Title: Patient outcomes associated with post-tuberculosis lung damage in Malawi: a prospective cohort study

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ABSTRACT

Background:

Post-tuberculosis lung damage (PTLD) is a recognised consequence of pulmonary TB (pTB). However, little is known about its prevalence, patterns, and associated outcomes, especially in sub-Saharan Africa and HIV-positive adults.

Methods:

Adult (≥15 years) survivors of a first episode of pTB in Blantyre, Malawi completed the St George's Respiratory Questionnaire, six-minute walk test, spirometry, and high-resolution computed tomography (HRCT) chest imaging at TB treatment completion. Symptom, spirometry, health seeking, TB-retreatment and mortality data were collected prospectively to one-year. Risk factors for persistent symptoms, pulmonary function decline, and respiratory-related health-seeking were identified through multivariable regression modelling.

Results:

Between February 2016 and April 2017, 405 participants were recruited. Median age was 35 years (IQR:28-41), 77.3% (313/405) had had microbiologically proven pTB, and 60.3% (244/403) were HIV-positive. Upon pTB treatment completion, 60.7% (246/405, 95% CI: 55.8 – 65.5%) reported respiratory symptoms, 34.2% (125/365, 95% CI: 29.4 – 39.4%) had abnormal spirometry, 44.2% (170/385, 95% CI: 39.1 – 49.3%) had bronchiectasis ≥1 lobe, and 9.4% (36/385, 95% CI: 6.6 – 12.7%) had ≥1 destroyed lobe on HRCT imaging. At one-year, 30.7% (113/368, 95% CI: 26.0 – 35.7%) reported respiratory symptoms, 19.3% (59/305, 95% CI: 15.1 – 24.2%) and 14.1% (43/305, 95% CI: 10.4 – 18.5%) of patients had experienced declines in FEV_1 or FVC of ≥100ml, 16.3% (62/380, 95% CI: 12.7 –

20.4%) had reported ≥1 acute respiratory event, and 12% (45/368, 95% CI: 9.1 – 16.0%) had symptoms affecting their ability to work.

Conclusions:

PTLD is a common and under-recognised consequence of pTB that is disabling for patients and associated with adverse outcomes beyond pTB treatment completion. Increased efforts to prevent PTLD and guidelines for management of established disease are urgently needed. Low-cost clinical interventions to improve patient outcomes must be evaluated.

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KEY MESSAGES

What is the key question?

What is the burden of post-tuberculosis lung damage (PTLD) amongst adults successfully completing pulmonary tuberculosis (pTB) treatment in urban Malawi, and what are the associated patient outcomes?

What is the bottom line?

pTB-survivors have a high burden of post-TB lung damage, which is largely undiagnosed within existing TB management pathways, and is associated with adverse patient outcomes including accelerated lung function decline, ongoing respiratory-related health seeking, persistent chest symptoms, and difficulty working in the year after treatment completion.

Why read on?

This work provides a detailed description of post-TB lung damage and associated outcomes amongst both HIV-positive and negative adults successfully completing pTB treatment in Malawi, and suggests research priorities for the prevention and management of disease.

INTRODUCTION

An estimated ten million incident cases of tuberculosis disease occurred globally in 2017, one quarter of which were in sub-Saharan Africa (sSA) where 30% (24-35%) of patients are HIV co-infected.(1) TB mortality is falling, and 82% of people treated for a first episode of TB now survive with treatment success (cure or completion).(1)

Post-TB lung damage (PTLD) is a recognised consequence of pulmonary TB (pTB) disease: adult pTB-survivors have two-to-four-fold higher odds of persistently abnormal spirometry (airway obstruction and restriction) compared to those without previous TB disease,(2-4) with parenchymal and airway abnormalities seen on imaging,(5, 6) and associated respiratory symptoms and reduced quality of life.(7-10) However, there are few estimates of the burden of disease at pTB treatment completion, and few prospective data on the medium or long-term consequences of PTLD or risk factors for adverse patient outcomes. Data are particularly scarce for adults in low-income settings with HIV co-infection.(5) There remain no standardised guidelines for the diagnosis and management of PTLD.(11)

Cohort studies from resource-rich settings suggest a correlation between the severity of chronic lung diseases and accelerated spirometry decline, hospital admissions, and increased mortality.(12-14) We hypothesise that adults with PTLD in low-income settings could experience similar – or more severe – adverse outcomes.

In this prospective cohort study in Malawi – one of the poorest countries in the world – we investigated the prevalence and pattern of residual lung damage at TB treatment completion using gold-standard respiratory investigations including high-resolution computed tomography (HRCT) imaging and spirometry, with findings disaggregated by HIV-status. The evolution of pathology in the year following treatment completion is described and predictors of adverse outcomes identified.

METHODS

HIV-positive and -negative adults expected to complete treatment for pulmonary TB (pTB) at nine health centres in urban Blantyre, Malawi between February 2016 and April 2017 were prospectively identified using the Malawi National Treatment Programme (NTP) registry. These individuals were screened by the study team at their monthly medication collection visits, with multiple opportunities available to identify each individual, and formal recruitment was completed at the end of treatment. Inclusion criteria were: age ≥15yrs; residence in urban Blantyre; treatment for a first episode of pTB with cure or completion as defined by the NTP. Those with persistent symptoms at treatment completion underwent additional screening with sputum smear & TB culture and were excluded if either were positive. We excluded patients treated as multi-drug resistant disease (MDR-TB prevalence amongst new TB cases in Malawi: 0.75%).(15)

Study visits were conducted at the central hospital within one-month of pTB treatment completion, and at six-months (home visit) and 12-months (hospital visit) after treatment end. Participants completed: questionnaires (demographics, respiratory exposures, socio-economic data); the St George's Respiratory Questionnaire (SGRQ); six-minute walk test; pre- and post- bronchodilator spirometry; blood tests (FBC, CD4 cell count, Aspergillus IgG). Imaging included chest radiography (CXR) at baseline and 12-months, and non-contrast high-resolution computed tomography (HRCT) chest imaging at baseline. Questionnaires and spirometry were repeated at all visits, and data on health seeking, TB retreatment and all-cause mortality were determined from participant-held health-records. Details of existing cardio-respiratory diagnoses were obtained from health-records, and TB microbiology at pTB diagnosis from NTP registers.

Questionnaires were conducted in the local language, Chichewa. HIV testing was offered to participants of unknown serostatus, and those who had tested over 1-month before recruitment

(Serial testing with Determine 1/2™; Alere, USA / Uni-Gold™; Recombigen® HIV, Trinity Biotech, Ireland). Plasma anti-aspergillus fumigatus IgG was measured by ELISA (Bordier Affinity Products), using a cut-off index >1.0 for a positive result. Six-minute walk tests and spirometry (EasyOne, ndd Medical Technologies) were conducted to American Thoracic Society (ATS) standards.(16, 17) HRCT imaging was performed using a pre-specified protocol (Appendix 1). Participants underwent protocol-driven clinical review for investigation results requiring urgent intervention but attended routine clinical services for all other illness episodes.

Quality control & data interpretation

Details of spirometry and imaging acquisition, quality control and interpretation are given in the online data supplement. Briefly, only spirometry data meeting BOLD-standards were included in analyses (Appendix 2). Data were standardised using the Global Lung Initiative 2012 (GLI-2012) African reference ranges.(18) Patterns of abnormality (obstruction: FEV_1/FVC ratio < lower limit of normal (LLN); low FVC: FEV_1/FVC ratio ≥LLN & FVC<LLN; normal: FEV_1/FVC ratio ≥LLN & FVC≥LLN) and reversibility (>200ml and >12% increase in absolute FEV_1 or FVC following bronchodilator) were described.(19) HRCT images were independently read by two consultant radiologists with consensus review of discrepant findings (Appendix 3). The extent and severity of Fleischner-defined airway, parenchymal and pleural pathologies were recorded.(20) Lobes where ≥90% of parenchyma was replaced by banding, atelectasis, or cavities/cystic airspaces were classified as 'destroyed'. Agreement between readers was measured using intraclass correlation coefficients and Kappa scores.

Statistical methods

A sample size of 400 allowed us to estimate the prevalence of PTLD with a margin of error less than 5% with 95% confidence (Appendix 4). We described the burden of respiratory pathology using

clinical, spirometry and imaging parameters, stratified by HIV-status. Chi-square, Student's t-test, Fisher's exact or Wilcoxon rank sum tests were used to compare between groups. We compared the age-stratified prevalence of abnormal spirometry to recent community-based data from urban Blantyre in sensitivity analyses.(21) Exploratory analyses were conducted to determine the relationship between symptoms, and spirometry and imaging parameters.

We determined the proportion of participants experiencing pre-specified adverse outcomes over one-year including: accelerated decline in FEV_1 and FVC (loss ≥100ml); chronic respiratory symptoms at one-year (cough, breathlessness, sputum, or wheeze ≥few days/month); TB-retreatment; and all-cause mortality. We recorded the number of acute respiratory events, defined as 'an unscheduled visit to health care provider, either outpatient or inpatient, due to a respiratory complaint (cough, breathlessness, sputum, wheeze, chest pain)'.

We used linear mixed-effects and logistic models to estimate predictors of FEV_1 and FVC over time and the prevalence of chronic respiratory symptoms and respiratory events by one-year. Models were built using a pre-specified set of covariates. Fixed effects and variance components were reported for linear mixed effects models, and coefficient estimates or odds ratios with 95% confidence intervals (CIs) otherwise. Separate outcome models were constructed using FEV_1 and FVC as predictors, due to co-linearity. Complete case analyses were performed in Stata 15 (StataCorp).

Approvals & permissions

All participants provided written informed consent. Ethical approval was obtained from the Liverpool School of Tropical Medicine (LSTM) (15.040RS) and Malawi College of Medicine Research Ethics (P.10/15/1813) Committees.

RESULTS

450 pTB-survivors were screened for eligibility, of whom 405 met inclusion criteria at TB treatment completion (Figure 1). 37/405 (9.1%) participants did not complete the final study visit: 22 relocated, 11 died, three withdrew and one was lost to follow-up. Participants not completing study procedures at one-year had similar characteristics (age, sex, HIV status, TB microbiology, SES, ever smoking/cannabis use) to those completing the study, but a higher prevalence of respiratory symptoms at baseline (75.7% [28/37] vs. 59.2% [218/368], p=0.051).

Participant characteristics

Median age was 35 years (interquartile range [IQR]: 28-41), 67.9% (275/405) were male, and 77.3% (313/405) had microbiologically proven pTB disease (Table 1). Amongst the 60.5% (244/403) who were HIV-positive, the majority were receiving antiretroviral therapy (91.8% [224/244]) and cotrimoxazole (90.2% [211/234]) with a median CD4 count of 229 cells/μL (IQR: 127–397) and median ART duration of 6.6 months (IQR: 5.5 – 25.6) by TB treatment completion. The median self-reported duration of illness prior to TB treatment initiation was 8.7 weeks (IQR: 4.0 – 13.0).

Socioeconomic deprivation was common: 38.0% (154/405) were educated to primary school level only, 31.6% (128/405) reported intermittent food insecurity, and 73.5% (298/405) had incurred dissaving (borrowing money, selling assets, or using savings) to cover health-care costs during TB illness or treatment.

Overall, 29.6% (285/405) of participants had ever-smoked, with a median of 2.7 pack-year (IQR: 0.7-6.0) exposure, and 13.3% (54/362) had ever-used cannabis. Use of biomass fuels for cooking/heating was reported by 94.8% (384/405). Only 2.2% (9/405) of the cohort had an established diagnosis of chronic lung disease (bronchitis n=4, asthma n=5) by treatment completion.

Table 1: Participant characteristics, stratified by HIV status[†]

Characteristic	Total (n=405)	HIV-negative (n=159)	HIV-positive (n=244)	p-value
Age (yrs) (median, IQR)	35 (28 – 41)	30 (24 – 37)	37 (32 – 42)	<0.001*
Male sex	275 (67.9%)	115 (72.3%)	158 (64.8%)	0.112
Urban SES quintile (n=372) [†]				
- Poorest	22 (5.9%)	10 (7.1%)	12 (5.2%)	0.638
- 2nd poorest	85 (22.8%)	28 (19.9%)	57 (24.9%)	
- Middle	95 (25.5%)	36 (25.5%)	58 (25.3%)	
- 2nd most wealthy	114 (30.7%)	48 (34.0%)	66 (28.8%)	
- Most wealthy	56 (15.1%)	19 (13.5%)	36 (15.7%)	
Maximum education level ≤ primary school	154 (38.0%)	49 (30.8%)	104 (42.6%)	0.017*
Intermittent difficulty procuring food for household	128 (31.6%)	47 (29.6%)	81 (33.2%)	0.443
Household dissaving incurred in past one-yr to cover illness costs [‡]	298 (73.6%)	109 (68.6%)	189 (77.5%)	0.047*
Monthly individual income ($US) [§]	41.32 (11.02 – 96.42)	37.47 (5.51 – 82.64)	46.83 (16.53 – 99.17)	0.206
Baseline TB microbiology				
- Smear positive	213 (52.6%)	118 (74.2%)	95 (38.9%)	<0.001*
- Xpert positive, Rifampicin sensitive	100 (24.7%)	21 (13.2%)	78 (32.0%)	
- Radiological diagnosis	54 (13.3%)	10 (6.3%)	43 (17.6%)	
- Clinical diagnosis	38 (9.4%)	10 (6.3%)	28 (11.5%)	
Self-reported illness duration prior to TB treatment (weeks)	8.7 (4.3 – 13.0)	8.7 (4.3 – 13.0)	8.7 (4.3 – 17.4)	0.759
ART use, if HIV-positive (n=244) [‖]			224 (91.8%)	
Duration on ART, if HIV-positive (months) (n=222)			6.6 (5.5 – 25.6)	
Prophylactic cotrimoxazole use, if HIV-positive (n=234)			211 (90.2%)	
CD4, if HIV-positive (cells/μL) (n=242)			229 (127 – 397)	
Ever smoker, cigarettes	120 (29.6%)	56 (35.2%)	62 (25.4%)	0.034*
Pack years, amongst smokers (n=120)	2.7 (0.7 – 6.0)	2.1 (0.7 – 5.6)	2.9 (0.7 – 7.0)	0.465
Ever smoker, cannabis (n=362)[†]	54 (14.9%)	35 (25.4%)	19 (8.6%)	<0.001*
Charcoal / wood as main fuel	384 (94.8%)	153 (96.2%)	229 (93.9%)	0.295

* Statistically significant difference between HIV-positive and negative groups, at p<0.05 level.
[†] Missing data: HIV status for n=2 (declined to test, included in 'total' column only), Socio-Economic Status (SES) for n=33 (unable to visit household to determine building materials), Cannabis use for n=43 (unbiased data collection error).
[‡] Borrowing money, using savings, selling assets to cover costs due to illness, in past 1yr (during TB illness and treatment).
[§] Income data collected in Malawi Kwacha, but standardised using exchange rate at study midpoint ($1 USD: 726 MK, March 2017).
[‖] 97% (218/224) receiving Regimen 5a (tenofovir, lamivudine, efavirenz) at TB treatment completion.

Residual lung pathology at TB treatment completion

A majority of participants, 60.7% (246/405, 95% CI: 55.8 – 65.5%), reported one or more respiratory symptom at TB treatment completion (Table 2). Median SGRQ total score was 8.8 (IQR: 1.3–23.4) and 40.0% (162/405, 95% CI: 35.2 – 45.0%) reported chest symptoms interfering with work. Median oxygen saturation was 98% (IQR: 97-99%). Hypoxaemia (<92%) was observed in 1.5% (6/405, 95% CI: 0.5 – 3.2%) at rest, and 3.8% (15/395, 95% CI: 2.1 – 6.2%) after the 6-minute walk test. 17.5% (71/405,

95% CI: 14.0 – 21.6%) of participants were underweight (BMI <18.5 kg/m^2). Median haemoglobin was 13.7 g/dL (IQR: 12.3 – 15.1). Few participants (0.7% [3/405, 95% CI: 0.1 – 2.1%]) had positive *A.fumigatus* IgG serology (ELISA index > 1.0).

BOLD standard post-bronchodilator spirometry data were available for 90.1% (365/405) of participants. Mean z-scores for the FEV_1, FVC, and FEV_1/FVC ratio were negative (-1.06 [standard deviation(SD): 1.26], -0.91 [1.23], -0.38 [1.26], respectively). When classified into patterns, 20.0% (73/365, 95% CI: 16.0 – 24.4%) had a low FVC pattern and 14.2% (52/365, 95% CI: 10.8 – 18.3%) had airway obstruction. Amongst those with airway obstruction 9.6% (5/52, 95% CI: 3.2 – 21.0%) had reversibility. When the age-stratified prevalence of moderate-severe obstruction and low FVC patterns were compared with recent community-based data from urban Blantyre,(21) the prevalence of both obstructive and low FVC patterns were higher in this post-TB cohort across age-strata (Appendix 5).

The prevalence of cough and exertional breathlessness were higher amongst HIV-negative compared to positive participants (45.9% [73/159] vs. 29.5% [72/244], p=0.002 and 50.0% [79/158] vs. 39.5% [96/243], p=0.038 respectively). Mean FEV_1 and FVC z-scores were also significantly lower amongst HIV-negative participants (-1.27 [SD:1.33] vs. -0.94 [1.19], p=0.015 and -1.08 [1.29] vs. -0.80 [1.18], p=0.037) (Appendix 6).

In total 385 HRCT scans were completed, with 77.7% (299/385) within two-months of TB treatment completion. Inter-reader agreement for the extent of Fleischner-defined parenchymal (ICC: 0.43 – 0.81) and airway abnormalities (Kappa: 0.42 – 0.72) were good to excellent (Appendix 3).(20) Moderate to severe bronchiectasis was seen in ≥1 lobe in 44.2% (170/385, 95% CI: 39.1 – 49.3%) of participants: 7.5% (29/385, 95% CI: 5.1 – 10.6%) had involvement of ≥3 lobes, and 12.7% (49/385, 95% CI: 9.6 – 16.5%) had cystic bronchiectasis. The median amount of abnormal parenchyma was

22.9% (IQR: 9.2 – 39.2%). Atelectasis and banding, and mosaicism were the most common patterns seen, and 9.4% (36/385, 95% CI: 6.6 – 12.7%) of participants had ≥1 destroyed lobe (Figure 2). On average, the majority of airways and parenchymal pathologies were more extensive in HIV-negative compared to HIV-positive participants (Figure 3, Appendix 7). However residual consolidation, ground glass opacification, and nodules were widespread (prevalence 69.4% [267/385, 95% CI: 64.5 – 73.9%], 36.6% [141/385, 95% CI: 31.8 – 41.7%], and 59.2% [228/385, 95% CI: 54.1 – 64.2%], respectively) with no significant difference by HIV-status.

Participants with weekly or monthly respiratory symptoms at TB treatment completion had lower FEV_1 z-scores (-1.23 [IQR:1.28] vs. -0.79 [IQR:1.19], p<0.001), lower FVC z-scores (-1.05 [IQR:1.25] vs. -0.68 [IQR:1.17], p=0.013), more abnormal lung parenchyma (27.3% [95% CI:10.0-42.9%] vs. 18.3% [95% CI: 7.1-34.6%], p=0.002), and a higher proportion had ≥1 destroyed lung lobe on HRCT imaging (29/234 [12.4%, 95% CI:8.5-17.3%] vs 7/151[4.6%, 95% CI: 1.9-9.3%], p=0.011) compared to those without regular symptoms. Those with regular cough had higher bronchiectasis severity scores than those without cough (3.0/18 [IQR: 1.0 – 5.5] vs. 2.0/18 [0.5 – 4.5], p=0.014) (Appendix 8).

Table 2: Clinical and respiratory parameters measured at TB treatment completion, 6-month and 12-month study visits

Parameter	TB treatment completion (n=405)	6-month visit (n=376)	12-month visit (n=368)	p-value: Baseline vs. 12-months [§]
Self-reported symptom prevalence (%, 95% CI) [†]				
Breathlessness				
- Never/only with chest infections	227 (56.0%, 51.1-60.9%)	283 (75.3%, 70.6-79.5%)	282 (76.6%, 72.0-80.9%)	<0.001*
- Few days per month	161 (39.8%, 35.0-44.7%)	79 (21.0%, 17.0-25.5%)	76 (20.7%, 16.6-25.2%)	
- ≥Several days per week	17 (4.2%, 2.5-6.6%)	14 (3.7%, 2.1-6.2%)	10 (2.7%, 1.3-4.9%)	
Cough				
- Never/only with chest infections	259 (64.0%, 59.1-68.6%)	284 (75.5%, 70.9-79.8%)	307 (83.4%, 79.2-87.1%)	<0.001*
- Few days per month	135 (33.3%, 28.8-38.2%)	76 (20.2%, 16.3-24.6%)	54 (14.7%, 11.2-18.7%)	
- ≥Several days per week	11 (2.7%, 1.4-4.8%)	16 (4.3%, 2.5-6.8%)	7 (1.9%, 0.8-3.9%)	
Sputum production				
- Never/only with chest infections	300 (74.1%, 69.5-78.3%)	300 (79.8%, 75.4-83.7%)	318 (86.4%, 82.5 -89.7)	<0.001*
- Few days per month	97 (23.9%, 19.9-28.4%)	70 (18.6%, 14.8-22.9%)	47 (12.8%, 9.5-16.6%)	
- ≥Several days per week	8 (2.0%, 0.9-3.9%)	6 (1.6%, 0.6-3.4%)	3 (0.8%, 0.2-2.4%)	
Wheeze				
- Never/only with chest infections	372 (91.8%, 88.7-94.3%)	346 (92.0%, 88.8-94.6%)	352 (95.7%, 93.0-97.5%)	0.091
- Few days per month	29 (7.2%, 4.8-10.1%)	28 (7.5%, 5.0-10.6%)	16 (4.3%, 2.5-7.0%)	
- ≥Several days per week	4 (1.0%, 0.3-2.5%)	2 (0.5%, 0.1-1.9%)	0	
Any respiratory symptom, ≥monthly	246 (60.7%, 55.8-65.5%)	138 (36.7%, 31.8-41.8%)	113 (30.7%, 26.0-35.7%)	<0.001*
Self-reported symptom impact (%, 95% CI)				
Impact of chest on activities				
- Does not stop any activities	200 (49.4%, 44.4-54.4%)	290 (77.1%, 72.5-81.3%)	295 (80.2%, 75.7-84.1%)	<0.001*
- Prevents 1-2 activities	165 (40.7%, 35.9-45.7%)	69 (18.4%, 14.6-22.6%)	57 (15.5%, 11.9-19.6%)	
- Prevents most / all activities	40 (9.9%, 7.2-13.2%)	17 (4.5%, 2.7-7.1%)	16 (4.3%, 2.5-7.0%)	

Impact of chest on work - Does not affect work - Interferes with / made me change work - Made me stop work	 243 (60.0%, 55.0-64.8%) 148 (36.5%, 31.8-41.4%) 14 (3.5%, 1.9-5.7%)	 309 (82.2%, 77.9-85.9%) 57 (15.2%, 11.7-19.2%) 10 (2.7%. 1.3-4.8%)	 323 (87.8%, 84.0-90.9%) 38 (10.3%, 7.4-13.9%) 7 (1.9%, 0.8-3.9%)	 <0.001*
Breathless at rest / during personal care	2 (0.5%, 0.1-1.8%)	2 (0.5%, 0.1-1.9%)	2 (0.5%, 0.1-1.9%)	1.000
Walks slower than peers / stops for rest at own pace	108 (26.8%, 22.5-31.4%)	57 (15.2%, 11.7-19.2%)	64 (17.4%, 13.7-21.7%)	0.002*
Breathless on hills	176 (43.7%, 38.8-48.7%)	82 (21.8%, 17.7-26.3%)	83 (22.6%, 18.4 – 27.2%)	<0.001*
Quality of life				
Self-reported general health (%, 95% CI) - Poor/fair - Good/excellent	 115 (28.4%, 24.1-33.1%) 290 (71.6%, 66.9-75.9%)	 54 (14.4%, 11.0-18.3%) 322 (85.6%, 81.7-89.0%)	 22 (6.0%, 3.8-8.9%) 346 (94.0%, 91.1-96.2%)	 <0.001*
SGRQ Total score (median, IQR)	8.8 (1.3 – 23.4)	0.4 (0 – 10.6)	0.4 (0 – 6.9)	<0.001*
SGRQ Symptom score (median, IQR)	10.3 (2.7 – 23.1)	2.7 (0 – 13.7)	2.7 (0 – 13.7)	<0.001*
SGRQ Activity score (median, IQR)	11.2 (0 – 35.5)	0 (0 – 11.9)	0 (0 – 6.2)	<0.001*
SGRQ Impact score (median, IQR)	5.6 (0 – 15.5)	0 (0 – 5.7)	0 (0 – 3.7)	<0.001*
Clinical observations				
BMI (kg/m^2) (median, IQR)	20.5 (19.0 – 22.3)	21.0 (19.4 – 22.7)	21.1 (19.5 – 23.2)	<0.001*
Oxygen saturations (%) (median, IQR)	98 (97 – 99)	98 (97 – 99)	98 (97 – 98)	<0.001*
Hypoxaemia (sats <92%) (%, 95% CI)	6 (1.5%, 0.5-3.2%)	6 (1.6%, 0.6-3.4%)	4 (1.1%, 0.3-2.8%)	0.706
Respiratory rate (breaths/minute) (median, IQR)	18 (17 – 20)	19 (18 – 21)	20 (19 – 22)	<0.001*
Heart rate (beats/minute) (median, IQR)	78 (68 – 89)	77 (68 – 86)	77 (67 – 86)	0.019*
Pedal oedema (%, 95% CI)	7 (1.7%, 0.7-3.5%)	3 (0.8%, 0.2-2.3%)	3 (0.8%, 0.2-2.4%)	0.317
Palatal Kaposi Sarcoma (n=368) (%, 95% CI)	8 (2.2%, 0.9-4.2%)	10 (2.7%, 1.3-4.8%)	1 (0.3%, 0.0-1.5%)	0.008*
Blood tests				
Haemoglobin (g/dL) (median, IQR)	13.7 (12.3 – 15.1)			
Positive aspergillus IgG ELISA (%, 95% CI)	3 (0.7%, 0.2-2.1%)		2 (0.5%, 0.1-1.9%)	0.564
6-minute walk test (n=395 / 355)				
Distance (m) (mean, sd)	568m (79.7m)		611.2m (71.0m)	<0.001*
Spirometry (n=365 / 341 / 336) ‡				
FEV_1 z-score (mean, sd)	-1.06 (1.26)	-0.90 (1.25)	-0.88 (1.19)	<0.001*
FVC z-score (mean, sd)	-0.91 (1.23)	-0.66 (1.19)	-0.61 (1.09)	<0.001*
FEV_1/FVC ratio z-score (mean, sd)	-0.38 (1.26)	-0.51 (1.28)	-0.54 (1.29)	<0.001*
Pattern of spirometry (%, 95% CI) - Obstruction (FEV1/FVC ratio <LLN) - Low FVC (FEV1/FVC ratio ≥LLN & FVC<LLN) - Normal (FEV1/FVC ratio ≥LLN & FVC≥LLN)	 52 (14.2%, 10.8-18.3%) 73 (20.0%. 16.0-24.5%) 240 (65.8%, 60.6-70.6%)	 61 (17.9%, 14.0-22.4%) 45 (13.2%, 9.8-17.3%) 235 (68.9%, 63.7-73.8%)	 60 (17.9%, 13.9-22.4%) 43 (12.8%, 9.4-16.8%) 233 (69.4%, 73.5-82.6%)	 <0.001*
CXR findings (n=403 / 361)				
% Abnormal parenchyma (median(IQR), [Range])	2.9 (0.4 – 9.2) [0 – 51.7]		2.1 (0 – 7.1) [0 – 70.8]	<0.001*
Ring and tramline severity score (0-18) (median(IQR), [Range])	1 (0 – 3) [0 – 13.5]		1 (0 – 2.5) [0 – 14.5]	0.100

* Statistically significant difference between baseline and 12-month values, at p<0.05 level.

† Symptom questions derived from SGRQ: Over the past 3-months I have (had shortness of breath / coughed / brought up sputum / had attacks of wheezing): not at all / only with chest infections / a few days a month / several days a week / most days a week; If you have tried to work in the past 3-months: my chest trouble does not affect my work / my chest trouble interferes with my work or made me change my work / my chest trouble made me stop work; Which of these statements best describes how your chest affects you: It does not stop me doing anything I would like to do / It stops me doing 1-2 things I would like to do / it stops me doing most of the things I would like to do / It stops me doing everything I would like to do.

‡ BOLD standard data available for n=365/405 at baseline, n=341/376 at 6-months, and n=336/368 at 12-month study visits. Data age / sex / height standardised using GLI 2012 African American reference ranges to generate z-scores.

§ Pairwise comparisons between baseline and 12-month data using McNemar's test for categorical variables, and Student's t-test / Wilcoxon rank sum for continuous variables.

Change in respiratory health over one-year

On average, recovery was seen in respiratory health in the year after treatment completion: the prevalence of monthly symptoms declined (60.7% [246/405] to 30.7% [113/368], p<0.001), and

average spirometry volumes increased (mean z-score change: FEV_1 +0.20 [95% CI: 0.14 – 0.27] and FVC +0.33 [95% CI: 0.26 – 0.39]). However, by one-year 12.2% (45/368, 95% CI: 9.1 – 16.0%) still had chest symptoms interfering with work, and mean spirometry z-scores remained negative (FEV_1 -0.88 [SD:1.19] and FVC -0.61 [SD:1.09]) (Table 2). In addition, 43.2% (159/368, 95% CI: 38.1 – 48.4%) of individuals had experienced a clinically significant deterioration in ≥1 respiratory parameter (symptoms, spirometry, or imaging), including 19.3% (59/305, 95% CI: 15.1 – 24.2%) and 14.1% (43/305, 95% CI: 10.4 – 18.5%) of participants with a decline in FEV_1 and FVC ≥100ml (Table 3).

Table 3: Proportion of participants experiencing clinically relevant improvement, deterioration or no change in respiratory parameters between baseline and one-year study visits, amongst those completing both visits (n=368). Median size of change shown for continuous variables.

Parameter	Classification of change	Proportion of participants with each pattern of change (n, %)* Median (IQR) change observed		
		Improvement	No change	Deterioration
Self-reported general health	Change of ≥1 category in self-reported general health (poor, fair, good, excellent)	115 (31.3%)	229 (62.2%)	24 (6.5%)
BMI (kg/m^2)	Change ≥1.46kg/m2 †	105 (28.5%) 2.7 (1.9 – 4.1)	244 (66.3%) 0.2 kg/m^2 (-0.2 – 0.8)	19 (5.2%) -2.4 kg/m^2 (-3.4 - -1.7)
SGRQ total score (n=366)	Change ≥4units ‡	167 (45.6%) -16.1 points (-23.8 - -9.2)	153 (41.8%) -0.4 points (-1.8 – 0)	46 (12.6%) +11.5 points (7.0 – 25.9)
6-minute walking distance (m) (n=348)	Change ≥26m ‡	201 (57.8%) 70m (46 – 105m)	102 (29.3%) 8m (-4 – 15m)	45 (12.9%) -49m (-65 - -38)
Presence of monthly respiratory symptoms	Change between present / absent monthly symptoms	133 (36.1%)	207 (56.3%)	28 (7.6%)
FEV1 volume (L) (n=305)	Change ≥100ml ‡	133 (43.6%) 230m (150 – 340)	113 (37.1%) 0ml (-40 – 40)	59 (19.3%) -200ml (-230 - -130)
FVC volume (L) (n=305)	Change ≥100ml ‡	164 (53.8%) 280ml (190 – 400)	98 (32.1%) 30ml (-40 – 60)	43 (14.1%) -160ml (-220 - -120)
% Abnormal parenchyma on CXR (n=359)	Change ≥4.68% †	58 (16.2%) -8.3% (-12.1 - -6.3)	283 (78.8%) 0 % (-1.7 – 0.4)	18 (5.0%) +7.9 % (6.3 – 13.3)
Ring and tramline score (0-18) on CXR (n=359)	Change ≥1.17 points †	79 (22.0%) -2.5 points (-4.0 –2.0)	218 (60.7%) 0 points (-0.5 – 0)	62 (17.3%) 2.0 points (1.5 – 3.0)

*Pattern of change over 1-year period, classified using 'Minimally important clinical difference (MCID)' cut-offs for continuous variables, and change in response category for ordinal variables. Improvement: Increase ≥MCID or improvement by ≥1 category; No change: remaining within +/-MCID of baseline reading, or remaining in same category; Deterioration: Reduction ≥MCID or deterioration by ≥1 category.

† No existing MCID agreed in literature: cut-off calculated by 0.5 x standard deviation of baseline data.

‡ MCID derived from COPD literature(22).

Mixed-effects models adjusted for spirometry at TB treatment completion found FEV_1 and FVC improved by an average of 70ml (95% CI: 45 – 96ml) and 131ml (95% CI: 101 – 161ml) respectively over one-year, with the greatest change seen in the first six-months (Table 4). However, recovery was incomplete and the strongest predictor of spirometry at any time point was spirometry at TB treatment completion (accounting for >90% of total model variance). Accelerated FEV_1 or FVC decline ≥100ml was seen in participants across a wide range of baseline FEV_1 and FVC measures (Appendix 9). The lowest spirometry volumes at one-year were seen in those with the most extensive parenchymal pathology or bronchiectasis on HRCT, or the presence of symptoms at TB treatment completion.

Table 4: Multi-level linear regression, to investigate parameters predicting spirometry values in the first year after TB treatment completion† (n=347).‡

Variable measured at TB treatment completion	Univariate (ml, 95% CI)	Multivariate, partial model (ml, 95% CI)	Multivariate, full model (ml, 95% CI)
Absolute FEV_1 (ml) over follow-up period			
Time from TB treatment end §			
6-months	66.70 (47.39 – 86.01)*	62.17 (41.78 – 82.56)*	65.30 (45.00 – 85.61)*
12-months	72.73 (48.26 – 97.19)*	65.57 (39.47 – 91.68)*	70.56 (44.58 – 96.54)*
HIV positive status	197.57 (83.03 – 312.11)*	193.75 (79.43 – 308.08)*	98.61 (-2.01 – 199.22)
Microbiologically proven TB	-61.81 (-194.79 – 71.17)	-9.12 (-140.23 – 121.99)	30.82 (-84.35 – 145.98)
BMI (kg/m2)	18.32 (9.26 – 27.38)*	7.39 (-1.96 – 16.74)	2.20 (-7.01 – 11.40)
Pack-year smoking history	-7.90 (-20.00 – 4.20)	-4.90 (-16.79 – 7.00)	-0.75 (-11.15 – 9.65)
Maximum education ≤ 1ry school	-108.59 (-225.94 – 8.76)	-108.26 (-224.69 – 8.18)	-37.49 (-139.97 – 64.99)
Respiratory symptoms ≥monthly	-198.98 (-310.07 - -87.90)*		-111.26 (-208.10 - -14.43)*
Bronchiectasis severity score (0-18) – 3-point increments ‖	-221.04 (-270.18 - -171.91)		-95.56 (-155.64 - -35.47)*
Abnormal parenchyma (%) – 10% increments **	-152.87 (-180.38 - -125.36)		-106.40 (-141.38 - -71.4)*
Variance components (% of model variance): change over time		*1.85%*	*2.53%*
Variance components (% of model variance): baseline FEV1		*94.22%*	*92.05%*
Absolute FVC (ml) over follow-up period			
Time from TB treatment end §			
- 6-months	124.49 (100.70 – 148.30)*	111.77 (87.04 – 136.50)*	115.38 (90.72 – 140.05)*
- 12-months	145.63 (117.66 – 173.59)*	125.21 (95.26 – 155.16)*	131.28 (101.41 – 161.15)*
HIV positive status	197.30 (75.42 – 319.18)*	184.22 (64.02 – 304.43)*	92.94 (-18.17 – 204.04)
Microbiologically proven TB	-18.24 (-159.57 – 123.09)	30.45 (-107.28 – 168.17)	65.99 (-61.11 – 193.09)
BMI (kg/m2)	40.58 (29.97 – 51.19)*	21.34 (10.73 – 31.94)*	15.35 (4.75 – 25.95)*
Pack-year smoking history	-6.04 (-18.88 – 6.81)	-4.38 (-16.86 – 8.10)	-1.87 (-13.34 – 9.59)
Maximum education ≤ 1ry school	-1.34 (-126.72 – 124.04)	-2.97 (-125.46 – 199.51)	63.45 (-49.78 – 176.68)
Respiratory symptoms ≥monthly	-200.30 (-318.52 - -82.08)*		-123.61 (-230.53 - -16.69)*
Bronchiectasis severity score (0-18) – 3-point increments ‖	-217.87 (-271.12 - -164.62)*		-133.62 (-200.01 - -67.23)*

Abnormal parenchyma (%) – 10% increments **	-131.74 (-162.76 - -100.73)*		-67.03 (-105.67 - -28.39)*
Variance components (% of model variance): change over time		*1.60%*	*2.01%*
Variance components (% of model variance): baseline FVC		*93.18%*	*91.26%*

* OR statistically significant at p<0.05 level.

† Model construction based on apriori selection of risk-factors / confounders, and elimination of co-linear variables. Interactions with time evaluated. All univariate & multivariate models coefficients represent the average change in FEV1 or FVC (ml) expected for a 1-unit change in the predictor, holding all other parameters still, and include adjustment for participant age (years), sex, and height (cm).

‡ Participants excluded if absent HIV status at TB treatment completion (n=2), no valid baseline spirometry (n=36), no baseline HRCT imaging (n=20). Includes participants contributing either 6-month (n=13) or 12-month (n=322) follow-up.

§ Negative correlation identified between FEV1 and time (partial model: -0.46 (-0.58 - -0.31) / full model: -0.37 (-0.51 - -0.21)) and FVC and time (partial model: -0.56 (-0.68 - -0.40)/ full model: -0.44 (-0.59 - -0.26)) in all models.

‖ Bronchiectasis severity score (0-18): unweighted sum of 6x lobar bronchiectasis scores ranging from 0 (no bronchiectasis) to 3 (severe dilatation >3 times diameter of adjacent vessel), such that increment of 3 points represents one additional lobe with severe airway dilatation, or combination of 1-3 lobes with less severe disease.

** Total % of parenchymal abnormalities across lung, including: parenchymal banding, atelectasis, consolidation, ground glass change, emphysema, emphysematoid destruction, cavities / cystic airspaces. Excluding mosaicism which represents airway/vascular rather than lung tissue abnormality.

Chronic respiratory symptoms

30.7% (113/368, 95% CI: 26.0 – 35.7%) reported respiratory symptoms at one-year, with breathlessness being most common (Table 2). On average, participants reporting respiratory symptoms at pTB treatment completion were significantly more likely to have symptoms one-year later compared to those without baseline symptoms (OR 2.42 [95% CI: 1.37 – 4.27] and 2.45 [95% CI: 1.39 – 4.32] for FEV_1 and FVC models). The odds of respiratory symptoms at one-year were lower in HIV-positive compared to HIV-negative participants (OR 0.33 – 0.40 [95% CI: 0.18 – 0.98] across CD4 groups and models) (Appendix 10).

Acute respiratory events

Of participants who contributed six- and 12-months of follow-up data, 25.0% (4/16, 95% CI: 7.3 – 52.4%) and 15.9% (58/364, 95% CI: 12.3 – 20.1%) experienced ≥1 acute respiratory event. The majority had one episode (77.4% [48/62]). Of the 70 unscheduled outpatient visits to local health centres or hospitals, 55.7% (39/70, 95% CI: 43.3 – 67.6%) were due to increased cough and 34.3%

(24/70, 23.3 – 46.6%) were related to increased breathlessness. Antibiotics were prescribed in 80% of cases.

Participants with respiratory symptoms at treatment completion were more likely to report a respiratory event during follow-up (OR 2.6 [95% CI: 1.25–5.42]) compared to those without baseline symptoms. HIV-positive adults (12.9% [30/232, 95% CI: 8.9 – 17.9%]) had lower odds of a respiratory event compared to HIV-negative participants (21.9% [32/146, 95% CI: 15.5 – 29.5%]) in all models and at CD4 counts above and below 200 cells/μL (OR 0.33 – 0.43 [95% CI: 0.13–0.90]) (Appendix 11).

Controlling for baseline lung pathology the presence of more than one respiratory event during follow-up was negatively correlated with FEV_1 and FVC volumes at one-year. On average, those with ≥1 acute respiratory event had FEV_1 and FVC volumes which were 82ml (95% CI: 17 –147ml) and 122ml (95% CI: 51-192ml) lower at one-year compared to those without events (Appendix 12).

TB retreatment and mortality

The TB symptom screen (≥1 of current cough, fevers, night sweats, weight loss, haemoptysis) was positive in 18.9% (71/376, 95% CI: 15.1 – 23.2%) and 10.6% (39/368, 95% CI: 7.6 – 14.2%) at the six- and 12-month visits, with current cough as the most common symptom reported (95.8% [68/71, 95% CI: 88.1 – 99.1%] and 92.3% [36/39, 79.1 – 98.4%] at six- and 12-months). Sputum was obtained at 100/110 of these visits, and only 4% (4/100) had MTB on culture. Three non-tuberculous mycobacteria (NTM) isolates were cultured but repeat samples were negative. TB-retreatment was initiated in 3.7% (15/404) during follow-up: two culture positive, five smear positive, four Xpert MTB/RIF positive, three radiological diagnosis, one unknown. 2.7% (11/404) of participants died, of whom 45.5% (5/11) had been initiated on TB retreatment and 90.9% (10/11) were HIV-positive.

DISCUSSION

This study used gold-standard measurement approaches to show that amongst a prospectively recruited, unselected cohort of pTB-survivors in a low income, high TB and HIV prevalence setting, the burden of PTLD is high: after a single episode of successfully treated pTB disease, one third of patients have abnormal spirometry, over 40% have bronchiectasis, and almost 10% have lobar destruction. This pathology is largely undiagnosed within existing TB management pathways, but is meaningful for patient outcomes, with accelerated lung function decline, ongoing respiratory-related health seeking, persistent chest symptoms, and symptoms impairing work seen in 12 – 31% of patients in the year after treatment completion. Patterns of PTLD were heterogenous, and although less severe amongst HIV-positive compared to negative patients, the burden of disease was marked in both groups.

The finding of a high burden of post-TB lung damage is consistent with previous literature which suggests 2-4 fold increased odds of airway obstruction and restriction amongst those who have previously had pTB disease compared to those who have not,(2-4) and ongoing airway and parenchymal imaging abnormalities following treatment success.(5, 6) Together, these data indicate a high population burden of respiratory pathology resulting from pTB disease.

To our knowledge, this is the first study to track change in lung function in an unselected patient cohort prospectively from pTB treatment completion. On average, FEV_1 and FVC values for the cohort improved over time. Recovery was incomplete, but most marked in the first 6-months. This pattern of partial recovery is consistent with previous models,(23) and is in keeping with the parenchymal destruction and airway dilatation seen on HRCT imaging which are unlikely to fully resolve.(24, 25) However, heterogeneity of lung function outcomes was observed between individuals within the cohort: whilst most experienced recovery, up to a fifth had a clinically meaningful decline in lung

function over time. These patients are of particular concern given the known associations between reduced FEV_1 and FVC, and increased mortality.(26-28) In keeping with data from other chronic lung diseases, our analyses suggest that acute respiratory events in the year following treatment completion may drive worsening spirometry.(12, 13)

Our data show that PTLD is relevant to patients' lives and livelihoods. Chest symptoms interfering with work were reported by 46% at pTB treatment completion and 12% one-year later. The high costs incurred by TB patients during diagnosis and disease treatment are well recognised and have been associated with adverse treatment outcomes.(29, 30) However, our findings suggest that post-TB morbidity may cause ongoing income losses even beyond treatment completion. These ongoing costs are not routinely included in calculations of the economic impact of TB disease, nor is the need to address them yet prioritised within the WHO 'End-TB' agenda, which aims to mitigate TB-related patient costs.(31)

Almost one third of patients reported ongoing respiratory symptoms at 1-year. Chronic cough is stigmatising in high TB and HIV burden settings,(32) and in this study also led to the WHO TB-symptom screening tool remaining positive for many patients, some months after their initial disease episode. Although pTB-survivors are at high risk of recurrent TB disease,(33) empirical TB retreatment of pTB-survivors based on chronic symptoms is also widespread.(34) In this study the majority of those reporting chronic cough during follow-up did not have microbiological evidence of pTB when retested, were not started on TB retreatment, and did not die, highlighting challenges with TB-screening in the post-TB population.

HIV-positive adults had less extensive PTLD compared to HIV-negative adults. This difference was observed despite little difference in self-reported illness duration prior to TB treatment initiation. The HIV-positive patients included in this study had profound immunosuppression with a median CD4

count of 229 cells/µL at TB treatment completion. HIV-TB coinfected adults with low CD4 counts have been shown to have less extensive CXR changes at TB diagnosis, due to impaired localised cellular immune responses to mycobacterial infection, and our data suggest that this translates into less extensive residual pathology at TB treatment completion.(35, 36) However, it is of note that although the burden of disease was lower amongst HIV-positive compared to HIV-negative adults, still moderate to severe bronchiectasis or abnormal spirometry was seen in a third of this group at pTB treatment completion. Most HIV-infected participants in this cohort were initiated on ART close to pTB treatment onset, and immune reconstitution on ART has been associated with lung inflammation and destruction during early treatment.(37, 38) Findings in this study may reflect a balance between the protective effect of low CD4 counts at TB diagnosis on lung tissue, and pro-inflammatory immune reconstitution with early initiation of ART.

Lastly, the heterogeneity of patterns of PTLD in this study was marked. Novel HRCT imaging findings included a high burden of mosaicism – this may reflect small airways disease but may also relate to pulmonary hypertension, and echocardiography in this cohort would be of value.(39) The high prevalence of consolidation, ground-glass and nodules even after six-months of TB treatment was striking, but consistent with PET-CT studies from South Africa which show ongoing metabolic activity in focal lung lesions of pTB-survivors, due either to persistent mycobacterial disease or a protracted host immune response to sterilised infection.(40) The long-term relevance of this residual inflammation is not yet clear.

This is one of the first studies to prospectively investigate the nature and outcomes of post-TB lung damage, from the point of TB treatment completion, in a resource poor setting in sSA. The broad eligibility criteria mean that findings can likely be generalised to a wide spectrum of adults completing treatment in similar settings. Multiple respiratory parameters were measured to comprehensively

describe pathology, with high standards of quality control and best-practice reporting, and outcome data were collected prospectively. The availability of CT imaging is limited in LMICs, and its inclusion is therefore of particular value. Although the study was completed within an urban setting with a highly mobile population, loss to follow up was under 10%.

As patients were not assessed prior to TB disease and no control group was included for comparison, the aetiology of lung pathology cannot be confirmed. The short follow-up duration of one-year means that models of patient outcomes may have been underpowered and precluded investigation of risk-factors for TB retreatment or mortality. Observed changes over time may be related to regression to the mean, test-retest variation, or participant learning, but MCID cut-offs were used to allow for this. Study recruitment required attendance at a central hospital, and a selection bias away from those with severe disease may exist. Although this study was observational, participants likely received more medical advice than routinely available, and findings may be biased towards improved outcomes.

In summary, this study has found that PTLD is a common and under-recognised consequence of pTB that is disabling for patients and associated with adverse outcomes beyond pTB treatment completion. Our data highlight the importance of preventing PTLD: further investigation of host, environment, and pathogen determinants of the nature and severity of PTLD, including HIV-specific factors, are required to identify upstream modifiable risk factor.(41) Host directed therapies, and earlier diagnosis through active case finding and improved diagnostics may reduce lung damage, and we suggest that the burden of PTLD should be included as a secondary outcome in studies investigating the impact of these approaches.

Evidence-based guidelines for the management of those with established disease are lacking but urgently needed.(11) It is not yet clear which interventions would be clinically and cost-effective at

maximising health and preventing ongoing decline after pTB treatment completion, but our data suggest that appropriate management of respiratory exacerbations, and improved screening pathways for recurrent pTB disease should be prioritised. Other low-cost strategies including pulmonary rehabilitation and airway clearance exercises require evaluation, and health systems capable of providing long-term care to pTB-survivors will be needed to deliver these services.(42) Ultimately, we suggest that renewed efforts by the global TB research and practice community to address the sequelae of TB disease, beyond treatment completion, will be required to improve long-term patient well-being.

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Authors' contributions:

JM, SBS and KM were responsible for study conceptualisation and design. JM performed data collection. JM, PB and JR provided clinical oversight of the cohort. SBG, ELC and SBS provided institutional support in Malawi. JM, EJ, JJ and HZ developed image reporting systems and performed image reading. JM, ML, PM and KM analysed and interpreted data. JM was the lead author, with input from all co-authors. JM had final responsibility for the decision to submit for publication. *KM and *SBS are joint senior authors.

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