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

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SUMMARY

OBJECTIVE: To examine the prevalence and magnitude of chronic lung disease (CLD) and its association with empiric anti-tuberculosis treatment (due to lack of bacteriologic confirmation) among recurrent tuberculosis (TB) survivors in a human immunodeficiency virus (HIV) prevalent setting.

METHODS: Prospective cohort study of retreatment TB survivors in Harare, Zimbabwe. At median follow-up of 2 years post-treatment initiation, we characterized mortality, respiratory impairment, and mental health.

RESULTS: Among 175 retreatment TB survivors, 65% of whom were HIV-positive and 21% had been empirically treated, multiparameter CLD was noted at follow-up among 14% of patients (95%CI 9.0–19.7), with a six-fold increase in age-adjusted death in the first year following treatment completion. Empirically treated TB (relative risk [RR] 3.4, 95%CI 1.4–8.3) was associated with CLD, as was the number of previous anti-tuberculosis treatment courses in dose-dependent fashion (three vs. one, RR 6.2, 95%CI 1.7–22.1). Among retreatment TB survivors, 33% (95%CI 26.0–40.1) had persistent respiratory symptoms (Chronic Obstructive Pulmonary Disease Assessment Test score ⩾ 10); 26% (95%CI 19.8–33.0) significant deficits in exercise capacity (median incremental shuttle walk test distance, 550 m; Q_1–Q_3 440–730 m); 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.

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Conflicts of interest: none declared.

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

RÉSUMÉ

Examiner la prévalence et la magnitude des maladies pulmonaires chroniques (CLD) et leur association avec un traitement empirique de la tuberculose (TB) parmi les survivants d'une TB récurrente dans un contexte de prévalence élevée du virus de l'immunodéficience humaine (VIH).

Etude prospective de cohorte des survivants de la TB en retraitement à Harare, Zimbabwe. Lors du suivi médian de 2 ans après la mise en route du traitement, nous avons caractérisé la mortalité, la gêne respiratoire et la santé mentale.

Parmi 175 survivants de TB en retraitement, dont 65% ont été positifs au VIH et dont 21% avaient reçu un traitement empirique, une CLD à multiples paramètres a été notée lors du suivi parmi 14% (IC95% 9,0–19,7), avec une multiplication par six des décès ajustés sur l'âge dans la première année suivant l'achèvement du traitement. La TB traitée empiriquement (risque relative [RR] 3,4; IC95% 1,4–8,3) a été associée à une CLD, comme l'a été le nombre de traitements de TB préalables d'une manière dépendante de la dose (trois contre une, RR 6,2; IC95% 1,7–22,1); 33% (IC95% 26,0–40,1) des survivants de TB récurrente ont eu des symptômes respiratoires persistants (score du Questionnaire d'évaluation bronchopneumopathie chronique obstructive ⩾10); 26% (IC95% 19,8–33,0), des déficits significatifs en termes de capacité physique (test de marche progressif médian 550 m; $Q_1 – Q_3$ 440–730 m); 83% (IC95% 75,7–89,7) ont des anomalies résiduelles à la radiographie pulmonaire; 12% (IC95% 6,6–16,1) ont une obstruction, de modérée à grave, à la spirométrie; et 13% (IC95% 7,6–17,5) ont une dépression majeure.

En dépit d'un traitement réussi, les survivants en retraitement de TB gardent un risque substantiel de morbidité et de mortalité.

RESUMEN

Examinar la prevalencia de enfermedad pulmonar crónica (CLD), su magnitud y la asociación con el tratamiento antituberculoso empírico en los sobrevivientes de una tuberculosis (TB) recurrente, en un entorno con alta prevalencia de infección por el virus de la inmunodeficiencia humana (VIH).

Fue este un estudio prospectivo de cohortes de sobrevivientes del retratamiento de la TB en Harare, Zimbabue. La mediana del seguimiento fue 2 años después del inicio del tratamiento y se caracterizaron la mortalidad, el deterioro de la función respiratoria y la salud mental.

En los 175 sobrevivientes del retratamiento de la TB, de los cuales el 65% era positivo frente al VIH y el 21% había recibido tratamiento empírico, se observaron múltiples criterios de enfermedad pulmonar crónica en el 14% durante el seguimiento (IC95% 9,0–19,7), con un aumento de seis veces en la mortalidad ajustada con respecto a la edad en el primer año después de la compleción del tratamiento. La administración de un tratamiento antituberculoso empírico (riesgo relativo [RR] 3,4; IC95% 1,4–8,3) se asoció con enfermedad pulmonar crónica, al igual que el número de ciclos anteriores de tratamiento antituberculoso, de manera dependiente de la dosis (tres episodios de tratamiento contra uno; RR 6,2; IC95% 1,7–22,1). En los sobrevivientes de una TB recurrente, el 33% (IC95% 26,0–40,1) exhibió síntomas respiratorios persistentes (cuestionario de evaluación de la enfermedad pulmonar obstructiva crónica ⩾10); el 26% (IC95%

19,8–33,0) tuvo deficiencias considerables en la resistencia al ejercicio (la mediana de la prueba de la caminata de carga progresiva fue 550 m; primer a tercer cuartil, 440–730 m); el 83% presentó anomalías residuales en la radiografía de tórax (IC95% 75,7–89,7); el 12% obstrucción de moderada a grave en la espirometría (IC95% 6,6–16,1); y el 13% sufrió una depresión mayor (IC95% 7,6–17,5).

Pese a un tratamiento exitoso, los sobrevivientes de un retratamiento de TB conservan un riesgo importante de morbilidad y mortalidad.

Keywords

post-tuberculosis sequelae; TB-HIV co-infection; chronic respiratory disease; chronic obstructive pulmonary disease; Zimbabwe

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TUBERCULOSIS (TB) IS 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 human immunodeficiency virus (HIV) infection.[1] Despite these disheartening statistics, long-term sequelae among TB survivors are 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 function[2–6] and/or persistent respiratory symptoms[4,7] 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 the number and severity of previous TB episodes,[5] and is associated with decreased quality of life.[7] Varying degrees of bronchiectasis, broncholiths, cicatricial atelectasis, and fibrosis are seen radiographically.[8]

Retreatment TB is programmatically defined among patients who have undergone ⩾1 month of anti-tuberculosis treatment in the past, regardless of bacteriology (World Health Organization guidelines).[9] Compared with those with newly diagnosed TB, retreatment cases are associated with an increased risk of multidrug-resistant TB (MDR-TB),[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 often 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 vs. unconfirmed TB cases. We hypothesized that CLD would be more strongly associated with empiric anti-tuberculosis 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 to June 2014, we prospectively enrolled consecutive adult participants requiring retreatment of TB in Harare (TRAP MDR-TB cohort).[14] Retreatment was defined as patients who presented with TB symptoms (cough, fever, night sweats, or weight loss) and had previously completed ⩾1 month of anti-tuberculosis treatment (relapse, treatment after default, or treatment failure).[14] At enrollment, all participants underwent comprehensive bacteriologic assessment for TB, including culture performed in duplicate on both solid (Löwenstein-Jensen media) and liquid (MGIT™ [Mycobacterial Growth Indicator Tubes]; BD, Sparks, MD, USA) media. Diagnostic classification of patients at baseline was based on bacteriologic confirmation of *Mycobacterium tuberculosis* (confirmed group) vs. institution of anti-tuberculosis treatment without such confirmation (unconfirmed group).[14]

From 2015 to 2016, at a median of 2 years post anti-tuberculosis treatment initiation, surviving TRAP MDR-TB participants were traced via telephone 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 CLD. Our objective was to have a minimum of 1 year follow-up after treatment initiation 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—acid-fast bacilli (AFB) sputum smear microscopy, Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), and a single liquid *M. tuberculosis* culture—were indicative of active TB due to the 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, Harare, and the University of California, San Francisco Human Research Protection Program, San Francisco, CA, USA.

Data collection

At the 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 anti-tuberculosis 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 four ways: 1) respiratory symptoms during a stable phase of disease (>6 weeks following any exacerbation) using the Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT);[15] 2) forced expiratory flow rates and

volumes (spirometry); 3) aerobic exercise testing; and 4) chest radiography (CXR). In addition, we assessed mental health parameters, as described below.

Mortality

Standardized mortality ratios (SMRs) were calculated as the ratio of the observed number of deaths of all study participants (regardless of bacteriologic confirmation at the 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 HIV population estimates of the Joint United Nations Programme on HIV/AIDS 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 intervals (CIs) for the SMRs.

Chronic Obstructive Pulmonary Disease Assessment Test

Consistent with the literature,[18] we defined significant respiratory symptoms as a CAT score of ⩾10 and severe respiratory symptoms as a CAT score of ⩾16.[15] Data for one of the eight response items ('chest wheeze') were imputed (see Appendix*). Exacerbation history over the previous 12 months was retrospectively determined by structured questionnaire using 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 American Thoracic Society (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 nebulized salbutamol (2.5 mg), followed by repeat testing for reversibility. The highest forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) measurements derived from traces meeting ATS quality criteria were eligible for analysis. All available spirometry tracings were reviewed by study investigators trained in pulmonary medicine, who were blinded to other patient data. Normal and abnormal predicted FEV_1, FVC and FEV_1:FVC measurements were determined using the 2012 Global Lung Function Initiative 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 (FEV_1:FVC < LLN, or 'reduced FVC' (FVC < LLN, with a normal FEV_1:FVC).[20] Obstruction was further classified by severity based on FEV_1 as mild (FEV_1 ⩾80%), moderate (50–79%) or severe (30–49%).

*The appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2019/00000023/00000002/art000 …..

Exercise testing

The incremental shuttle walk test (ISWT) was performed according to published guidelines.[21] Briefly, participants were 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 ISWT. ISWT distances were compared with an age-, sex- and body mass index (BMI) adjusted prediction model for healthy adults.[22] Maximal oxygen consumption (VO_2 max) was extrapolated from ISWT distance using model equations described previously.[23] The age-, sex-, height- and BMI-adjusted LLN for VO_2 max was derived from the same study and used as a reference.[23]

Chest radiography

Posteroanterior (PA) and lateral CXRs were taken. Details of parenchymal abnormalities were recorded through blinded interpretation by two US-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 previous 12 months; along with at least one of the following criterion: 3 i) spirometry abnormality, as defined above; ii) ISWT results <50% predicted; or iii) 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 16 meeting the 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 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) guidelines (with scores >30 indicating PTSD).[25]

Statistical analysis

Sample size was 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 comprised 37 individuals with bacteriologically unconfirmed TB and 138 individuals with bacteriologically confirmed TB. Based on the prevalence of spirometric obstruction in previous studies and given our conservative definition of CLD, we assumed the presence of CLD in respectively 30% and 10%[6] of unconfirmed and confirmed TB patients, yielding a power of 90% ($\alpha = 0.05$) to reject the null hypothesis that these proportions would be equal. Multivariate associations with CLD 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). Proportions were compared using χ^2 tests; continuous variables were compared using the Wilcoxon rank-sum test. We applied a test for the linear trend of the log odds to test for trends in categorical data. All *P* values were two-sided, with $P = 0.05$ as the significance level. Data were analyzed using Stata 14 (Stata Corp, College Station, TX, USA) and R v 3.4.3 (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

Of the 486 patients who were prospectively recruited within the original TRAP MDR-TB cohort between November 2011 and June 2014,[14] 128 (26%) had been diagnosed with rifampicin (RMP) resistant TB, 177 (36%) with RMP-susceptible TB, and 181 (37%) empirically treated, culture-negative re-treatment TB. For the current study, at follow-up, a median of 26 months (quartile $(Q)_1$–Q_3, 20–30 months) after treatment initiation, 280 (58%) participants were unavailable for further evaluation. Of these patients, 58/280 (21%) had died, 128/280 (46%) had moved or were untraceable, 68/280 (24%) declined study follow-up procedures, and 26/280 (9%) discontinued the initial TB treatment due to an alternative diagnosis (Figure 1). Of the remaining 206 patients, 10/206 (5%) were found to have undiagnosed bacteriologically confirmed recurrent active TB at follow-up, 18/206 (9%) remained on treatment for MDR-TB with fewer than four negative cultures in a month, and 3/206 (1%) could not participate due to severe respiratory disability or inability to ambulate. Of the final population analyzed ($n = 175$), 138 (79%) had bacteriologically confirmed TB at the time of original recruitment, and 37 (21%) had been empirically treated. The median age was 41 years (Q_1–Q_3 33–48); 113 (65%) were HIV-positive, 93 (82%) of whom had been on antiretroviral medications at the time of the original TB diagnosis. 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 age, 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 ($n = 21/26$, 81% vs. $n = 65/111$, 59%; $P = 0.03$); other potential associations with CLD were similar (Table 1).

Compared with the Zimbabwe HIV-specific and the general population, individuals who successfully completing anti-tuberculosis retreatment (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, respectively, during the first year of post-treatment follow-up.

Symptomatology and chronic lung disease

Moderate or 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 up hills was reported among 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 Appendix Table A.1), and was associated with unconfirmed TB in multivariate analysis (RR 3.4, 95%CI 1.4–8.3, P < 0.01), but age, HIV, or tobacco exposure were not (Table 3). The association of CLD with the 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 vs. two and one vs. 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% (610 m) vs. 88% (870 m) 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 CXRs (Figure 2). Bronchiectasis (ring or tramline opacities), non-cavitating nodules, and volume loss occurred among respectively 82% (n = 95/116), 70% (n = 81/116), and 66% (n = 77/116). Radiographic patterns among the unconfirmed and confirmed groups were not significantly different (Appendix Table A.2).

Pulmonary function

Overall, 36% (n = 58/162, 95%CI 29.0–43.4%) of participants had spirometry abnormalities (Figure 3), with 12% having moderate-to-severe obstruction. Thirty-two patients (20%) had isolated reduced FVC (Table 2). Per cent predicted FEV_1, FVC, and FEV_1:FVC did not demonstrate clinically significant differences between confirmed and unconfirmed groups.

Mental health

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), six of whom 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 CLD and one in 10 experiencing major depression. Although 35% of the population analyzed were HIV-negative, the rate of death among retreatment TB patients was six-fold that of the general HIV-positive Zimbabwe referent population. Compared with those with bacteriologically confirmed, recurrent TB at initial enrollment, patients who had been treated empirically for recurrent 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.

COPD contributes to 3.17 million deaths annually, or about 5% of total deaths worldwide.[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 <40%.[4] In our cohort of patients with retreatment TB, neither exposure to tobacco smoke, indoor biomass, occupational dusts or fumes, nor HIV had a clear association with CLD. Although statistical power was limited, these findings support the hypothesis that the impact of active TB on lung health in LMICs may be on par with 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 toward universal testing and treatment of HIV in LMICs has led to the emergence of an older HIV-positive population at an increased risk of chronic non-communicable diseases. Patients with HIV are predisposed to chronic airway obstruction due to lymphocytic alveolitis, recurrent respiratory infections, and oxidative stress.[26,27] In the context of TB-HIV comorbidity, the independent role of HIV infection in causing pulmonary dysfunction is less clear, with studies both demonstrating association,[7] and lack of association between HIV and TB-related respiratory disability.[5] Mechanistically, HIV in co-infected patients may downregulate expression of specific matrix metalloproteinases (MMPs), there-by ameliorating TB-associated lung damage.[28] Conversely, initiation of antiretroviral therapy and subsequent recovery of CD4 T-cells has been shown to reconstitute MMP levels, contributing to the pathology associated with TB-immune reconstitution inflammatory syndrome and, potentially, subsequent chronic lung disease.[29] Despite the complex interplay of TB-HIV co-infection, the increased mortality of co-infected patients demonstrated previously,[7,12] and in our cohort of primarily HIV-positive individuals, reinforces the importance of primary prevention of TB-HIV co-infection.

High TB-HIV-associated mortality, limited diagnostic resources, and scarcity of health care access contribute to increased rates of empiric anti-tuberculosis treatment in high TB-HIV burden settings.[30] Accessing the national TB program may be the most expedient pathway for individuals with chronic respiratory symptoms to receive health care, considering the substantial cost burden, wait times, and logistical difficulties in the wider system.[31] The association between unconfirmed, empirically treated TB and CLD, which persists following adjustment for the number of previous TB episodes, suggests that pre-existing lung disease may contribute to both TB overdiagnosis and TB re-treatment. Other regional investigators have found higher mortality among sputum smear-negative and clinically diagnosed patients than in those who are sputum smear-positive, even after controlling for HIV status,[12] and in those tested for TB but found to be bacteriologically negative and not ultimately treated for TB;[32] this may indicate unrecognized non-TB disease.[12]

M. tuberculosis causes destruction of pulmonary extracellular regions through as yet poorly understood dysregulation of the host immune response, including inflammatory cytokine and MMP secretion.[6] Phenotypically, these pathways may result 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 broad definition of CLD) outside of entity-specific scores.[33] Imperfect correlations between pulmonary disease and spirometry[34] and radiographic[35] measures further complicate objective assessment. Hence, we used a simple and conservative (but 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 from depression and PTSD. In COPD, the impact of comorbid depression and anxiety is associated with increased hospitalization stay, increased symptom burden, and reduced quality of life.[36] Furthermore, TB and TB-associated treatment are known but under-appreciated risk factors for both depression and anxiety.[37] Our findings highlight the importance of the investigation and treatment of psychiatric comorbidities in TB survivors.

Our study had five main limitations. First, we did not recruit an age- and HIV-matched control series without a known history of TB. Second, we did not undertake measures of respiratory and psychiatric morbidity before the index TB episode, and therefore cannot comment on pre-TB health trajectory. Similarly, we did not 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 highly biased. Fifth, although we used AFB smear microscopy, Xpert, microscopic-observation drug susceptibility, 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 documented increased 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 pre-eminent importance of prevention over ‘cure’, and emphasize broader efforts toward establishing access and quality standards for universal health care.

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APPENDIX

METHODS

Correction of the Chronic Obstructive Pulmonary Disease Assessment Test score

To impute the missing values for the Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT) questionnaire 'chest wheeze' response, we carried out a two-step approach. First, we used the SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD) cohort[1] to develop a proportional odds model for the missing response involving the other seven responses, including interaction terms. In brief, SPIROMICS is a US multicenter study designed to identify COPD subpopulations and to validate intermediate outcome measures. Participants (aged 40–80 years, enrolled between 12 November 2010 and 31 July 2015) included healthy never smokers and current or former smokers of more than 20 pack-years with or without airflow obstruction (defined as post-bronchodilator forced expiratory volume in one second:forced vital capacity ratio of ⩾0.70). Second, we fitted the selected model for the missing response to the combined (SPIROMICS and TRansmission And Pathogenesis of MDR-TB [TRAP]) data, and obtained the predicted values for the missing response. Third, in the TRAP data, we randomly imputed the missing chest wheeze response based on the expected values for each participant 20 times, computing the average complete CAT scores across the 20 imputed data sets.

Table A.1

Characteristics of TB patients with CLD

Parameter	Without CLD (*n* = 151) *n* (%)	With CLD (*n* = 24) *n* (%)	*P* value
TB status			
Confirmed TB	124 (82)	14 (58)	<0.01
Unconfirmed TB	27 (18)	10 (42)	
Spirometry, % predicted (Q_1, Q_3) *			
FEV_1	90 (76, 103)	66 (54, 79)	<0.0001
FVC	92 (83, 103)	73 (61, 78)	<0.0001
FEV_1:FVC	96 (91, 102)	96 (82, 106)	1.0
Spirometry LLN			
Normal	99 (72)	5 (22)	
Isolated reduced FVC	20 (14)	12 (52)	<0.0001
Obstruction †	20 (14)	6 (26)	
Moderate	12 (60)	4 (66)	
Severe	2 (10)	2 (33)	
CAT score			
Absolute scores (Q_1 Q_3)	7 (4–11)	16 (10–17)	<0.0001
<10	111 (74)	6 (25)	

Parameter	Without CLD (*n* = 151) *n* (%)	With CLD (*n* = 24) *n* (%)	*P* value
⩾10 < 15	25 (16)	4 (17)	<0.0001
⩾15 < 20	13 (9)	11 (45)	
⩾20	2 (1)	3 (13)	
Exacerbations (previous 12 months)			
Number of exacerbations (Q_1, Q_3)	1 (1–1)	2 (1–3)	<0.0001
No exacerbations	30 (20)	1 (4)	
1 exacerbation	97 (64)	9 (38)	<0.0001
2 exacerbations	19 (13)	6 (25)	
⩾3 exacerbations	5 (3)	8 (33)	
ISWT distance			
Absolute distance, m, median (Q_1, Q_3)	840 (660, 1050)	630 (440, 775)	<0.001
Percentage of predicted (Q_1 Q_3)	87 (70, 100)	68 (49, 87)	<0.01
ISWT below LLN	35 (23)	11 (46)	0.02
Oxygen saturation ⩾88%	24 (16)	11 (46)	<0.01
VO_2 max, less than LLN[‡]	16 (11)	9 (38)	<0.001
X-ray field score[§]			
Normal	20 (21)	0	
1–25% abnormal	47 (49)	7 (33)	<0.01
26–50% abnormal	21 (22)	8 (38)	
51–75% abnormal	7 (7)	5 (24)	
76–100% abnormal	0	1 (5)	
Major depression[¶]	17 (11)	5 (21)	0.19
PTSD[#]	5 (3)	2 (8)	0.24

[*] A total of 162 of 175 participants completed spirometry.

[†] Moderate obstruction: 50% ⩽ predicted FEV_1 < 80%; severe obstruction: 30% ⩽ predicted FEV_1 < 50%.

[‡] VO_2 max (normal) = 268.6 + (age × −21.1) + (weight 9.2) + (height/100 × 1101.1) + (sex × 535.6)

[§] Totals based on those who performed CXR (*n* = 116).

[¶] Defined as CES-D score >16.

[#] PTSD is defined as PCL score >30.

TB = tuberculosis; CLD = chronic lung disease; Q1 = quarter 1; Q3 = quarter 3; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; LLN = lower limit of normal; CAT = COPD Assessment Test; ISWT = incremental shuttle walk test; VO_2 max = peak oxygen uptake; PTSD = post-traumatic stress disorder; CXR = chest X-ray; CES-D = Center for Epidemiologic Studies Depression Scale; PCL = PTSD Checklist; COPD = chronic obstructive pulmonary disease.

Table A.2

CXR characteristics of the study population[*]

CXR characteristic	Confirmed (*n* = 93) *n* (%)	Unconfirmed (*n* = 23) *n* (%)	*P* value
X-ray field score			
Normal	14 (15)	6 (26)	
1–25% abnormal	44 (47)	10 (44)	

CXR characteristic	Confirmed (*n* = 93) *n* (%)	Unconfirmed (*n* = 23) *n* (%)	*P* value
26–50% abnormal	27 (29)	2 (9)	0.06
51–75% abnormal	7 (8)	5 (22)	
76–100% abnormal	1 (1)	0	
Lung patterns			
Any abnormality	82 (88)	18 (78)	0.31
Chronic pattern[†]	79 (85)	17 (74)	0.21
Ring/tramline opacities	78 (84)	17 (74)	0.27
Non-cavitating nodules	67 (72)	14 (61)	0.30
Volume loss (any)	66 (71)	11 (49)	0.05
Paucity of vessels	46 (49)	9 (39)	0.37
Cavitating nodules	18 (19)	6 (26)	0.48
Consolidation	18 (19)	5 (22)	0.78
Ground glass opacifications	5 (5)	3 (13)	0.19
Pleural effusion	4 (4)	3 (13)	0.12
Pleural calcification	6 (6)	2 (9)	0.67
Fibrosis	0	1 (4)	0.20
Mass	2 (2)	1 (4)	0.49

[*] Totals based on those who performed CXR (*n* = 116).

[†] Ring/tramline opacities, pleural calcification, fibrosis, mild or severe volume loss, hyper-expansion.

CXR = chest radiography.

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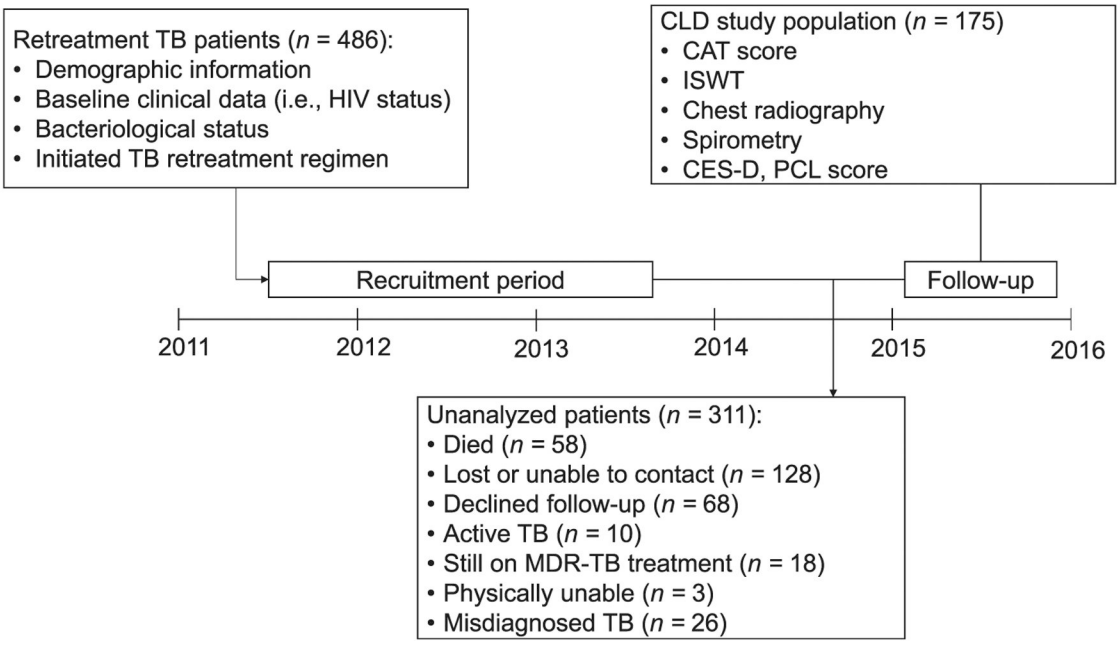

Figure 1.

Study population. TB = tuberculosis; HIV = human immunodeficiency virus; CLD = chronic lung disease; CAT = COPD Assessment Test; ISWT = incremental shuttle walk test; CES-D = Center for Epidemiologic Studies Depression Scale; PCL = PTSD Checklist; MDR-TB multidrug-resistant TB; COPD = chronic obstructive pulmonary disease; PTSD = post-traumatic stress disorder.

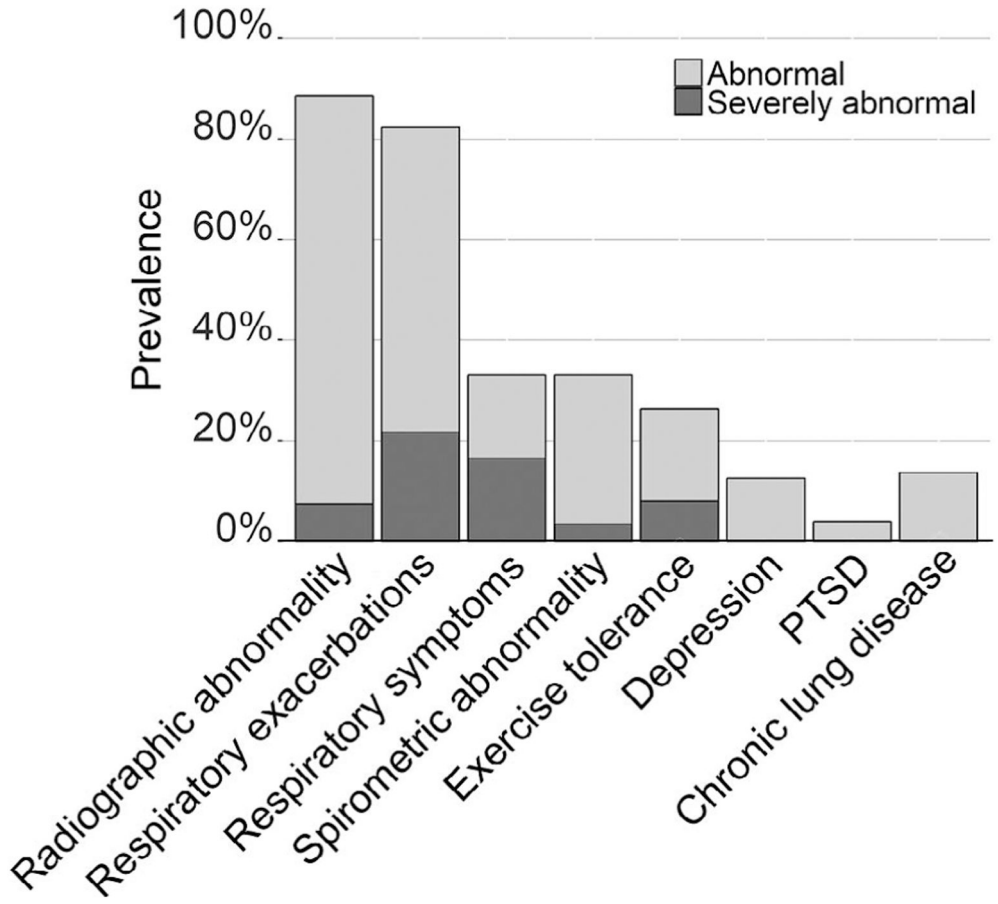

Figure 2.

Respiratory morbidity in individuals previously treated for TB. Parameters demonstrating any abnormality (light gray) and severe abnormality (dark gray) were defined as follows: radiographic abnormalities (any abnormality, field abnormality >50%); history of respiratory exacerbations in the past year (1, ⩾2 exacerbations); spirometric abnormality (FVC or FEV_1, < 80% predicted; FVC or FEV_1 <50% predicted); respiratory symptoms (CAT score 10–15, CAT score ⩾16); exercise tolerance (ISWT LLN; ISWT <50% predicted), depression (Center for Epidemiologic Studies Depression Scale >16) or PTSD (PTSD Checklist score >30); chronic lung disease (see Methods). No severe disease categories were defined for the last three parameters. PTSD = post-traumatic stress disorder; FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; CAT = COPD Assessment Test; ISWT = incremental shuttle walk test; LLN = lower limit of normal; COPD = chronic obstructive pulmonary disease.

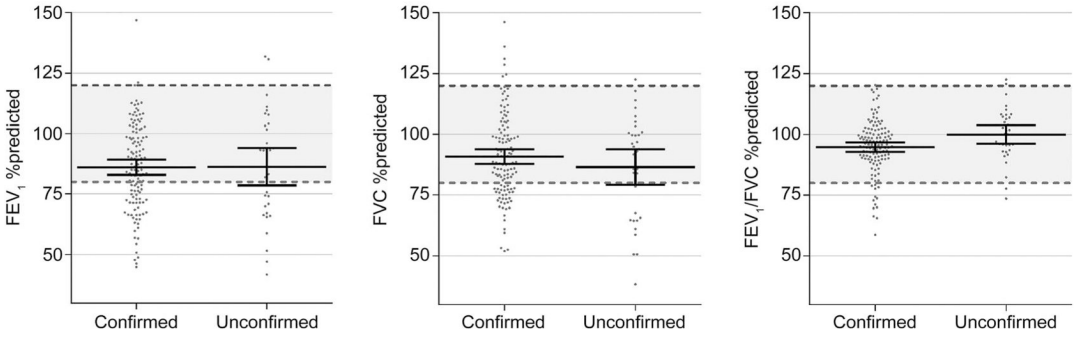

Figure 3.

Post-bronchodilator spirometry assessment, stratified by bacteriologically confirmed vs. unconfirmed, empirically treated TB. Dot plots of participants with spirometry results (n = 162). Dotted lines/shaded area represent the upper limit and lower limit of normal. Bars illustrate the means and standard deviations of each group. FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; TB = tuberculosis.

Table 1

Baseline characteristics of the study population at the time of original TB diagnosis

Characteristic	Confirmed TB (*n* = 138) *n* (%)	Unconfirmed TB (*n* = 37) *n* (%)	*P* value
Age, years, median (Q_1, Q_3)	39 (33, 46)	47 (39, 52)	<0.01
Male	82 (59)	20 (54)	0.45
Interval follow-up time, months, median (Q_1, Q_3)	27 (20, 30)	23 (19, 28)	0.09
Body mass index, kg/m^2			
<18	27 (20)	5 (14)	
18–25	96 (71)	27 (75)	0.68
>25	12 (9)	4 (11)	
TB diagnosis*			
Unconfirmed	0	37 (100)	
Drug-susceptible	51 (37)	0	NA
Rifampin-monoresistant	40 (29)	0	
Multidrug-resistant	47 (34)	0	
Previous TB episodes, *n*, median (Q_1, Q_3)	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 before original treatment initiation (days, median)	135 (65, 304)	311 (79, 437)	0.09
Tobacco smoke exposure			
Ever smoked	55 (40)	13 (35)	0.60
Smoking, years, median (Q_1, Q_3)	19 (14, 28)	28 (27, 32)	<0.01
Current smoker	7 (13)	3 (23)	0.39
Secondhand 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 the time of initial TB diagnosis	35 (25)	8 (22)	0.64

Characteristic	Confirmed TB (*n* = 138) *n* (%)	Unconfirmed TB (*n* = 37) *n* (%)	*P* value
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†			
First	30 (22)	7 (19)	
Second	30 (22)	14 (38)	0.21
Third	30 (22)	8 (22)	
Fourth	47 (34)	8 (22)	

*TB diagnosis using culture or Xpert.

†First quartile (US$0–99/month); second quartile (US$100–199/month); third quartile (US$200–299/month); fourth (US$300–2000/month).

TB = tuberculosis; Q_1 = quartile 1; Q_3 = quartile 3; HIV = human immunodeficiency virus; ART = antiretroviral therapy.

Table 2

TB survivor clinical characteristics at follow-up

Parameter	Confirmed (*n* = 138) *n* (%)	Unconfirmed (*n* = 37) *n* (%)	*P* value
CLD*	14 (10)	10 (27)	<0.01
Spirometry, % predicted, Q_1, Q_3†			
FEV_1	85 (73, 99)	87 (70, 103)	0.99
FVC	89 (78, 100)	92 (66, 100)	0.65
FEV_1: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 (Q_1 Q_3)	7 (4, 10)	13 (9, 17)	<0.0001
<10	105 (76)	12 (32)	
⩾10 < 15	18 (13)	11 (30)	
⩾15 < 20	14 (10)	10 (27)	<0.001
⩾20	1 (1)	4 (11)	
Exacerbations in previous 12 months			
Exacerbations, *n*, (Q_1, Q_3)	1 (0, 1)	1 (1, 2)	<0.01
No exacerbations	29 (21)	2 (5)	
1 exacerbation	84 (61)	22 (59)	
2 exacerbations	19 (14)	6 (16)	<0.01
⩾3 exacerbations	6 (4)	7 (19)	
ISWT distance, m			
Absolute distance, median (Q_1, Q_3)	870 (670, 1070)	610 (450, 780)	<0.0001
Percentage of predicted (Q_1 Q_3)	88 (70, 100)	68 (54, 86)	<0.001

Parameter	Confirmed (*n* = 138) *n* (%)	Unconfirmed (*n* = 37) *n* (%)	*P* value
ISWT below LLN	28 (20)	18 (49)	0.01
Oxygen saturation ⩾ 88%	26 (19)	9 (24)	0.52
VO_2 max, less than LLN[¶]	12 (9)	13 (35)	<0.0001
X-ray field score[#]			
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	
Major depression**	13 (9)	9 (24)	0.01
PTSD[††]	2 (1)	5 (14)	<0.01

[*] 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 previous 12 months; and at least one of the following: 1) FEV_1, FVC, or FEV_1:FVC below LLN; 2) ISWT results <50% predicted; or 3) oxygen desaturation to ⩽88% during exercise testing.

[†] A total of 162 of 175 participants completed spirometry.

[‡] Moderate obstruction: 50% ⩽predicted FEV_1 <80%; severe obstruction: 30% ⩽predicted FEV_1 <50%.

[¶] VO_2 max (normal) = 268.6 + (age * −21.1) + (weight 9.2) + (height/100 * 1101.1) + (sex * 535.6).

[#] Totals based on those who performed CXR (*n* = 116).

[*] Defined as CES-D score >16.

[††] Defined as PCL score > 30.

TB = tuberculosis; CLD = chronic lung disease; Q_1 = Quartile 1; Q_3 = Quartile 3; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; LLN = lower limit of normal; CAT = COPD Assessment Test; ISWT = incremental shuttle walk test; VO_2 max = peak oxygen uptake; PTSD = post-traumatic stress disorder; CXR = chest X-ray; CES-D = Center for Epidemiologic Studies Depression Scale; PCL = PTSD Checklist; COPD = chronic obstructive pulmonary disease.

Table 3

Multivariate risk factors for CLD* among retreatment TB patients

	Multivariate	
Parameter	***P* value**	**RR (95%CI)**
Age, years	0.17	1.0 (0.9–1.1)
Previous TB episodes, *n*		
1 (reference)	—	1
2	0.02	3.2 (1.2–8.4)
⩾3	<0.01	6.2 (1.7–22.7)
Unconfirmed TB†		
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 smoke‡		
No	—	1
Yes	0.16	1.1 (0.5–2.1)

*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 previous 12 months); and at least one of the following: 3i) FEV_1, FVC, or FEV_1:FVC below LLN; ii) ISWT results <50% predicted; or iii) oxygen desaturation to ⩽88% during exercise testing.

†Empirically treated without bacteriological confirmation for the most recent TB episode.

‡Defined as active smoking or ⩾20 years smoking history.

CLD = chronic lung disease; TB = tuberculosis; RR = relative risk; CI = confidence interval; HIV = human immunodeficiency virus; CAT = COPD Assessment Test; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; LLN = lower limit of normal; ISWT = incremental shuttle walk test; COPD = chronic obstructive pulmonary disease.