**Chronic lung disease in adult recurrent tuberculosis survivors in Zimbabwe: a cohort study**

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**Running Head:** Post-TB lung disease

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**ABSTRACT**

**Objective:** To examine chronic lung disease (CLD) prevalence, magnitude, and association with empiric tuberculosis (TB) treatment among recurrent TB survivors in an HIV prevalent setting.

**Methods**: Prospective cohort study of retreatment TB survivors in Harare, Zimbabwe. At median follow-up of two years post-treatment initiation, we characterized mortality, respiratory impairment, and mental health.

**Results:** Among 175 retreatment TB survivors, of whom 65% were HIV-positive and 21% had been empirically treated, multi-parameter CLD was noted at follow-up among 14% (95% CI 9.0-19.7%), with a 6-fold increase in age-adjusted death in the first year following treatment completion. Empirically treated TB (RR 3.4, 95% CI 1.4-8.3) was associated with CLD, as were number of previous TB treatment courses in dose-dependent fashion (three vs. one, RR 6.2, 95% CI 1.7-22.1). Thirty-three percent (95% CI 26.0-40.1%) of recurrent TB survivors demonstrated persistent respiratory symptoms (CAT score ≥10); 26% (95% CI 19.8-33.0%) significant deficits in exercise capacity (median ISWT, 550 meters; Q1-Q3 440-730 meters); 83% (95% CI 75.7-89.7%) residual radiographic abnormalities on chest x-ray; 12% (95% CI 6.6-16.1%) moderate to severe obstruction on spirometry; and 13% (95% CI 7.6-17.5%) major depression.

**Conclusions:** Despite successful treatment, retreatment TB survivors retain substantial risk of morbidity and mortality.

**Keywords:** post-tuberculosis sequelae; TB/HIV co-infection; chronic respiratory disease; chronic obstructive pulmonary disease; Zimbabwe.

**INTRODUCTION**

Tuberculosis (TB) remains the leading infectious cause of death worldwide. In 2016, there were an estimated 10.4 million TB cases and 1.3 million premature deaths, including one of every three deaths among persons living with HIV.1 Despite these disheartening statistics, long-term sequelae among TB survivors is estimated to account for up to 75% of the total global burden of disease attributable to TB,1 a public health dilemma paradoxically worsened as treatment regimens for both TB and HIV improve.

Deficits in lung function2-6 and/or persistent respiratory symptoms4, 7 following microbiologic cure of TB have been noted in a majority of large population-based surveys. A syndrome of severe post-TB respiratory impairment is well-recognized,4, 5 potentially occurring years after the primary episode. Although representing a broad clinical spectrum, TB-associated respiratory impairment is characterized by restrictive or mixed restrictive/obstructive deficits,2-6 exhibits dose-response with number and severity of prior TB episodes,5 and is associated with decreased quality of life.7 Radiographically, varying degrees of bronchiectasis, broncholiths, cicatricial atelectasis, and fibrosis are seen.8

Retreatment TB is programmatically defined among patients undergoing at least one month or more of anti-TB therapy in the past, regardless of bacteriology (WHO guidelines).9 Compared to those with newly diagnosed TB, retreatment cases are associated with an increased risk for multidrug resistance (MDR),10 treatment failure/relapse,10 and chronic respiratory impairment.6 HIV co-infection is also associated with TB retreatment,11 and may contribute to additional chronic respiratory debility and overall mortality.7, 12 Unfortunately, studies from Sub-Saharan Africa or among HIV-positive individuals are scarce, and oftentimes subject to bias.4

The TRansmission And Pathogenesis of MDR-TB (TRAP MDR-TB) cohort study (2011-2014) prospectively recruited and evaluated patients undergoing TB retreatment in Harare, Zimbabwe. Our aims in this follow-up cohort study among a subset of these participants were two-fold: (1) to assess mortality, respiratory symptomatology, radiographic abnormalities, pulmonary function, exercise capacity, and psychosocial morbidity in the post-retreatment TB period; and (2) to examine the prevalence and magnitude of post-retreatment TB chronic lung disease (CLD) among bacteriologically-confirmed versus -unconfirmed TB cases. We hypothesized that CLD would be more strongly associated with empiric TB treatment due to lack of established health care pathways for individuals with chronic respiratory symptoms in low-income countries.13

**METHODS**

*Study Population*

From November 2011 through June 2014, we prospectively enrolled consecutive adult participants requiring retreatment of TB within Harare, Zimbabwe (TRAP MDR-TB cohort).14 Retreatment was defined as patients who presented with clinical symptoms of TB (cough, fever, night sweats, or weight loss) and had previously completed at least one month of anti-TB therapy (relapse, treatment after default, or treatment failure).14 At enrollment, all participants underwent comprehensive bacteriologic assessment for TB (including cultures performed in duplicate on both solid (Löwenstein-Jensen media) and liquid media (Mycobacterial Growth Indicator Tubes (MGIT); Becton Dickinson, Sparks, MD, USA)). Diagnostic classification of patients at baseline was based on bacteriologic confirmation of *M. tuberculosis* (confirmed group) versus institution of TB treatment without such confirmation (unconfirmed group).14 From 2015 through 2016, at a median of two years since TB treatment initiation, surviving TRAP MDR-TB participants were traced via phone contact (and home visits by a dedicated participant tracker, if necessary) to ascertain vital status, domicile, and willingness to participate in a follow-up study of chronic lung disease. Our objective was to have a minimum of one-year follow-up after treatment initiation in order to assess post-treatment mortality, lung function, and mental health. Surviving, traceable participants were excluded if they could not undertake study procedures due to physical or cognitive impairment; if symptomatic and bacteriologic reassessment (AFB sputum smear microscopy, Xpert MTB/RIF, and a single liquid *M. tuberculosis* culture) were indicative of active TB (due to hazard of transmission to staff through study procedures); or if they declined participation for any reason. All participants provided written informed consent, and ethical approval was obtained from the Medical Research Council of Zimbabwe and the University of California, San Francisco Human Research Protection Program.

*Data Collection*

At time of initial recruitment and follow-up, we collected demographic, clinical, and socio-economic data; history of TB (by patient self-report and examination of TB treatment cards, if available); tobacco and marijuana smoke exposure (by self-reported age at initiation and approximate number of cigarettes/day); and occupational dust, gas, or fume exposure history. At follow-up (only), in addition to mortality, we assessed the presence and severity of lung disease in the following ways: (1) respiratory symptoms during a stable phase of disease (>6 weeks following any exacerbation) using the COPD Assessment Test (CAT);15 (2) forced expiratory flow rates and volumes (spirometry); (3) aerobic exercise testing; and (4) chest radiography. In addition, we assessed mental health parameters, as below.

*Mortality*

Standardized mortality ratios (SMR) were calculated as the ratio of observed number of deaths of all study participants (regardless of bacteriologic confirmation at time of initial enrollment) during the first year of post-treatment follow-up to expected number of deaths. Mortality rates were standardized to age-specific expected rates for 1) the general contemporaneous Zimbabwe population, with age-specific average mortality rates 2009-2015 provided by the 2015 Zimbabwe Demographic and Health Survey (DHS);16 and 2) HIV-specific mortality rates, derived from UNAIDS HIV population estimates for Zimbabwe.17 For each reference population, we calculated the overall SMR and SMR stratified by unconfirmed/confirmed TB, and obtained 95% Fisher’s exact confidence interval for the SMRs.

*COPD Assessment Test*

Consistent with prior literature,18 we defined significant respiratory symptoms as a CAT score ≥10 and severe respiratory symptoms as a CAT score of ≥16.15 Data for one of the eight response items (“chest wheeze”) was imputed (*see Supplemental*). Exacerbation history over the previous 12 months was retrospectively determined by structured questionnaire utilizing standard criteria (increase in dyspnea, wheeze, chest tightness, sputum production for ≥2 days, or hospitalization or use of antibiotics for a respiratory event).18

*Spirometry*

Spirometry was performed according to ATS standards using EasyOne World spirometers (ndd Medical Technologies, Inc., Andover, MA, USA).19 Each participant underwent up to eight forced exhalation measurements in a sitting position. If spirometers indicated an abnormal score, patients were administered 2.5 mg nebulized salbutamol, followed by repeat testing for reversibility. Highest measuring forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) measurement derived from traces meeting ATS quality criteria were eligible for analysis. All available spirometric tracings were reviewed by study investigators trained in Pulmonary Medicine, who were blinded to other patient data. Normal and abnormal predicted FEV1, FVC and FEV1:FVC measurements were determined using the GLI 2012 equation that determines race and sex specific reference values, adjusting for height and age.20 Abnormality was defined using the lower limit of normal (LLN), defined as the 10th percentile (z-score < -1.64).20 Abnormalities were recorded as ”obstruction” (FEV1: FVC < LLN or “reduced FVC” (FVC < LLN with a normal FEV1: FVC).20 Obstruction was further classified by severity based on FEV1 as mild (FEV1 ≥ 80%), moderate (50-79%) or severe (30-49%).

*Exercise testing*

Incremental shuttle walk test (ISWT) was performed according to published guidelines.21 Briefly, participants instructed to walk between two markers within a set time and at incrementally increasing distances. Oxygen saturation, respiratory rate and heart rate were monitored immediately before and after the test. ISWT distances were compared to an age, sex and BMI adjusted prediction model for healthy adults.22 Maximal oxygen consumption (VO2 max) was extrapolated from ISWT distance using model equations described by previously.23 Age, sex, height and BMI adjusted lower limit normal for VO2 max was derived from the same study and used as a reference.23

*Chest radiography*

Participants underwent posteroanterior (PA) and lateral chest radiographs. Details of parenchymal abnormalities were recorded through blinded interpretation by two U.S.-based attending chest radiologists (TC and JV); disagreements were resolved by consensus. Lung abnormality was graded semi-quantitatively on a five-point scale based on percentage of abnormal lung on PA film (0 = no abnormality; 1 = 1-25%; 2 = 26-50%; 3 = 51-75%;4 **=** 76-100%).

*Definition of chronic lung disease*

Based on these validated assessments, we defined CLD as both (1) radiographic evidence of volume loss, bronchiectasis, fibrosis, or hyperexpansion; and (2) respiratory symptoms (CAT ≥10) and/or at least two respiratory exacerbations in the prior 12 months; and at least one of the following: (a) spirometric abnormality; (b) ISWT results <50% predicted; or (c) oxygen desaturation to ≤88% during exercise testing.

*Mental Health*

Major Depressive Disorder (MDD) was assessed using the 20-item self-report Centers of Epidemiological Studies measure (CES-D 20), with scores of sixteen or meet criteria for depression.24 The Posttraumatic Stress Disorder (PTSD) Checklist Questionnaire (PCL), a validated 17-item self-report measure, was used to assess PTSD as defined by DSM-V guidelines (scores >30 indicate PTSD).25

*Statistical Analysis*

Sample size was practically limited to all consenting adults initially recruited within the TRAP MDR-TB cohort who were alive and traceable at time of follow-up. Our final sample size was comprised of n=37 individuals with bacteriologically-unconfirmed TB and n=138 individuals with bacteriologically-confirmed TB. Based on prevalence of spirometric obstruction in previous studies and given our conservative definition of CLD, we assumed presence of CLD in 30% and 10%6 of unconfirmed and confirmed TB patients, respectively, yielding a power of 90% (at an alpha of 0.05) to reject the null hypothesis that these proportions would be equal. Proportions were compared using χ2 tests, and continuous variables were compared using the Wilcoxon rank-sum test. We applied a test for linear trend of the log odds to test for trends in categorical data. All p-values were 2-sided with a p = 0.05 as the significance level. Multivariate associations with chronic lung disease among retreatment TB patients were examined using a generalized linear model with a log link and robust standard errors to generate relative risk (RR) estimates; the model was a priori specified to include age, number of previous TB episodes, unconfirmed TB group, HIV, and exposure to tobacco smoke (defined as active smoker or previous smoker with ≥20 years smoking history). Data were analyzed by using Stata 14 (Stata Corporation, College Station, TX, USA) and R, version 3.4.3 (Foundation for Statistical Computing, Vienna, Austria).

**RESULTS**

*Patient Characteristics*

Four hundred eighty-six patients were prospectively recruited between November 2011 and June 2014 within the original TRAP MDR-TB cohort.14 Among these patients, 128 (26%) had been diagnosed with RIF-resistant TB, 177 (36%) with RIF-sensitive TB, and 181 (37%) empirically treated culture-negative retreatment TB. For the current study, at follow-up a median of 26 months post-treatment initiation (Q1-Q3, 20-30 months), 280 (58%) participants were unavailable for further evaluation. Of these patients, 58/280 (21%) had died, 128/280 (46%) lost to follow-up, 68/280 (24%) declined follow-up, and 26/280 (9%) were determined to have misdiagnosed TB and had treatment withdrawn (Figure 1). Of the remaining 206 patients, 10/206 (5%) were found to have bacteriologically confirmed recurrent active TB at follow-up (i.e., determined via active case finding), 18/206 (9%) remained on treatment for MDR-TB with fewer than four negative cultures, and 3/206 (1%) were unable to participate due to respiratory debility or inability to ambulate. Of the final analysis population (n=175), 138 (79%) had bacteriologically confirmed TB at time of original recruitment, and 37 (21%) were empirically treated. Median age was 41 years (Q1-Q3, 33-48 years), and 113 (65%) were HIV-positive, of which 93 (82%) were on antiretroviral medications. Post-treatment follow-up times were similar between the two groups (median 23 vs. 27 months for unconfirmed vs. confirmed, respectively; p=0.1). Those with unconfirmed TB were older (median, 47 vs. 39 years; p<0.01), had a longer pre-treatment symptomatic period (311 vs. 135 days; p=0.09), and greater reported exposure to workplace dust and fumes (n=21 (81%) vs. n=65 (59%); p=0.03); other potential associations with CLD were similar (Table 1).

Compared to the Zimbabwe HIV-specific and general population, individuals successfully completing retreatment TB treatment (regardless of initial bacteriologic confirmation) had a 6.0 (95% CI 3.8-8.9) and 14.6 (95% CI 9.6-21.2) -fold increased rate of death during the first year of post-treatment follow up, respectively.

*Symptomatology and chronic lung disease*

Moderate to severe respiratory symptoms (CAT ≥10) were present in 33% (n=58/175, 95% CI 19.8-33.0%) of individuals. Breathlessness when walking upstairs or hills was reported amongst 74% (n=129/175) of patients, with 16% (n=20/129) rating breathlessness as severe (Figure 2). The bacteriologically unconfirmed group had significantly higher CAT scores (median score, 13 vs. 7; p<0.0001), and a greater proportion with severe symptoms (38% vs. 11%; p<0.001) (Table 2).

CLD was present in 13.7% (n= 24/175, 95% CI 9.0-19.7%) of the total cohort (27% vs. 10% in the unconfirmed and confirmed groups, respectively; p<0.01) (Table 2, and Supplemental Table 1), and was associated with unconfirmed TB in multivariate analysis (RR 3.4, 95% CI 1.4-8.3; p<0.01), but not age, HIV, or tobacco exposure (Table 3). The association of CLD with number of previous TB episodes increased incrementally (RR 3.2, 95% CI 1.2-8.4; p=0.01 and RR 6.2, 95% CI 1.7-22.7; p<0.01, for one versus two and one versus three episodes, respectively) (Table 3).

*Exercise Capacity*

Overall, 26% (n=46/174, 95% CI 19.8-33.0%) of participants had abnormally low ISWT distances. Participants with unconfirmed TB had significantly worse ISWT distances than confirmed cases: median 68% (610m) vs. 88% (870m) predicted (p<0.001). There was no difference in oxygen desaturation between groups.

*Chest Radiography*

Radiographic abnormalities were documented among 83% (n=96/116, 95% CI 75.7-89.7%) of participants with available chest radiographs (Figure 2). Bronchiectasis (ring or tramline opacities), non-cavitating nodules, and volume loss occurred among 82% (n=95/116), 70% (n=81/116), and 66% (n=77/116), respectively. Radiographic patterns among the unconfirmed and confirmed groups were not significantly different (Supplemental Table 2).

*Pulmonary Function*

Overall, 36% (n=58/162, 95% CI 29.0-43.4%) of participants had spirometric abnormalities (Figure 2), with 12% having moderate-to-severe obstruction. Thirty-two patients (20%) had isolated reduced FVC (Table 2). Percent predicted FEV1, FVC, and FEV1/FVC did not demonstrate clinically significant differences between the confirmed and unconfirmed groups.

*Mental Health*

Major depressive disorder (MDD; CES-D >16) was documented in 13% (n=22/175, 95% CI 7.6-17.5%) of patients. Seven patients (4%) had PTSD (PCL >30), of which six had concurrent MDD. While neither depression nor PTSD were associated with our definition of CLD, participants with unconfirmed TB (relative to those with confirmed TB) were more likely to have both MDD (24% vs. 9%; p=0.02) and PTSD (14% vs. 1%, p=0.03).

**DISCUSSION**

In this prospective study of retreatment TB survivors from a high-HIV burden country, we found a high prevalence of residual respiratory symptoms, functional deficits, and radiographic abnormalities, with approximately one in seven demonstrating frank chronic lung disease and one in ten experiencing major depression. Although 35% of the analysis population were HIV-negative, the rate of death among retreatment TB patients was 6-fold that of the general HIV-positive Zimbabwe referent population. Compared to those with bacteriologically confirmed TB at initial enrollment, patients treated empirically for unconfirmed TB were more symptomatic, and had a greater number of documented previous TB treatment courses, worse exercise tolerance, and a greater prevalence of depression and PTSD.

Chronic obstructive pulmonary disease (COPD) contributes to 3.17 million deaths annually, or about 5% of total deaths globally.4 Although exposure to tobacco smoke is the single greatest cause of COPD,18 its population attributable risk (PAR) in low- to middle- income countries (LMIC) may be less than 40%.4 In our cohort of patients with retreatment TB, neither exposure to tobacco smoke, indoor biomass, occupational dusts or fumes, nor HIV had clear association with CLD. Although power was limited, these findings support the hypothesis that the impact of active TB on lung health in LMICs may plausibly exceed that expected from these commonly cited etiologies, independently.

HIV infection is a well-recognized risk factor for the acquisition of TB, TB treatment failure, and relapse.11 Progress towards universal testing and treatment in LMICs has led to the emergence of an older HIV-positive population at elevated risk of chronic noncommunicable diseases. Patients with HIV are predisposed to chronic airway obstruction due to lymphocytic alveolitis, recurrent respiratory infections, and oxidative stress.26, 27 The role of HIV infection on pulmonary dysfunction in TB/HIV co-infected patients is less clear, as studies have demonstrated a positive association between HIV and TB-related respiratory disability,7 while others have not.5 Mechanistically, HIV in co-infected patients may downregulate specific matrix metalloproteinases (MMPs), ameliorating TB-associated lung damage.28 Conversely, initiation of ART therapy and subsequent recovery of CD4 T-cells has been shown to reconstitute MMP levels, leading to chronic lung impairment.29 Despite the complex interplay of TB/HIV co-infection, the increased mortality of co-infected patients demonstrated in previous studies7, 12 and in our cohort of primarily HIV-positive individuals, reinforces the importance of primary prevention of TB/HIV co-infection and further substantiates the need for additional clinical research among these high-risk patients.

High TB/HIV-associated mortality, limited diagnostic resources, and scarcity of healthcare access contribute to elevated rates of empiric TB treatment in high-TB/HIV burden settings vis-à-vis high income countries.30 The TB program may be the most expedient pathway for individuals with chronic respiratory symptoms to receive healthcare, considering substantial cost burden, wait times, and logistical difficulties in the wider system.31 The association between unconfirmed TB and chronic lung disease, which persists following adjustment for number of previous episodes, suggests that pre-existing lung disease may contribute to both TB diagnosis and TB retreatment. Other regional investigators have found higher mortality among sputum smear-negative and clinically diagnosed patients, relative to those who are sputum smear-positive, despite controlling for HIV status; this may indicate unrecognized non-TB pathology.12

*M. tuberculosis* causes destruction of the pulmonary extracellular through as yet poorly understood dysregulation of host immune response, including inflammatory cytokine and MMP secretion.6 Phenotypically, this results in ventilatory defects, suppurative bronchiectasis, and, ultimately, fibrosis and severe cicatricial atelectasis.2-6, 8 Definitive determination of the causal effect of a single TB episode and its principal mediators is complicated by control group selection, understanding of pre-TB health trajectory, and high probability of substantial measured and unmeasured confounding. In addition, the exposure (a clinical course modified by host, pathogen, and environmental factors) is highly variable, and there is no widely accepted and validated definition for the outcome (i.e., a definition of CLD) outside of entity-specific scores.32 Imperfect correlations between disease and spirometric33 and radiographic34 measures further complicate objective assessment. For these reasons, we used a simple and conservative (though unvalidated) categorical description requiring respiratory symptoms, radiographic abnormality, and functional impairment.

Participants who had been empirically treated for TB without bacteriologic confirmation were more likely to suffer depression and PTSD. In COPD, the impact of co-morbid depression and anxiety is associated with increased hospitalization stay, increased symptom burden, and reduced quality of life.35 Further, TB and TB-associated treatment are known but under-appreciated risk factors for both depression and anxiety.36 Our findings highlight the importance of investigation and treatment of psychiatric co-morbidities in TB survivors.

Our study has several limitations. First, we did not recruit an age- and HIV-matched control series without known history of TB. Second, we did not undertake measures of respiratory and psychiatric morbidity prior to the index TB episode, and therefore cannot comment on pre-TB health trajectory. Similarly, we did not formally assess for newly diagnosed HIV during the study period and thus could not measure the effect of incident HIV. Third, given the programmatic nature of our study, data on the severity of the index TB episode (e.g., time to sputum smear- or culture-negativity, or radiographic extent of lung disease) were incomplete. Fourth, due to socio-politico-economic hardship and an urban mobile population, many individuals immigrated during the study period; separately, approximately one-quarter of individuals who were alive and re-contacted declined to participate, often citing work obligations and no longer being sick. Thus, while our mortality estimates excluded individuals lost to follow up (and thus is conservative), the prevalence of significant respiratory impairment or mental health issues excluded individuals who had often returned to work and may be biased high. Fifth, although we used AFB smear microscopy, Xpert, MODS, and up to four separate *M. tuberculosis* cultures to evaluate the TB episode, misclassification of the unconfirmed TB group is always possible, with resultant unclear direction of bias.

In conclusion, we document elevated morbidity and mortality among individuals apparently cured of TB. These findings support reconceptualization and upward estimation of the global burden of disease attributable to TB, the preeminent importance of prevention over “cure,” and support other calls for improving the basic provisions of healthcare in LMICs.

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**Figure 1. Study Population.**



**Figure 2. Respiratory morbidity in the total study population**. Parameters demonstrating any abnormality (light grey) and severe abnormality (dark grey) were defined as follows: radiographic abnormalities (any abnormality; field abnormality > 50%); history of respiratory exacerbations in the past year (1; 2 or more exacerbations); spirometric abnormality (FVC or FEV1 < 80% predicted; FVC or FEV1 < 50% predicted); respiratory symptoms (COPD Assessment Test (CAT) score 10-15; CAT score ≥16); exercise tolerance (ISWT LL; ISWT < 50% predicted), depression (Center for Epidemiologic Studies Depression Scale > 16) or post-traumatic stress disorder (PTSD checklist score > 30); chronic lung disease (see *Methods*)*.*

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**Figure 3. Post-bronchodilator spirometric assessment, stratified by confirmed vs. unconfirmed TB.** Dot plots of participants with spirometry results (n=162). Dotted lines/shaded area represent upper limit and lower limit of normal. Bars illustrate the mean and the standard deviations of each group.

**Table 1. Baseline characteristics of the study population at time of original TB diagnosis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic**  | **Confirmed TB** **(n=138)** | **Unconfirmed TB****(n=37)** |  | **P-value** |
| **Age, median years (Q1,Q3)** | 39 (33, 46) | 47 (39, 52) |  | <0.01 |
| **Male (%)** | 82 (59) | 20 (54) |  | 0.45 |
| **Interval follow-up time, median months (Q1,Q3)****Body Mass Index (%)**  | 27 (20, 30) | 23 (19, 28) |  | 0.09 |
| <18 | 27 (20) | 5 (14) |  |  |
| 18-25 | 96 (71) | 27 (75) |  | 0.68 |
| >25 | 12 (9) | 4 (11) |  |  |
| **TB diagnosis (%)1**  |  |  |  |  |
| Unconfirmed  | 0 (0) | 37 (100) |  |  |
| Drug sensitive  | 51 (37) | 0 (0) |  | n/a |
| Rifampin monoresistant | 40 (29) | 0 (0) |  |  |
| Multidrug resistant (MDR)  | 47 (34) | 0 (0) |  |  |
| **Number of previous TB episodes,** **median (Q1,Q3)** | 1 (0, 1) | 1 (1, 2) |  | <0.001 |
| **HIV Infection** | 86 (63) | 27 (73­) |  | ­0.25 |
| On ART (%)  | 70 (81) | 23 (85) |  | 0.73 |
| **Symptomatic period prior to treatment initiation** | 135 (65, 304) | 311 (79, 437) |  | 0.09 |
| **Tobacco smoke exposure** |  |  |  |  |
| Ever smoked (%) | 55 (40) | 13 (35) |  | 0.60 |
| Median years smoking (Q1,Q3) | 19 (14, 28) | 28 (27, 32) |  | <0.01 |
| Current smoker (%) | 7 (13) | 3 (23) |  | 0.39 |
| Second hand smoke exposure | 57 (41) | 15 (41) |  | 0.93 |
| **Other smoke exposure (%)** |  |  |  |  |
| Cooks with biomass/paraffin | 103 (76) | 26 (70) |  | 0.45 |
| Uses paraffin lighting | 16 (12) | 4 (11) |  | 0.87 |
| Occupational exposure | 65 (59) | 21 (81) |  | 0.03 |
| **Employment (%)** |  |  |  |  |
| Unemployed at primary TB diagnosis | 35 (25) | 8 (22) |  | 0.64 |
| Unemployed at follow-up  | 19 (14) | 8 (22) |  | 0.25 |
| **Education (%)** |  |  |  |  |
| Primary or less | 23 (17) | 9 (24) |  |  |
| Secondary  | 101 (74) | 24 (63) |  | 0.53 |
| Tertiary | 13 (9) | 4 (11) |  |  |
| **Household income (quartiles)2** |  |  |  |  |
| First | 30 (22) | 7 (19) |  |  |
| Second | 30 (22) | 14 (38) |  | 0.21 |
| Third | 30 (22) | 8 (22) |  |  |
| Fourth | 47 (34) | 8 (22) |  |  |

TB, tuberculosis; Q1, first quartile; Q3, third quartile; ART, antiretroviral therapy; CES-D, Center for Epidemiologic Studies Depression scale; PCL, PTSD Checklist

1TB diagnosis by culture or by Xpert.

2First quartile ($0-99/month); second quartile ($100-199/month); third quartile ($200-299/month); fourth ($300-2000)/month

**Table 2. TB survivor clinical characteristics at follow-up**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Confirmed** **(n=138)** | **Unconfirmed** **(n=37)** |  | **P-value** |
| **Chronic Lung Disease1** | 14 (10) | 10 (27) |  | <0.01 |
| **Spirometry, % predicted (Q1,Q3)2** |  |  |  |  |
| FEV1  | 85 (73, 99) | 87 (70, 103) |  | 0.99 |
| FVC  | 89 (78, 100) | 92 (66, 100) |  | 0.65 |
| FEV1/FVC | 96 (90, 101) | 100 (94, 107) |  | 0.01 |
| **Spirometry, LLN (%)**  |  |  |  |  |
| Normal | 82 (65) | 22 (61) |  |  |
| Isolated reduced FVC | 23 (18) | 9 (25) |  | 0.62 |
| Obstruction | 22 (17) | 5 (14) |  |  |
| Moderate  | 14 (64) | 2 (40) |  |  |
| Severe  | 3 (14) | 1 (20) |  |  |
| **CAT Score**  |  |  |  |  |
| Absolute Scores (Q1,Q3) | 7 (4-10) | 13 (9-17) |  | <0.0001 |
| < 10 (n, %) | 105 (76) | 12 (32) |  |  |
| ≥ 10 < 15 (n, %) | 18 (13) | 11 (30) |  |  |
| ≥ 15 < 20 (n, %) | 14 (10) | 10 (27) |  | <0.001 |
| ≥ 20 (n, %) | 1 (1) | 4 (11) |  |  |
| **Exacerbations (prior 12 months)** |  |  |  |  |
| Number of exacerbation (Q1,Q3) | 1 (0,1) | 1 (1,2) |  | <0.01 |
| No exacerbations | 29 (21) | 2 (5) |  |  |
| One exacerbation | 84 (61) | 22 (59) |  |  |
| Two exacerbations | 19 (14) | 6 (16) |  | <0.01 |
| Three or more exacerbations | 6 (4) | 7 (19) |  |  |
| **Shuttle walk distance** |  |  |  |  |
| Absolute distance, median meters (Q1,Q3) | 870 (670, 1070) | 610 (450, 780) |  | <0.0001 |
| Percent of predicted (Q1,Q3) | 88 (70, 100) | 68 (54, 86) |  | <0.001 |
| ISWT below LLN (%) | 28 (20) | 18 (49) |  | 0.01 |
| Oxygen saturation ≥ 88% (%) | 26 (19) | 9 (24) |  | 0.52 |
| **VO2 Max, less than LLN (%)5** | 12 (9) | 13 (35) |  | <0.0001 |
| **X-ray field score (%)5** |  |  |  |  |
| Normal | 14 (15) | 6 (26) |  |  |
| 1-25% abnormal | 44 (47) | 10 (44) |  |  |
| 26-50% abnormal | 27 (29) | 2 (9) |  | 0.06 |
| 51-75% abnormal | 7 (8) | 5 (22) |  |  |
| 76-100% abnormal | 1 (1) | 0 (0) |  |  |
| **Major depression (%)7** | 13 (9) | 9 (24) |  | 0.01 |
| **Post-traumatic stress disorder (%)8** | 2 (1) | 5 (14) |  | <0.01 |

FEV1, forced expiratory volume (one second); FVC, forced vital capacity; LLN, lower limit of normal, CAT, COPD Assessment Test; VO2Max, peak oxygen uptake.

1Chronic lung disease (CLD) was defined as having both (1) radiographic evidence of volume loss, bronchiectasis, fibrosis, or hyperexpansion, and (2) CAT ≥10 and/or at least two respiratory exacerbations in the prior 12 months; and at least one of the following: (a) FEV1, FVC, or FEV1/FVC below LLN; (b) ISWT results <50% predicted; or (c) oxygen desaturation to ≤88% during exercise testing

2 A total of 162 out of 175 participants completed spirometry

3 Moderate obstruction: 50% ≤ predicted FEV1 < 80%; severe obstruction: 30% ≤ predicted FEV1 < 50%,

5VO2 Max (normal) = 268.6 + (age \* -21.1) + (weight 9.2) + (height/100 \* 1101.1) + (sex \* 535.6)

6Totals based on those who performed CXR (n=116)

7Depression is defined as CESD score > 16

8PTSD is defined as PCL score > 30

**Table 3: Multivariate risk factors for chronic lung disease among retreatment TB patients**

|  |  |  |
| --- | --- | --- |
|  | **Multivariate** |  |
| **Parameter** | **P-value** | **RR (95% CI)** |
| **Age (years)** | 0.17 | 1.0 (0.9-1.1) |
| **Number of previous TB episodes** |  |  |
| One (reference) | - | 1 |
| Two | 0.02 | 3.2 (1.2-8.4) |
| Three or more | <0.01 | 6.2 (1.7-22.7) |
| **Unconfirmed TB1**  |  |  |
| No  | - | 1 |
| Yes | <0.01 | 3.4 (1.4-8.3) |
| **HIV-positive**  |  |  |
| No | - | 1 |
| Yes | 0.21 | 0.6 (0.3-1.3) |
| **Exposure to tobacco smoke2** |  |  |
| No | - | 1 |
| Yes | 0.16 | 1.1 (0.5-2.1) |

RR, relative risk. Chronic Lung Disease (CLD) defined as having both (1) radiographic evidence of volume loss, bronchiectasis, fibrosis, or hyperexpansion, and (2) respiratory symptoms (CAT ≥ 10) and/or at least two respiratory exacerbations in the prior 12 months); and at least one of the following: (a) FEV1, FVC, or FEV1/FVC below LLN; (b) ISWT results <50% predicted; or (c) oxygen desaturation to ≤88% during exercise testing

1Empircally treated without bacteriological confirmation for the most recent TB episode

2Tobacco smoke exposure defined as active smoking or ≥ 20 years smoking history