contribute to the delays[31,32,33].

It is reasonable to think that any of these delays would be associated with poorer prognosis including ventilatory function abnormalities even after a successful microbiologic cure. There is evidence for this hypothesis in the literature[31,32]. However, result of this study conflict with this suggestion and is not entirely unexpected as an earlier study[30] found that, the correlation between the delay in TB diagnosis and treatment and change in lung function indices (ΔFEV1/FVC) was not statistically significant (r = 0.03, P = 0.7659). In addition, the mean delay in TB diagnosis and treatment in subjects with normal pulmonary function tests (PFTs) was not significantly different from that in subjects with impaired PFTs (P = 0.339).
In other words, patients who had longer delays before TB diagnosis and before commencing treatment are not more likely to have pulmonary function impairment. Furthermore, in a subgroup analysis of duration of symptoms to TB diagnosis and lung function in the Dar es Salaam study[34], there was no significant difference among patients who were diagnosed and started treatment within 1-month against those who were diagnosed and started treatment after 1-month. This relationship was also not significant for any of the various patterns of ventilatory impairment suggesting that simply having tuberculosis imparts a risk irrespective of how soon treatment is started. Similarly, another study in Vietnam also found no significant relationship between TB treatment outcome and diagnostic delays[33]. This could possibly be because patients that eventually develop ventilatory abnormalities may be clinically more ill and therefore seek medical attention earlier. Alternatively, they may have more typical radiographic abnormalities suggestive of pulmonary TB and therefore receive the correct diagnosis sooner. It is also possible that the lung parenchymal and airway distortions that subsequently result in functional impairment occur early in the disease process, before treatment initiation. While early diagnosis and treatment are undoubtedly important in curtailing the rate of transmission of TB,[31,32] this finding suggests that earlier diagnosis may not directly translate to lower rates of ventilatory function abnormalities.

Sputum smear status was not significantly associated with ventilatory function abnormality even though majority had a smear positive disease Perhaps, patients with sputum smear positive disease where more likely to be diagnosed and commenced on treatment early, compared with those with smear negative disease. Smear-positive disease, which suggests either a high mycobacterial load or endobronchial involvement, has been shown to be an important predictor of pulmonary function deterioration and obstructive ventilatory defects after the completion of pulmonary TB treatment[35]. A study in South African gold miners also found that sputum smear positive status is independently associated with excess decline in FEV1 and FVC[36].

Treatment compliance and interruptions equally do not have a significant relationship with ventilatory function. Perhaps if a larger number of subjects had interrupted their treatment, compliance may have had a significantly impact on ventilatory function as reported in Saudi Arabian study. The study found significantly higher rate of abnormal spirometry in patients with poor compliance (poor 58.3% vs. good 17.6%).[26]

Likewise, treatment extension did not have significant impact on ventilatory function. Although some studies have reported relationship between prolonged duration of treatment and deterioration in ventilatory function[35]. However, it is important to note that only 6.8% of the cases studied had their treatment extended in this study.

Even though several studies revealed significant relationship between previous pulmonary TB and various forms of ventilatory function abnormalities,[7,37]This study could not establish such a relationship, possibly on account of few study participants having previous PTB treatment. In particular, a study found risk of pulmonary function impairment increasing with the number of episodes of tuberculosis[7]. Furthermore, a study in Dar es Salaam[34] found TB recurrence to be a significant predictors of lung function abnormality (AOR 2.789, CI 1.274 - 6.106).

Although we had no access to pre-treatment CXRs, we found significant relationship between grade of radiographic abnormality (radiographic score) after 5 months of treatment with ventilatory function abnormality. This is because radiographic abnormalities are a manifestation of underlying structural abnormalities and therefore the extent of the abnormalities would be related to ventilatory impairment as reported in previous studies.[26,35] Studies have linked initial radiographic abnormalities at diagnosis (rather than residual radiographic abnormalities at the end of treatment) as equally significant predictors of subsequent evolution of lung function abnormalities.[36,38] Consequently initial and end of treatment radiographic score are therefore important risk factors for the development of ventilatory function abnormalities following pulmonary TB.

This study has a number of limitations; Spirometry indices such FEV1 and FVC have limited positive predictive value but a high negative predictive value for restrictive pulmonary dysfunction. As such we could only approximate occurrence of restrictive ventilator disorder. Although spirometry can exclude 97% of those persons without a restrictive pattern, a more positive prediction of restriction can better be described with total lung capacity[39]. Total lung capacity was not measured in this study because of non-availability of whole body plathysmograph.

Chest x-rays were not done for the control group even though that could have allowed for exclusion of those with obvious previous pulmonary TB lesion or other lesions that could affect their lung function. This was because many controls are not likely to consent to a test that may potentially be harmful.

Preventive strategies as either "right" or "wrong" with respect to the risk factors identified could not be given as the study could not confirm a cause and effect relationship between the factors and post TB ventilatory abnormalities.

Excluding persons purely based on self-reported current or past history of tobacco smoking may be insufficient to rule out subjects with tobacco related ventilatory abnormalities

Further studies with larger population and longer follow-up period would be required to further characterize appropriate management options, and elucidate mechanistic pathways involved in the progression of the disease.

The prevalence of ventilatory function abnormalities following pulmonary TB is indeed high in both microbiologically cured and treatment completed subjects irrespective of the pre-diagnosis duration of illness. This calls for increased need for care of persons with TB beyond the period of targeted microbiological treatment, and a more concerted care for non-communicable disease among persons affected by communicable diseases. TB treatment guidelines should factor this emerging consideration in order to mitigate untoward sequel that may emerge as a result of ventilatory dysfunction. This among other measures should include targeted screening spirometry at end of treatment for both symptomatic and asymptomatic post-TB patients.

Authors' contributions

HB, MBM and MB conceived the study; HB, MBM and MB MA IH designed the study protocol; HB, MBM and MB MA, IH carried out the clinical assessment, HB and MBM carried out analysis and interpretation of these data. HB, MBM, IA, JRI, IHA, OJ and MB drafted the manuscript; critically revised the HB, MBM, IA, JRI, IHA, OJ, MA and MB manuscript for intellectual content. All authors read and approved the final manuscript. HB and MBM are guarantors of the paper. HB and MBM are the guarantors of the paper.

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