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Clinical and Imaging Features of Adults with Recurrent Pulmonary Tuberculosis - A Prospective Case-Controlled Study

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ABSTRACT

Background: Recurrent pulmonary tuberculosis (RPTB) is a growing, important and neglected problem affecting treated TB patients and TB health services across the world, particularly in sub-Saharan Africa. Analyses and identification of differences in clinical features between recurrent PTB and newly diagnosed PTB may lead to improved management recommendations.

Methods: Between September 1st 2019 and January 31st 2020, we performed a prospective case controlled study of clinical and imaging features of patients with recurrent pulmonary tuberculosis and compared them with those of newly diagnosed PTB cases. Recurrent PTB was defined as a patient with bacteriologically confirmed active PTB who was previously successfully treated for PTB and was cured. A control was defined as a patient who presents for the first time with bacteriologically confirmed PTB. Clinical and radiological features were assessed and documented. Chi-square and t-test were used to test the difference between proportion and continuous data, respectively. Logistic regression analysis was done to determine factors associated with RPTB using SPSS version 23 software.

Results: A total of 312 patients with PTB were enrolled (104 RPTB cases and 208 newly diagnosed controls). Clinically hemoptysis was more common in RPTB compared to controls 28/104 (26.9%) vs 35/208 (16.8%), P = 0.036. Chest pain was significantly less common among patients with RPTB compared to controls 33 (31.7%) vs 92 (44.2%), P = 0.034. A higher proportion of RPTB presented with cavitation 34/104 (32.7%) compared to control 44/208 (21.2%) P = 0.027. The median score for lung pathology was higher among patients with RPTB (50) compared to controls (30); P = 0.001. Lung function of patients with RPTB at diagnosis of index TB were more likely to show mixed restrictive and obstructive pattern 36/104 (34.6%) compared to controls 31/208 (14.9%). p<0.001. Multivariate analysis showed that patients older than 45 years of age (adjusted odds ratio [aOR]: 3.59, 95% CI: 1.38 – 9.32), those with hemoptysis (aOR 1.96, 95% CI: 1.04 – 3.69) p=0.04) and fibrosis on chest x rays (aOR 2.18, 95% CI: 1.16 – 4.10) were significantly associated with recurrent PTB.

Abbreviations: AFB, Acid Fast Bacilli; ART, Anti-Retroviral Therapy; DM, Diabetes Mellitus; DR–TB, Drug Resistant Tuberculosis; DST, Drug Susceptibility Testing; E, Ethambutol; EPTB, Extra Pulmonary Tuberculosis; FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume; GOLD, Global Initiative for Obstructive Lung Disease; H, Isoniazid; HIV, Human Immunodeficiency Virus; HPF, High Power Field; IBM, International Business Machines Corporation; IDU, Intravenous Drug Use; LAM, Lipoarabinomannan; LFT, Lung Function Test; MDR–TB, Multi Drug Resistance Tuberculosis; MUHAS, Muhimbili University of Health and Allied Sciences; NTLP, National Tuberculosis and Leprosy control Program; PWID, People Who Inject Drugs; PTB, Pulmonary Tuberculosis; RPTB, Recurrent Pulmonary Tuberculosis; RR, Rifampicin Resistant TB; R, Rifampicin; S, Streptomycin; TB, Tuberculosis; WHO, World Health Organization; Z, Pyrazinamide.

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Conclusions: Hemoptysis, lung parenchymal damage, and patients being older than 45 years of age are significant features of RPTB. Management should focus on risk factors for recurrence, and a more holistic model of care to prevent long term lung injury.

BACKGROUND

Tuberculosis (TB) is a curable disease and up to 85% of people who develop active pulmonary TB (PTB) disease can be successfully treated with an anti-TB 6-month drug regimen (World Health Organization, 2020). However, worldwide, TB remains one of the top ten causes of mortality, and the leading infectious cause of death (World Health Organization, 2020). In 2019, the WHO estimated that there were 10 million incident cases of TB of which 1.5 million died. Tuberculosis disease among previously treated individuals constitutes 5–30% of the global TB burden, with higher proportions found in high-TB prevalence settings. In Tanzania, a total of 81,000 cases of all clinical forms of TB were notified in 2019 and a substantial proportion of these were recurrent pulmonary TB (RPTB) cases (World Health Organization, 2020). Recurrent TB patients are defined as patients who were previously treated for TB and cured and then are diagnosed with a recurrent episode of TB (either due to reactivation of the disease or by reinfection (Hermans et al., 2020). Recurrent PTB has been considered to be an indicator of community control of TB and a proxy of TB drug-resistance (Hermans et al., 2020; Gadoev et al., 2017).

The rate of TB recurrence is variable due to differences in epidemiology and risk factors, ranging from 4.9 to 47 per 100.000 populations (Gadoev et al., 2017). Risks for recurrent TB include poor adherence to TB treatment, male gender, poverty and malnutrition; smoking, alcoholism and substance abuse; and other comorbidities such as diabetes mellitus, renal failure, and malignancy (Sonnenberg et al., 2001; Shimeles et al., 2019; Cacho et al., 2007; Anon, 2021a; Yen et al., 2012; Alavi-Naini et al., 2012; Mahishale et al., 2015; Leung et al., 2015; Yoo et al., 2008; Batista et al., 2008; Imtiaz et al., 2017). Recurrent pulmonary tuberculosis (TB) is a neglected and important problem affecting patients and TB health services in sub-Saharan Africa. Despite microbiological cure, each episode of Pulmonary TB (PTB) is associated with scaring and long-term sequelae not fully and systematically addressed by anti-tuberculosis treatment. As such, repeated episodes of PTB predisposes the patient to further lung injury. Analyses and identification of differences in clinical features between new and recurrent cases of TB could identify underlying differences which may lead to improved management recommendations. We performed a prospective case-controlled study of clinical and imaging features of patients with RPTB and compared them with those of newly diagnosed PTB cases.

METHODS

Ethical review

Ethical approval for conducting this research was obtained from the Research Ethical Committee of Muhimbili University of Health and Allied Science (MUHAS) (reference number. DA.287/298/01A). Permission to access health facilities was provided by respective municipal directors for health. All participants provided informed written consent.

Study design and recruitment sites

A case-control study was conducted in Dar es Salaam region, Tanzania between September 2019 to January 2020. Dar es Salaam has the highest TB notifications in Tanzania (20%) (Anon, 2021a). Six clinics with the highest TB notification rates were selected for patient recruitment.

Study participants

Participants were adults (18 years or above), treated at one of the participating facilities and consented to take part in the study. Cases were bacteriological confirmed TB cases previously treated with WHO-recommended standard anti TB and declared cured at end of TB treatment course (Solá et al., 2016). Controls were bacteriologically confirmed TB patients with first ever TB episode. Participants were consecutively enrolled to the study in all study sites until sample size was attained. Interviewer administered questionnaire was used to collect information on socio-demographic characteristics of the participants including age, sex, marital status, economic status and level of education. Other information collected included: Clinical and factors associated with recurrent PTB such as clinical history (fever, loss of weight, cough, hemoptysis and other self-reported symptoms from the participants were documented in the case report form [CRF]). Patient's lifestyle such as smoking history and alcohol consumption were documented (Anon, 2021b). Medical history such as diabetes mellitus and HIV infection was documented.

History, Demographics, Physical examination and anthropometric measurements

All patients had a comprehensive history taken, physical examination performed, anthropometric measurements taken in accordance with standard clinical practice.

Laboratory investigations

Peripheral blood was collected aseptically from the tip of the finger by a picker, a drop of blood was collected for measurement of Fasting FBG, and then was analyzed on-spot using a portable glucometer *(Accucheck Performa®, Roche)*. Diabetes mellitus was defined as fasting blood glucose of 7.0 mmol/l or previous diagnosis of diabetes mellitus with use of medications (American Diabetes Association, 2004).

Spirometry was done using an *EasyOne*™ portable machine and interpreted according to the GOLD guidelines (Strategy et al., 2016).

Chest X-rays

Standard posterior-anterior Chest X - rays were performed on all patients and reviewed by the first author and a senior radiologist, any differences were settled by discussions for consensus. The following abnormalities were recorded, in a prepared x-ray reporting tool. presence of cavity, fibrosis, infiltrates, nodules, collapse, mass, mycetoma, glass ground infiltrations, pleural abnormalities, central structures abnormalities and lymphadenopathy (Ralph et al., 2010).

The extent of lung pathology was graded using a validated Ann Ralph chest radiograph scoring tool, a simple, validated, numerical score (Ralph et al., 2010). A minimum score of 0 (no any radiological abnormality) and a maximum score of 140 points was possible in any chest radiographs depending on the severity of the pathology.

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences version 23 (SPSS Software, Chicago Inc., USA). Continuous variables were summarized using mean ± standard deviation (SD) or median/Interquartile Range (IQR). Categorical variables were expressed as proportion and analyzed using Chi Square test; whereas Continuous variables were analyzed using student t test. Mann Whitney U test was used to test the difference between median chest X ray scores between patients with recurrent PTB and the controls. Risk factors associated with recurrent PTB were analyzed using logistic regression. Multivariate analysis was done to all factors that showed statistics p<0.2 in the univariate analysis plus age and gender. A P value <0.05 was considered statically significant.

RESULTS

Participants' social demographic and clinical characteristics

A total of 312 bacteriological confirmed pulmonary TB patients were recruited; 104 recurrent PTB and 208 control. Overall, most of the participants were males 237(75.9%). Most of the participants were married 136 (43.5%), self-employed 174(55.8%), and 193 (61.9%) attained primary education. 106/312 patients came from Mwananyamala hospital among which 40/106 (37.7%) had recurrent PTB.

Among patients with recurrent PTB 36/104(34.6%) were older than 45 years of age compared to controls 38/208(18.3%) **P < 0.001.** Proportion of married TB patients were similar in both recurrent PTB 45 (43.3%) and controls 91(43.8%) P = 0.31.

Among the recurrent PTB group 66/104 (63.5%) were self-employed compared to controls 108/208 (51.9%) P = 0.06. With respect to family income, the majority of participants had income ranging between two to four hundred thousand Tanzanian Shillings (1 USD is approximately 2300 TZS)) per month 52/104 (50%) with recurrent PTB compared to controls 117/208 (56.3) P = 0.92. Regarding household size, both the patients with recurrent PTB and controls have similar proportion of participants dwelling in households with more than six individuals. More patients with recurrent pulmonary tuberculosis had smoked 56/104 (53.8%) compared to controls (patients with first ever episode of TB in their lifetime) 68/208 (32.7%) P = 0.01.

The proportion of ever alcohol drinkers was higher in recurrent PTB group 69/104 (66.3%) compared to controls 105/208 (50.5%) P = 0.01. Likewise, illicit drug use was commoner in recurrent PTB group 19/104 (18.3%) compared to controls 23/208 (11.1%) however the difference was not statistically significant, P = 0.07. The proportion of HIV was higher in recurrent PTB group 26/104 (25%) compared to controls 45/208 (21.6%) P = 0.50. Although not statistically significant, Diabetes was less common in recurrent PTB 4/104 (3.8%) compared to controls 11/208 (5.3%) P = 0.84 (Table 1).

Clinical presentations of patients with RPTB and controls among adults

The majority of patients with recurrent PTB presented with hemoptysis 28/104 (26.9%) compared to controls 35/208 (16.8%), p = 0.036. On the contrary patients with recurrent PTB were less likely to report chest pain at recruitment 33/104(31.7%) compared to control 92/208 (44.2%) p = 0.034. Furthermore, patients with recurrent pulmonary TB were less likely to present with vomiting 8/104(7.7%) as it was with controls 37/208(17.8%) p = 0.017. In addition, there was no statistically significant difference in the proportions of patients presenting with fever, cough, night sweats, weight loss, difficulty in breathing, loss of appetite between recurrent PTB and new TB groups (Table 2).

Chest radiological features of patients with RPTB and controls

There was a higher proportion of patients with cavities on chest x rays among recurrent PTB group 34/104 (32.7%) compared to 44/208 (21.2%) among the controls, p = 0.027. Fibrosis was a common feature in recurrent PTB 37/104(35.6%) compared to control 37/208(17.8%), p < 0.001. Infiltrations in lung parenchyma were dominant in recurrent PTB group 94/104 (90.4%) than in control 169/208 (81.3%), p = 0.037. Similarly, nodules ≤2 mm were common in recurrent PTB 21/104 (20.2%) compared to controls 22/208(10.6%) p = 0.02. Alveolar patterns of infiltrates were commoner in recurrent PTB 91/104 (87.5%) than in controls 158/208 (76.0%) p = 0.02. There was no difference in distribution of other radiological features including macro-nodules (>2 mm), masses, lung collapse, mycetoma and ground glass appearance between recurrent PTB and control (Table 3).

Distribution of total lung score of patients with RPTB and controls among adults

Total lung score of affected lungs ranged from 0 to 140 with median (IQR) 50 ± (26.0-73.0) for recurrent pulmonary

Table 1
Participants socio-demographic and co-morbidity characteristics of adults with RPTB (N = 104) and controls (N = 208).

Variable	Total n = 312 n (%)	Recurrent PTB (n = 104) n (%)	Control[a] (n = 208) n (%)	P value
Age group (years)				
18–25	52 (16.7)	8 (7.7)	44 (21.2)	<0.001
26–45	186 (59.6)	60 (57.7)	126 (60.6)	
>45	74 (23.7)	36 (34.6)	38 (18.3)	
Gender				
Male	237 (76.0)	86 (82.7)	151 (72.6)	0.05
Female	75 (24.0)	18 (17.3)	57 (27.4)	
Marital status				
Single	115 (36.9)	34 (32.7)	81 (38.9)	0.31
Married	136 (43.6)	45 (43.3)	91 (43.8)	
Widow/widower	61 (19.6)	25 (24.0)	36 (17.3)	
Education level				
No formal education	29 (9.2)	9 (8.7)	20 (9.6)	0.27
Primary	193 (61.9)	72 (69.2)	121 (58.2)	
Secondary and above	90 (28.8)	23 (25.9)	67 (38.5)	
Occupation				
Employed	119 (38.1)	32 (30.8)	87 (41.8)	0.06
Unemployed	19 (6.1)	6 (5.8)	13 (6.3)	
Self employed	174 (55.8)	66 (63.5)	108 (51.9)	
Family income (TZS[b])/month				
<200,000	106 (34.0)	39 (37.5)	67 (32.2)	0.92
200,000–400,000	169 (54.2)	52 (50.0)	117 (56.3)	
>400,000	37 (11.8)	13 (12.5)	24 (11.5)	
Number of members living in a household				
<3 people	90 (28.8)	42 (40.4)	48 (23.1)	0.09
3–6 people	173 (55.4)	45 (43.3)	128 (61.5)	
>6 people	36 (14.8)	15 (14.4)	31 (14.9)	
HIV	71 (22.8)	26 (25.0)	45 (21.6)	0.50
Diabetes (Yes)	15 (4.8)	4 (3.8)	11 (5.3)	0.84
Alcohol use (Yes)	174 (55.8)	69 (66.3)	105 (50.5)	0.01
Ever Cigarette smoker(Yes)	124 (39.7)	56 (53.8)	68 (32.7)	0.01
Mean pack-years of cigarette smoking		6.8 ± 6.7	3.8 ± 14.0	0.17
Illicit drug users (Yes)	42 (13.6)	19 (18.3)	23 (11.1)	0.07

[a] Controls = patients with first tuberculosis episode in their lifetime.
[b] TZS = Tanzanian shillings (1USD = 2300 TZS at the time of the study).

Table 2
Clinical presentation of patients with RPTB and controls among adults.

Variable	Recurrent PTB n = 104 n (%)	Controls[a] n = 208 n (%)	P value
Fever	69 (66.3)	144 (69.2)	0.606
Cough	88 (84.6)	190 (91.3)	0.072
Night sweats	75 (72.1)	154 (74.0)	0.717
Weight loss	79 (76.0)	141 (67.8)	0.136
Hemoptysis	28 (26.9)	35 (16.8)	0.036
Chest pain	33 (31.7)	92 (44.2)	0.034
Difficulty in breathing	36 (34.6)	70 (33.7)	0.866
Loss of appetite	53 (51.0)	111 (53.4)	0.689
Yellow coloration of eyes	2 (25.0)	6 (75.0)	0.610
Nausea	8 (7.7)	31 (14.9)	0.069
Vomiting	8 (7.7)	37 (17.8)	0.017

RPTB = Recurrent Pulmonary Tuberculosis.
[a] Controls = patients with first tuberculosis episode in their lifetime.

tuberculosis whereas median (IQR) was 30 ± (18.0-60.0) for controls. The difference in median between the two groups was statistically significant $p < 0.001$ (Figure 1).

Factors associated with RPTB and controls among adults

At univariate analysis factors associated with recurrent pulmonary TB included; age >45 years was associated with a fivefold increase in recurrent PTB (cOR 5.21, 95% CI (2.16 – 12.57) $p < 0.01$, and middle age patients 26 – 45 years was associated with threefold increase in recurrent PTB (cOR 2.62, 95% CI (1.16 – 5.91) p = 0.02). Moreover, recurrent PTB was also associated with alcohol use (cOR 1.93, 95% CI (1.19 – 3.15) p = 0.008), ever smoker (cOR 2.40, 95% CI (1.48 – 3.89) $p < 0.001$. Patients who presented with hemoptysis were associated with increased recurrent PTB (cOR 1.85, 95% CI (1.05 – 3.28) p = 0.03. Chest pain was associated with reduced risk for recurrent PTB (cOR 0.58, 95% CI (0.36 – 0.97) p = 0.03.

With regards to radiological features, cavitation was associated with an almost twofold increase in recurrent PTB (cOR 1.81 95% CI (1.07 – 3.07) p = 0.028, while fibrosis was also associated with 2.5 increased risk for pulmonary Tuberculosis fibrosis (cOR = 2.55, 95% CI (1.49 – 4.36) p = 0.001. In multivariate analysis, age >45 years was independently associated with fourfold increased risk for recurrent pulmonary TB (aOR = 3.59, 95% CI (1.38 – 9.32) p = 0.01. Similarly, fibrosis was associated with twofold increased the risk for recurrent PTB (aOR 2.18, 95% CI (1.16 – 4.10) p = 0.015. Furthermore, hemoptysis was associated with almost double the likelihood for recurrent PTB (aOR 1.96, 95% CI (1.04 – 3.69) p = 0.04 (Table 4).

Table 3
Chest radiological features of patients with RPTB and controls.

Variable	Recurrent PTB n = 104; n (%)	Controls; n = 208; n (%)	P - value
Cavitation	34 (32.7)	44 (21.2)	0.027
Fibrosis	37 (35.6)	37 (17.8)	<0.001
Infiltrates	94 (90.4)	169 (81.3)	0.037
Nodules ≤2mm	21 (20.2)	22 (10.6)	0.020
Nodules >2mm	12 (11.5)	23 (11.1)	0.899
Mass	1 (1.0)	3 (1.4)	1.000
Mycetoma	2 (1.9)	0 (0.0)	0.110
Collapse	8 (7.7)	9 (4.3)	0.217
Ground-glass attenuation	23 (22.1)	39 (18.8)	0.483
Volume loss	12 (11.5)	14 (6.7)	0.148
Alveolar pattern	91 (87.5)	158 (76.0)	0.017

Controls = patients with first tuberculosis episode in their lifetime.
RPTB = Recurrent Pulmonary Tuberculosis.

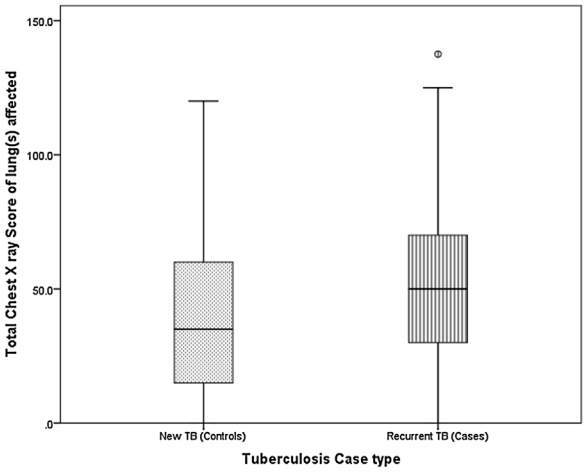

Figure 1. Distributions of total score of affected lungs of patients with RPTB and controls.

DISCUSSION

Our study compared the social, demographic, clinical and radiological features of patients with recurrent pulmonary tuberculosis (RPTB) with those of newly diagnosed PTB cases. There were four significant findings from our study: *First*, Patients with recurrent pulmonary TB have an increased frequency of hemoptysis. *Second*, cavitation, infiltration, and nodules ≤2 mm were the most common radiographic findings in recurrent pulmonary TB participants. *Third*, in patients aged > 45 years, hemoptysis, and fibrosis were independently associated with recurrent PTB. *Fourth*, there was a significant decrease in lung function as observed by higher mixed patterns of both restriction and obstruction in recurrent PTB participants.

Our finding that patients aged above 45 years were three times more risk of RPTB compared to other age groups was similar to a study done in Addis Ababa by Shimeles et al., where 45.8% of patients aged > 45 years had RPTB (Shimeles et al., 2019). This age group is involved in risk social-economic activities and cultural factors including poor health-seeking behaviors which makes them more likely to default from TB treatment (Shimeles et al., 2019). Additionally, our study observed no difference in gender distribution between recurrent and new TB participants. Contrary to other studies, more males had recurrent PTB than females (Mulu et al., 2015; Abal et al., 2001).

Hemoptysis was a major presentation among patients with recurrent pulmonary TB two times more compared to controls. This was attributed to TB sequelae such as bronchiectasis changes and lung cavities which increases chances of hemoptysis (Abal et al., 2001). Hemoptysis has been associated with TB sequelae caused by destruction and structural remodeling of the lung parenchyma and its vasculature. However various studies have reported varied ranges of hemoptysis. Abal and colleagues reported that the majority of patients with recurrent PTB had hemoptysis (Abal et al., 2001). As reported by Prado and colleagues (Prado et al., 2017) no significant differences were seen among other clinical presentations, among RPTB patients and controls. indicating similar underlying inflammatory and immunological in both newly diagnosed PTB and recurrent PTB patients (Leung et al., 2015).

Importantly, radiological changes including cavitation and fibrosis, were more significantly seen in patients with RPTB (32.7% and 35.6% respectively). These findings are similar to another study from South Africa (Ehrlich et al., 2011). In RPTB, fibrosis observed on chest X-ray at presentation may represent

Table 4
Univariate and multivariate factors associated with RPTB and controls in six hospitals in Dar es Salaam.

	Univariate analysis			Multivariate analysis		
Variable	cOR	95% CI	p-value	aOR (World Health Organization, 2020)	95% CI	P-value
Age groups						
>45	5.21	2.16– 12.57	<0.001	3.59	1.38 – 9.32	0.01
18- 45	2.62	1.16 – 5.91	0.020	2.21	0.91 – 4.96	0.07
Gender (Male)	1.80	0.99 – 3.26	0.051	0.97	0.47 – 1.98	0.93
Alcohol use	1.93	1.19 – 3.15	0.008	1.24	0.61 – 2.33	0.51
Ever smoked	2.40	1.48 – 3.89	<0.001	1.87	0.95 – 3.69	0.06
Hemoptysis	1.85	1.05 – 3.28	0.03	1.96	1.04 – 3.69	0.04
HIV	1.21	0.6 – 2.10	0.50	[a]	[a]	[a]
Diabetes	1.06	0.473 – 2.36	0.86	[a]	[a]	[a]
Illicit drug use	1.80	0.93 – 3.48	0.08	1.18	0.53 – 2.57	0.69
Chest pain	0.58	0.36 – 0.97	0.03	0.60	0.35 – 1.02	0.06
Cavitation	1.81	1.07 – 3.07	0.028	1.37	0.76 – 2.48	0.29
Fibrosis	2.55	1.49 – 4.36	0.001	2.18	1.16 – 4.10	0.01
Infiltrate	2.17	1.04 – 4.54	0.040	1.54	0.49 – 4.74	0.46
Nodule ≤2mm	2.14	1.11 – 4.10	0.022	1.51	0.73 – 3.13	0.27
Volume loss	1.81	0.80 – 4.06	0.152	0.99	0.40 – 2.53	0.99
Alveolar pattern	2.22	1.14 – 4.30	0.019	1.10	0.40 – 3.01	0.85

RPTB = Recurrent Pulmonary Tuberculosis.
[a] Did not attain significance level for inclusion in multivariate model.

residual sequela of previous PTB, and cavitation could be a sign of ongoing infection (Naidoo and Dookie, 2018). Furthermore, the difference in radiological features observed by total lung score showed that RPTB patients had more total lung score of affected lungs (median ± IQR, 50 ± (26-60.0). This was comparable to a study by Ralph et al. Ralph and colleagues reported that the tool collates with clinical and microbiological severity (Ralph et al., 2010). CT or PET Scans can identify more cases of extra-pulmonary TB and can detect cryptic changes which may not be visible on chest X-rays. However these imaging facilities are not available (PET) or not accessible for TB diagnosis in our country and many resoource poor regions (Bomanji et al., 2020a; Bomanji et al., 2020b).

Our study found that alcohol users were two times more likely to have RPTB in univariate analysis (cOR 1.93, 95% CI (1.19 - 3.15) p < 0.001) but was not significant in multivariate analysis. In comparison, Lonnroth et al (Baker et al., 2011) and Imtiaz et al (Imtiaz et al., 2017), found alcohol use was associated with three fold increase in recurrent PTB (Baker et al., 2011). This may reflect the fact that alcohol use impairs the immune system resulting in increased susceptibility to TB. In addition, abnormal social behaviors in alcohol users increases risks of TB exposure as well as macro and micro nutrient deficiency which has been studied in Tanzanian population (Aibana et al., 2019).

Notably, we found smoking is associated with the rate of RPTB in univariate analysis with (cOR 2.40, 95% CI (1.48 – 3.89) p < 0.001 for every smoker. Similarly, these findings are similar to various studies that showed significant association between PTB recurrence and smoking. As noted in our study current smoking was associated with twofold increase in RPTB. The effect of smoking in tuberculosis is well established in other studies (Prado et al., 2017; Ehrlich et al., 2011; Baker et al., 2011) both current or former smokers have increased risk of RPTB by 2% to 19% (36.37). It has been postulated that smoking directly destroys lung parenchyma and is linked to altered immune response which disrupt the ciliary function resulting to multiple defects in immune cells such as macrophages, monocytes and CD4 lymphocytes induced by nicotine hence augments the risk for RPTB.

Our study did not find an association of illicit drug use and TB status. Contrary to other studies, which showed association between RPTB and illicit drug use. Illicit drug use has been associated with default to treatment, immunodeficiency including HIV and hepatitis C which together increase the rate of recurrence in TB (Gadoev et al., 2017; Sonnenberg et al., 2001; Cacho et al., 2007). Despite a well-established pathogenesis of the above factors our study could not show such association. This could be accounted for by the low number of the illicit users recruited in the study which was inadequate to show such association.

Notably, the proportion of HIV-TB co-infection was 71 (22.7%) which is comparable to Tanzania national data with co-infection 28.0% (n77). Our study showed no difference in HIV infection between recurrent PTB and new TB. HIV infected patients with recurrent PTB were 26 (25.0%) while new TB 45 (21.6%) p = 0.5. It has been reported that there is nearly three-fold higher incidence of recurrent Pulmonary TB among individuals living with HIV (Paridah et al., 2016). Nevertheless, this fact was not shown in our study. This may be due to the improved joint HIV/TB treatment programs including testing and treating all the TB diagnosed patients during the commencement of TB treatment (Solá et al., 2016).

With the ongoing COVID-19 pandemic now overwhelming health services, patient compliance for both newly diagnosed and recurrent PTB cases may be affected. Retreated cases are at more risk of developing hot spot *Mtb* mutations and increased risk of resistance with poor treatment outcome (Allwood et al., 2021; Kabir et al., 2020). Thus a rise in numbers of cases of MDR-TB or RPTB could be predicted in light of this. Post- TB lung disease is an under recognized Global challenge National guidelines should be updated for heightened awareness of RPTB, MDR-TB and include longer term follow up with monitoring lung function after treatment completion hemoptysis in those aged 45 and over.

Overall our findings suggest that management of patients with PTB should focus on identifying anthropological, demographic, clinical and imaging risk factors for preventing relapse and limiting long term lung damage and functional disability. There is an important need for developing a more holistic approach (Zumla et al., 2020; Harries et al., 2021) for managing PTB patients including host-directed therapies to prevent relapse, recurrent TB and long term sequalae.

Study limitations

We were unable to access baseline CD4 count which rendered it difficult to examine the impact of severe immunosuppressant on

recurrent PTB. The pleurisy due to pneumonia may limit inspiratory effort and hence lead to skew pulmonary function and may be interpreted as restricted. Availability of CT scan would increase identification of subtle lung parenchyma changes.

Strengths of the study

A large study population group from six centers located in three districts of Dar es Salaam. It is a unique that has described the clinical, radiological, and associated factors with recurrent PTB. Additionally, Dar es Salaam is the leading region in Tanzania with the majority of TB patients (Hermans et al., 2020).

CONCLUSIONS

Hemoptysis, lung parenchymal damage, and patients being older than 45 years of age are significant features of recurrent PTB. Other factors associated with recurrent TB include cigarette smoking and alcohol drinking. Long term follow-up of patients after completion of pulmonary TB treatment is important to assess functional disability and detect recurrence of TB early. Management should focus on risk and causative factors for recurrence, and a more holistic model of care to prevent long term lung injury. We recommend that national TB guidelines to propagate longer follow up of patients at appropriate clinics.

Availability of data and materials

The datasets analyzed during this study are available from the corresponding author upon request.

Conflict of interest

The authors declare that they have no competing interests.

Funder role

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Authors' contribution

All authors are part of the Muhimbili University of Health and Allied Sciences TB Research group. TN, MAM, MMM conceived, designed and conducted the study, supervised data collection and analyses. FM, EK, GS, AZ and MM contributed to study design and supervision of data collection and/or data interpretation. Radiological interpretation was done by MM and ZN. TN and MAM drafted the manuscript and all authors contributed to the writing and finalization of the manuscript.

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