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RESEARCH ARTICLE

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The prevalence of pulmonary hypertension after successful tuberculosis treatment in a community sample of adult patients

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Abstract

There are an estimated 155 million survivors of tuberculosis (TB). Clinical experience suggests that post tuberculosis lung disease (PTLD) is an important cause of Group 3 pulmonary hypertension (PH). However, TB is not listed as a cause of PH in most guidelines. A cross-sectional, community-based study was conducted in nonhealthcare seeking adults who had successfully completed TB treatment. Subjects underwent questionnaires, spirometry, a 6-min walk distance test (6MWD) and transthoracic echocardiography (TTE). Screen probable PH was defined on TTE as an estimated pulmonary artery peak systolic pressure (PASP) of ≥40 mmHg. One hundred adults (71 males) were enrolled, with a mean age of 42 years (*SD* 13.8 years) and a median of one TB episode (interquartile range:

Abbreviations: 6MWD, 6-min walking distance test; CLD, chronic lung disease; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FEV_1/FVC, forced expiratory volume in 1 s/forced vital capacity ratio; FEV_1%pred, percentage predicted forced expiratory volume in one second; FVC, forced vital capacity; FVC%pred, percentage predicted forced vital capacity; IVC, inferior vena cava; LA, left atrial; LVEF, left ventricular ejection fraction; MRC, medical research council; PASP, pulmonary artery systolic pressure; PH, pulmonary hypertension; PH-postTB, PH following TB; PTLD, posttuberculosis lung disease; RAP, right atrial pressure; RVID, right ventricular diameter in diastole; TAPSE, tricuspid annular plane systolic excursion; TB, tuberculosis; TRVmax, maximum tricuspid regurgitant velocity; TTE, transthoracic echocardiography.

1–2). Co-morbidities included hypertension (21%), diabetes (16%), human immunodeficiency virus (10%) and asthma/COPD (5%). Only 25% had no residual symptoms after TB. Probable PH was found in 9%, while 7% had borderline raised PASP values (PASP 35–40 mmHg). An association was found between PH and the number of previous TB episodes, with each additional episode of TB increasing the odds of PH-postTB 2.13-fold (confidence interval [CI]: 1.17–3.88; $p = 0.013$). All of those found to have PH were smokers or ex-smokers yielding an unadjusted odds ratio for PH-postTB of 3.67 (95% CI: 0.77–17.46). There was no statistical difference in spirometry or 6MWD, between those with and without PH. Neither symptoms nor co-morbidities demonstrated significant association with PH. PH after TB was a common finding in this community-based population. Further research is needed to confirm and determine the significance of these findings.

KEYWORDS

chronic lung disease, echocardiography, ethnic racial or social disparities in lung disease and treatment, post tuberculosis lung disease, pulmonary hypertension

INTRODUCTION

It is estimated that 1% of the global population have pulmonary hypertension (PH), with an increasing prevalence in those over 65 years of up to 10%.[1] The two most common causes of PH are secondary to left heart disease (Group 2 PH) and chronic lung disease (CLD, Group 3 PH).[1–3] Between 29% and 42% of all cases of PH are secondary to CLD.[4] The causative conditions for Group 3 PH cited in the literature are chronic obstructive pulmonary disease (COPD), interstitial lung disease, obstructive sleep apnea and hypoventilation syndromes.[5] In some high TB burden countries, post tuberculous lung disease has been found to be the third leading cause of group 3 PH, yet it is not mentioned as a cause of PH in the most recent guidelines.[6,7] Globally, it is estimated that there are currently 155 million survivors of TB,[8] however the sequela, including pulmonary hypertension post TB (PH-postTB), may contribute significantly to the unmeasured burden of disease and mortality that TB survivors experience after treatment completion.[9–11]

PH was found in almost 10% of new hospitalized cases of acute pulmonary TB and was associated with a threefold increase in in-hospital mortality.[12] It is uncertain if PH may evolve or improve in the post-treatment period or even develop years after the initial episode of TB. PH-postTB has been described since the 1950s,[13] however, much of the literature on PH-postTB predates the 1980s and was conducted even before the advent of effective chemotherapeutic agents. The development of PH in other non-TB CLD is known to be associated with a poorer prognosis[2,3] and it has been reported in a small study that patients with PH-postTB have increased mortality compared to non-TB related group 3 PH and also had increased readmission rates.[14]

Although PH-postTB is well-recognized by clinicians in high-TB burden areas[6,15,16] all current data are from cohorts influenced by marked selection bias, and rely on patients seeking healthcare and having overt radiological features or clinical features suggestive of PH, implying advanced disease. To our knowledge, there is no data on the prevalence of post-TB PH in nonhealthcare seeking patients after successful treatment completion. However, with the shift towards earlier diagnosis and intervention in all forms of PH, reliable estimation and identification of post-TB PH has become essential.

This study aims to determine the prevalence of screen probable PH in survivors of pulmonary TB, in a randomly selected nonhealthcare-seeking community setting, at least 1 year after treatment completion, and to explore possible associations, risk-factors and effect modifiers for the presence of PH after TB.

METHODS

Study design, setting, and participants

This was a cross-sectional study conducted in a low-to-middle-income suburb (Ravensmead) of Cape Town, Western Cape, South Africa. A complete list of all

patients in the community (diagnosed and treated for TB, between 1 and 5 years before the study) were taken from the National TB register. Of note: Tuberculosis in South Africa is a "notifiable" condition, thus all TB cases treated in the geographical region over the time frame would have been included in the TB register upon new diagnosis and commencement of TB treatment.

A random sample was generated from this list and people were invited to participate in the study during door-to-door visits and thus, they were not healthcare seeking patients.

Only adults older than 18 years, who have provided informed written consent, were enrolled. Specific exclusion criteria were: active malignancy, dementia, patients deemed medically too unstable for enrollment, patients with a known medical condition that would make echocardiographic measurement of the pulmonary pressures unreliable (e.g., pericardial tamponade), and current (active) TB.

Demographic data, previous medical history, a detailed history of TB, including the number of TB episodes (the number of times they were treated for TB), dates of treatment, duration of treatment, as well as symptoms were obtained by conducting questionnaires. All participants underwent lung function testing to assess residual post-TB lung damage using an EasyOne® (NDD Medical Technologies) spirometer by a trained technologist, as well as a 6-min walk distance test (6MWD), according to standardized American Thoracic Society/European Respiratory Society criteria.[17] Low forced vital capacity (FVC) and low forced expiratory volume in 1 s (FEV_1) were defined as values less than 80% predicted using the Global Lung function Initiative (GLI) 2012 reference ranges or less than the lower limit of normal and low FEV/FVC was defined both as a value less than 70% and an FEV1/FVC less than the lower limit of normal.[18]

Subjects underwent transthoracic echocardiography (TTE) as a screening tool for PH. An abbreviated TTE protocol was utilized according to the British Society of Echocardiography TTE guidelines.[19] The pulmonary artery systolic pressure (PASP) was estimated using the modified Bernoulli equation and the regurgitant tricuspid jet velocity (TRV) and adding estimated right atrial pressure (RAP) using the inferior vena cava diameter and collapsibility during inspiration/sniff. Additionally, the tricuspid annular plane systolic excursion (TAPSE), right ventricular diameter in diastole, right ventricular wall motion with tricuspid E/A ratio, tricuspid E/E' ratio, tricuspid S' were measured. Left atrial size and left ventricular diastolic filling pressures were estimated using the ratio of the transmitral E wave velocity and tissue doppler of the mitral valve annulus E'. Left ventricular ejection fraction was also estimated by Simpson's biplane method. PH was defined as screen "probable" if the PASP was 40 mmHg or greater. It was considered as screen "possible PH" if the PASP was 35–39 mmHg with other echocardiographic features of PH present (low TAPSE: <1.7 cm; dilated RV in diastole >4.2 cm; evidence of RV systolic/diastolic dysfunction on tricuspid E/A ratio and tricuspid E/E' ratio and tricuspid S'). A PASP less than 35 mmHg was considered normal. If PH was found screen probable or possible, based on these parameters, assessment for a possible Group 2 PH cause (i.e., secondary to left heart disease) was made and documented, as per guidelines. Diastolic dysfunction was determined by using mitral valve E/A ratio and recorded as present or absent.

Ethical clearance to conduct the study was approved by the Stellenbosch University Human Ethics Research Committee (REF N18/08/091).

Statistical analysis

Means and standard deviations were used to summarize data with a normal distribution, and medians and interquartile ranges (IQR) for data that did not have a normal distribution. Chi-squared and Fisher's exact test were used to compare categorical data. Both adjusted and unadjusted analysis with multivariable logistic regression model for the presence of probable PH in relation to age, sex, smoking status, number of episodes of TB, time since first episode of TB, duration of treatment for TB, degree of pulmonary impairment on spirometry, presence of co-morbid disease and clinical symptomatology and 6MWD were done. Where continuous variables had a normal distribution, *t*-tests were used to compare means, and if not normally distributed, data were analyzed using Mann–Whitney *U*-tests. A significant *p*-value was set at $p < 0.05$. A priori variables (age, sex, and human immunodeficiency virus [HIV] status) were adjusted in the multivariable model combining with factors associated with PH at $p < 0.15$ in unadjusted univariable logistic regression were included in a multivariable model to identify predictor variables associated with PH. Adjusted odds ratios (OR) and their 95% confidence intervals (CI) were used as a measure of association. STATA® version 15 (Statacorp, LLC) was used for data analysis.

RESULTS

Demographic data

Of 103 adults enrolled, three did not attend their echocardiographic appointment and, therefore, only 100

was included in the analysis (Figure 1). Most of the subjects were male ($n = 71$) with a mean age of 42 years (*SD* 13.8 years). A significant proportion were current ($n = 72$) or previous smokers ($n = 12$) with a combined median of 8 pack-years (IQR: 3–22 pack-years). Ten subjects (10%) were HIV positive and all, except one, were receiving antiretroviral treatment, while other comorbidities (Table 1) included hypertension (21%), diabetes (16%), and asthma/COPD (5%). Two subjects had a history of previous multidrug-resistant TB (MDR TB) and none had a history of extensively drug-resistant TB (XDR TB). Only 24 (25%) of patients had no residual symptoms after TB (Table 1).

Spirometry

There was a high burden of spirometric abnormalities, where, 78% of all subjects had abnormal lung functions (67% for those with probable PH) with a low FEV_1 being the most common abnormality (72%). The median FEV_1 was 66.7%pred (IQR: 45.7%–75.2%), and the FVC 71.9% pred (IQR: 61.7%–80.4%). The mean 6MWD was 455 m (*SD* 85.4). Dyspnoea (MRC ≥ 2) was found in 35% of subjects (Table 1). The presence of any spirometric abnormality was associated with the presence of one or more symptoms (OR: 2.96; 95% CI: 0.92–9.42, $p = 0.046$).

Imaging

Only 36 of the participants had chest radiographs available, of which 75% of them had some form of parenchymal lung disease.

Prevalence of PH

On TTE it was possible to estimate PASP in 99 subjects and the remaining subject was classified as having normal echocardiography, as no TR jet was observed and there was no indirect evidence of PH. The mean PASP was 29 mmHg and RAP was estimated in 99 subjects with values ≤5 mmHg in 57 (57%); 5–10 mmHg in 34 (34%); and >10 mmHg in 8 (8%). Probable PH-postTB was observed in 9 subjects, yielding a prevalence of 9% (95% CI: 4.4%–16.7%). None of the subjects with probable PH had evidence of left sided cardiac disease on TTE. A further seven (7%) had borderline raised PASP values of between 35 and 40 mmHg (Table 2 and Figure S2).

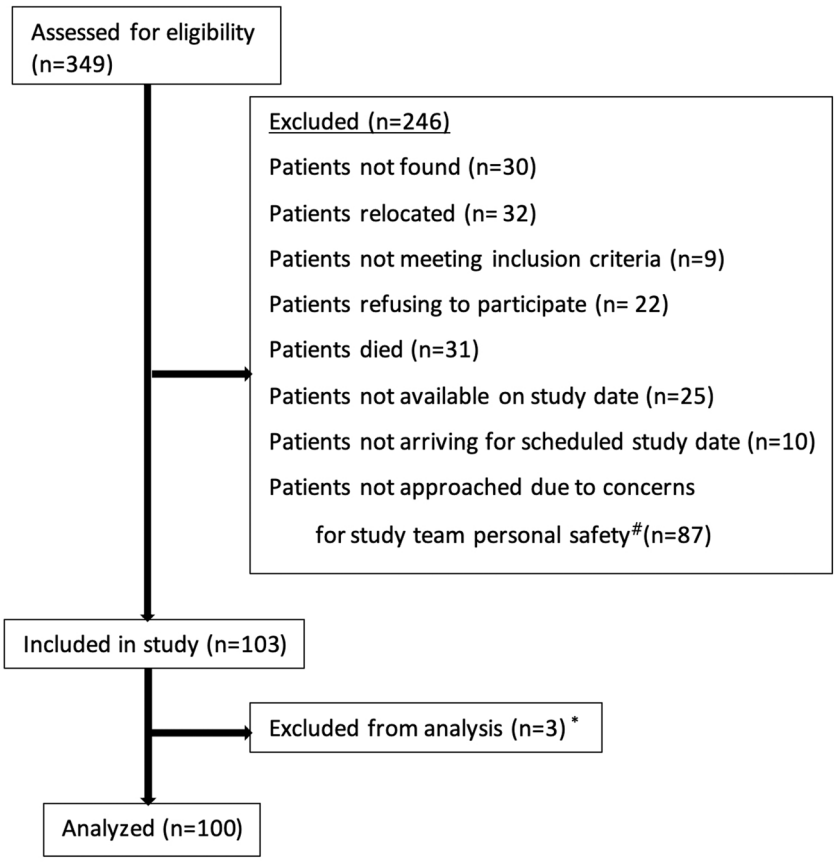

FIGURE 1 Consort diagram of patient recruitment. #In this community certain areas have a high incidence of violence and it was deemed not safe for the recruiters to enter these areas. *The patients did not attend their echocardiographic appointments

TABLE 1 Clinical characteristics of subjects

Characteristics	Value
Age (years)	42 (*SD* 13.8)
Sex	
Male	71 (71%)
Female	29 (29%)
Smoking status	
Never	16 (16%)
Ex-smoker	12 (12%)
Current smokers	72 (72%)
Smoking amount (packyears)	8 (IQR: 3–22)
Time since first TB diagnosis (IQR years)	4 (IQR: 3–6)
Time since last TB diagnosis (IQR years)	3 (IQR: 2–5)
Number of TB episodes (IQR)	1 (IQR: 1–2)
Comorbidities	
HIV	10 (10%)
Hypertension	21 (21%)
Asthma/COPD	5 (5%)
Diabetes	16 (16%)
Symptoms ($n = 97$)	
No symptoms	24 (25.0%)
Cough	44 (45.8%)
Sputum	41 (42.7%)
Wheeze	37 (38.5%)
Dyspnoea present	35 (36.5%)
MRC 1	61 (63.5%)
MRC 2	10 (10.4%)
MRC 3	4 (4.2%)
MRC 4	8 (8.3%)
MRC 5	13 (13.5%)
Spirometry	
FVC (L)	2.99 (*SD*: 0.97)
FVC (% predicted)	71.9 (IQR: 61.7–80.4)
FEV1 (L)	2.11 (*SD*: 0.82)
FEV1 (% predicted)	66.7 (IQR: 45.7–75.2)
FEV1/FVC	0.73 (IQR: 0.63–0.80)
FEF25/75	1.48 (IQR: 0.94–2.45)
Low FVC[a] [*n* (%)]	66 (66%)
Low FEV1[a] [*n* (%)]	72 (72%)
Low ratio FEV1/FVC[b] [*n* (%)]	33 (33%)
FEV1/FVC < LLN [*n* (%)]	37 (37%)
Positive bronchodilator response[c] [*n* (%)]	15 (15%)
Interpretation	
Normal spirometry	22 (22%)
Obstruction	14 (14%)
Possible restriction	33 (33%)
Obstruction with reduced FVC	31 (31%)
6MWD (meters)	455 (*SD*: 85.4)

Note: Data are presented in number and percentages (%); or means with standard deviation (*SD*); or median with interquartile ranges (IQR).

Abbreviations: 6MWD, 6-min walking distance test; FEF, forced expiratory volume; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HIV, human immunodeficiency virus; IQR, interquartile range; LLN, lower limit of normal.

[a]Low FVC and Low FEV1 are values less than the lower limit of normal as defined by GLI 2012 reference ranges.

[b]Low FEV/FVC ratio was defined as values less than 70%.

[c]Positive bronchodilator response means increase in FEV1 >12% and ≥200 ml from baseline FEV1 after inhalation off four puffs of 100 mcg of salbutamol.

Unadjusted associations

A significant association was found between probable PH and the number of previous episodes of TB, with each additional episode of TB increasing the odds of probable PH-postTB 2.13-fold (CI: 1.17–3.88; $p = 0.013$) (Figure S6). Of the patients with probable PH, 67% (6 of 9) had more than one episode of TB, while 29% (2 of 7) of those with possible PH, and 35% (29 of 84) of subjects without PH had more than one episode of TB. Smoking status ($p = 0.082$) and shorter time since last episode of TB ($p = 0.055$) showed a trend to significance (Table 3 and Figure S9). All of the subjects found to have probable PH were smokers or previous smokers yielding an unadjusted odds ratio for probable PH-postTB of 3.67 (95% CI: 0.77–17.46) (Table 4). Other co-morbidities, including HIV, did not demonstrate significant associations with probable PH.

There was no correlation of symptoms, including cough, sputum, wheeze, and dyspnoea with probable PH ($p = 1.00$). Additionally, there was no correlation between probable PH and any of 6MWD ($p = 0.139$) or measured lung function parameters, including FVC (in litres, $p = 0.889$), FEV_1 (in litres, $p = 0.984$), FEV_1/FVC ($p = 0.444$) and forced expiratory $volume_{25–75}$ ($p = 0.857$). Similarly, no associations were found with spirometric

TABLE 2 Echocardiographic data of subjects with probable pulmonary hypertension post TB (PH-postTB) and possible PH-postTB

Age, sex	TRVmax (m/s)	RVP (mmHg)	RAP (mmHg)	PASP (mmHg)	RVID (cm)	Mitral valve E/E′	Diastolic dysfunction Yes/no	LA size (cm)	TAPSE (cm)	Tricuspid E/A	Tricuspid E/E′	Tricuspid TDI S′ (m/s)	LVEF (%)
PH probable													
50,M	3.32	44	10	54	3.9	6	No	2.6	2.7	1.5	–	0.1	64
43,M	3.97	63	10	73	4.6	7.8	No	3.8	2.0	1.0	–	0.1	60
36,F	3.08	38	5	42	2.4	5.5	No	2.8	1.9	1.8	5.5	0.05	–
22,M	3.24	42	5	47	3.2	6.7	No	3.0	1.5	1.5	0.6	0.61	–
53,M	2.87	33	20	53	3.7	4.9	No	2.5	2.9	1.5	5.3	0.13	67
65,M	2.83	32	20	52	–	–	No	4.3	1.9	0.2	–	–	–
55,M	2.96	35	10	45	2.8	6.4	No	2.8	2.0	1.3	5.9	0.12	56
26,M	2.60	27	20	47	3.3	8.0	No	2.0	1.7	2.1	7.8	0.08	65
30,M	2.40	23	20	43	3.86	4.7	No	2.9	2.3	1.4	4.1	0.16	60
Possible PH													
67,M	2.55	26	10	36	3.85	1.2	No	4.4	2.4	1.6	1.3	0.12	–
37,M	2.74	30	5	35	4.1	6.7	No	2.6	2.5	1.5	–	–	65
35,F	2.87	33	5	38	5.0	7.3	No	3.2	2.7	2.3	–	–	60
34,F	2.40	23	15	38	3.58	5.6	No	3.1	2.8	1.2	3.9	0.19	69
24,M	2.55	26	10	36	3.76	4.1	No	3.0	3.6	1.9	4.0	0.12	60
37,M	2.45	24	15	39	3.4	6.7	No	2.5	2.4	1.5	7.4	0.13	64
58,M	2.74	30	5	35	3.6	7.0	No	2.3	2.6	1.6	8.7	0.12	66

Abbreviations: LA, left atrial; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; PH, pulmonary hypertension; RAP, right atrial pressure; RVID, right ventricular diameter in diastole; RVP, right ventricular pressure; TAPSE, tricuspid annular plane systolic excursion; TRVmax, maximum tricuspid regurgitant velocity.

TABLE 3 Comparison of patients with and without probable pulmonary hypertension

Clinical characteristics	No PH ($n = 91$)	Probable PH ($n = 9$)	p-value
Age (years)	40 (IQR: 30–55)	40 (IQR: 30–54)	0.933
Sex			0.215
Male	63 (69.2%)	8 (88.9%)	
Female	28 (30.8%)	1 (11.1%)	
Smoking status			0.082
Nonsmoker	16 (17.6%)	0 (0%)	
Previous smoker	9 (9.9%)	3 (33.3%)	
Current smoker	66 (72.5%)	6 (66.7%)	
Smoking amount (packyears)	7.5 (IQR: 3–22)	10.5 (IQR: 3–12.5)	0.988
Comorbidities			
HIV	8 (8.9%)	2 (22.2%)	0.194
Hypertension	19 (20.9%)	2 (22.2%)	0.925
Asthma/COPD	5 (5.5%)	0 (0%)	1.0
Diabetes	14 (15.4%)	2 (22.2%)	0.633
Time since first TB diagnosis (years)	4 (IQR: 3–6)	5 (IQR: 2–13.5)	0.7
Time since last TB diagnosis (years)	3 (IQR: 2–5)	1 (IQR: 1–4)	0.055
Number of TB episodes	1 (IQR: 1–2)	2 (IQR 1–3)	0.019
Symptoms ($n = 97$)			
No symptoms	21 (63.6%)	3 (75.0%)	1.00
Cough	41 (46.1%)	3 (42.9%)	1.00
Sputum	38 (42.7%)	3 (42.9%)	1.00
Wheeze	35 (39.3%)	2 (28.6%)	0.703
Dyspnoea present	32 (36.0%)	3 (42.9%)	0.703
MRC 2	10 (11.2%)	0 (0%)	
MRC 3	3 (3.8%)	1 (14.3%)	
MRC 4	7 (7.9%)	1 (14.3%)	
MRC 5	12 (13.5%)	1 (14.3%)	
Spirometry			
FVC (L)	2.9 (*SD*: 0.99)	3.03 (*SD*: 0.72)	0.889
FVC (% predicted)	72 (IQR: 62.8–80.4)	71.7 (IQR: 53.8–80.3)	0.740
FEV1 (L)	2.11 (*SD*: 0.83)	2.12 (*SD*: 0.78)	0.984
FEV1 (% predicted)	66.5 (IQR: 46.8–75.8)	66.7 (IQR: 46.7–75.2)	0.870
FEV1/FVC	0.73 (IQR: 0.63–0.82)	0.70 (IQR: 0.66–0.73)	0.444
FEF25/75	1.47 (IQR: 0.9–2.47)	1.48 (IQR:1.12–1.62)	0.857
Low FVC[a,b]	61 (67.0%)	5 (55.6%)	0.485
Low FEV1[a]	66 (72.5%)	6 (66.7%)	0.707

(Continues)

TABLE 3 (Continued)

Clinical characteristics	No PH ($n = 91$)	Probable PH ($n = 9$)	p-value
Low ratio FEV1/FVC (< 70%)	29 (31.9%)	4 (44.4%)	0.472
Low ratio FEV1/FVC (< LLN)	33 (36.3%)	4 (44.4%)	0.722
Positive bronchodilator response[b]	15 (20.0%)	0 (0%)	0.340
Interpretation			0.180
Normal	19 (21%)	3 (33%)	
Obstruction	12 (13%)	2 (22%)	
Possible restriction	33 (36%)	0 (0%)	
Obstruction with reduced FVC	27 (30%)	4 (44%)	
6MWD	450.3 (*SD*: 81.4)	494.9 (*SD*: 111.3)	0.139
Echocardiographic details			
PASP (mmHg)	27 (IQR: 23–31)	47 (IQR: 45–53)	<0.001
TRVmax (m/s)	2.18 (IQR: 1.94–2.43)	2.96 (IQR: 2.83–3.24)	<0.001
RAP (mmHg)	5 (IQR: 5–10)	10 (IQR: 10–20)	0.002
TAPSE (cm)	2.35 (*SD*: 0.5)	2.10 (*SD*: 0.45)	0.158
RVID (cm)	3.41 (*SD*: 0.49)	3.47 (*SD*: 0.69)	0.753
E/E' ratio MV	6.7 (*SD*: 2.1)	5.5 (*SD*: 2.3)	0.132
LVEF (%)	61.2 (*SD*: 6.3)	61.2 (*SD*: 5.0)	0.978

Note: Data are presented in number and percentages (%); or means with standard deviation (*SD*); or median with interquartile ranges (IQR).

Abbreviations: 6MWD, 6-min walking distance test; FEF, forced expiratory volume; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HIV, human immunodeficiency virus; IQR, interquartile range; LLN, lower limit of normal; LVEF, left ventricular ejection fraction; PH, pulmonary hypertension.

[a]Low FVC and Low FEV1 are values less than the lower limit of normal as defined by GLI 2012 reference ranges.

[b]Positive bronchodilator response means increase in FEV1 >12% and ≥200 ml from baseline FEV1 after inhalation off four puffs of 100 mcg of salbutamol.

values (Table 3, Figures S3–S5, Figures S7 and S8) when analysed as a percentage of predicted (%pred).

Assessment of correlation with TRVmax was performed against a range of other parameters, thereby excluding the contribution of echocardiographic overestimation of RAP in PASP calculations. Similarly, no significant correlation between TRVmax and any of age, FEV1/FVC, FEV_1 (%pred), FVC (%pred) and 6MWD were found (Table 5 and Figures S10–12).

Adjusted analysis

A multivariable logistic regression model exploration yielded a best model analysis that included: the number of previous TB episodes, sex, age, and HIV status. In this model, the number of previous episodes of TB yielded a 2.26 odds of having probable PH-postTB (adjusted OR: 2.26 [95% CI: 1.03–4.98]) (Table 4). Smoking status was not included in the multivariate analysis models, as the very high prevalence of previous or current smoking in our population, made the inclusion redundant.

DISCUSSION

In this randomly-selected, community sample of 100 adult patients who have completed TB treatment at least 1 year before enrollment, probable PH prevalence was 9%, with a further 7% having borderline raised values. An increased number of TB episodes was significantly associated with probable PH, while cigarette smoking

TABLE 4 Univariate/multivariate analysis for probable pulmonary hypertension post TB

Variables	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Smoking previous/ current	3.67 (0.77–17.46)	0.172	–	–
Number of previous TB episodes	2.13 (1.17–3.88)	0.013	2.26 (1.03–4.98)	0.043
Time since first TB diagnosis	1.04 (0.97–1.12)	0.291	–	–
Hypertension	1.08 (0.21–5.69)	0.925	–	–
Sex: female	0.28 (0.03–2.38)	0.245	0.56 (0.05–6.07)	0.637
Age	1.00 (0.95–1.05)	0.973	0.98 (0.89–1.07)	0.638
HIV status: positive	3.67 (0.54–18.55)	0.201	2.23 (0.28–17.9)	0.451

Note: Multivariate analysis adjusted for number of previous TB episodes, sex, age, and HIV status.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; TB, tuberculosis.

TABLE 5 Correlations of age, FEV1/FVC ratio, FEV1 (%pred), FVC (%pred), and 6MWD with TRVmax

Variable	Correlation coefficient	*p*-value
Age	0.11	0.281
FEV/FVC ratio	−0.087	0.443
FEV1 (%pred)	−0.066	0.563
FVC (%pred)	−0.06	0.598
6MWD	0.129	0.244

Note: Correlations of age, forced expiratory volume in 1 s/forced vital capacity ratio, 6-min walking distance, maximum tricuspid regurgitant velocity.

Abbreviations: 6MWD, 6-min walking distance test; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; TRVmax, maximum tricuspid regurgitant velocity.

and shorter times from the last episode of TB showed trends to significant associations. Spirometric measures of lung damage (reduced FVC, FEV_1 and FEV_1/FVC ratio), although common, were surprisingly not associated with the finding of probable PH, neither was 6MWD, age or HIV status.

Marjani et al.,[12] found 9% of 777 patients admitted with TB to have PH on TTE, however, they assessed patients at the time of TB treatment and only included patients with disease severe enough to warrant inpatient treatment, thus limiting the applicability to both less severe as well as post-TB patients. Although right heart catheterization is the gold standard to establish the diagnosis of PH, this is not commonly available in low-to-middle income countries and it therefore remains an important noninvasive screening tool.[20] Utilizing TTE for screening requires an understanding that echocardiographic measurements rely on assumptions and are limited by well described measurement errors for TTE. Specifically, TTE has a propensity to not only overestimate pressures, but can also underestimate the pressures while not differentiating between Groups 2 and 3 PH.[21] Examination of the right heart may prove difficult with suboptimal views, especially in patients with altered anatomy and destroyed lungs due to TB. The PASP remains only an estimation using the tricuspid regurgitant jet and RAP estimate.[22] The quality of the acquired continuous wave Doppler signal of the tricuspid regurgitant jet is an important factor in underestimation of pulmonary artery pressures[23–26] and the traditional classification into 5 mmHg ranges for use of RAP does not always correlate well with invasive measurement during right heart catheterization.[27] It is possible that the one patient in which PASP could not be estimated due to insufficient TR jet could have been misclassified, as up to 25% of patients with PH may have an insufficient TR jet for estimation of PASP.[28] Echocardiographic abnormalities may be subtle in early disease, and measurements beyond a simple PASP derived from a TR jet and RAP is needed, as advised in the recent ERS guideline on classification into low, intermediate and high probability for PH.[28,29]

Traditionally a PASP cut-off point of 40 mmHg has been used to define PH on TTE, corresponding to a mean pulmonary artery pressure (mPAP) of greater than or equal to 25 mmHg measured by right heart catheterization.[30,31] However, subsequent to writing of this protocol, the mPAP used to define PH, has been lowered from 25 to 20 mmHg,[7,29] this is estimated to equate to an PASP of 30 mmHg.[31] Thus, it is possible that many of the 7% of patients in our study with borderline raised PASP values, could now be reclassified as mild PH if the cutoff points

for TTE diagnosis of PH is also lowered. However in Group 3 PH many clinicians will use a mPAP of 35 mmHg to define severe disease.[32] This corresponds to an echocardiographic PASP of 54 mmHg.[31] Thus lowering the definition of PH, will technically increase the number of patients with probable PH in our study, though the number of patients with clinically severe disease will likely remain the same. The number of patients with PASP >50 mmHg in this study was four (4%). However, even mild PH has been associated with increased mortality[33] and thus the momentum is towards earlier diagnosis and intervention in all forms of PH, including that secondary to CLD.

The unexpectedly high prevalence of probable PH in this nonhealthcare seeking population, has important implications for the epidemiology of PH secondary to CLD. To-date, TB and PH-postTB has been omitted from guidelines as a potential cause for Group 3 PH,[7,29] compounding neglect for this condition. Certainly, in studies from medium TB burden countries 28%–39% of PH-CLD were due to PH-postTB,[6,14] and had both higher mortality and readmissions rates compared to other causes of group 3 PH.[14]

Although much work has been performed on PH secondary to COPD, the precise mechanisms following TB remain elusive. There are several potential mechanisms for the development of PH-postTB. Perhaps the most widely considered mechanism is the destruction and occlusions of the pulmonary arterial bed that occurs concomitant with the parenchymal destruction.[34] Our data found a surprising lack of association between spirometric measurements and the presence of probable PH, suggesting that fibrosis and parenchymal destruction were not a primary mechanism in our population. In contrast, recurrent TB, with its increased destructive potential, was significantly associated with probable PH in our population. This paradox needs consideration. Post-TB lung disease is known to be a complex heterogenous group of phenotypes, including both restrictive and obstructive, parenchymal and airway components, that may differ both between individuals, as well as within different regions of the lungs of an individual.[34,35] Chest radiograph data was not available in all our subjects, as this is not routinely performed at the diagnosis of TB on sputum at primary care level in South Africa. Other markers of lung damage and PH like pulmonary artery diameter on CT and diffusion capacity tests were also not available for our cohort. It has been reported that up to 70% of patients with prior TB have some form of fibrosis on their chest radiographs.[36] However, in post-TB lung disease, chest radiography has been observed to be less sensitive than spirometry in detecting residual abnormalities, particularly obstructive defects.[37] For this reason, we chose to utilize spirometry as the primary marker of lung damage. Our study contrasts somewhat with a series of 14 patients with TB related PH, 86% of whom had fibrosis or fibrocavitatory changes on their chest radiographs,[38] implying that structural damage plays a role, with the caveat of significant selection bias in this series.

However, it is doubtful whether fibrotic destruction of the vascular bed during TB is the sole mechanism at play, as surgical pneumonectomy for non-TB indications removes half of the vascular bed, yet does not inevitably result in elevation of pulmonary arterial pressures.[39] It should be considered whether the additive and opposing effects of fibrosis (restriction) in combination with obstruction may cause "pseudonormalisation" of spirometry in post-TB lung disease of certain individuals. This may be analogous to the high proportions of PH seen in combined pulmonary fibrosis and emphysema (CPFE), where spirometry is frequently disproportionately normal in a patient who is severely dyspnoeic.[40] Again, this is an unlikely explanation in our post-TB population, as the expected hallmark of severe dyspnea (as seen in CPFE), was not observed in our probable PH-postTB patients, and there was a lack of association between 6MWD and the presence of probable PH.

Chronic thromboembolism or the development of in situ pulmonary thrombosis may contribute to the observed PH[41] and certainly there is an association between acute TB and PE.[42] Finally, increased blood flow through a reduced pulmonary vascular bed may, over time, induce vascular changes similar to those seen in idiopathic pulmonary arterial hypertension.[34] It is plausible that acute TB elicits arterial changes which lessen over time, however in our study, patients with probable PH also had a numerically longer time since their first episode of TB, and a significantly increased number of episodes of TB, potentially accounting for this unexpected inverse association. Furthermore, approximately 20% of our original random sample of 349 patients had either died (9%) or were not found (9%) (Figure 1)—a noteworthy finding in its own right. It is now known that mortality is increased post-TB possibly through respiratory and nonrespiratory mechanisms,[9] and it appears that PH-postTB may be associated with a threefold increased mortality compared to nontuberculosis related PH.[14] Thus, vascular changes and remodeling that evolve over time is a hypothesis that also warrants further study.

It is important to consider the role of other potentially confounding or effect modifying factors in these data. Our study included a higher proportion of males, which mirrors the male TB predominance well documented in low-to-middle income high-TB burden countries.[43]

Interestingly, HIV—a cause of PH in its own right—was found in 10% of our population, but demonstrated no association with probable PH-postTB. It is possible that uncontrolled HIV or HIV related PH may have added to early mortality with the initial TB episodes, thereby excluding these patients from this study, or immune dysregulation may be a protective factor in the development of PH-postTB. Further study in HIV-positive patients with PH during the initial TB episode as well as follow-up thereafter for the development of PH-postTB are needed. Cigarette smoking (ever smokers) was reported by 84% of our population, and apart from being a primary cause of chronic lung damage and disease, is associated with increased risk of both TB itself, and a decrease in treatment success rates.[44] Although only a nonsignificant trend to association between smoking and probable PH was noted in unadjusted analysis, the high proportion of smokers in this study, makes isolation of the contributing role for smoking difficult, both in the development of PH and the high proportion of lung function abnormalities.

An important implication of this study's findings is how it relates to screening patients for PH-postTB. Despite a high proportion of our study population having abnormal lung function, they had good functional reserve as reflected by 6MWD with relatively few symptoms. This lack of correlation between PH, symptoms, lung function and 6MWD is important in that they do not appear to be useful in identifying patients at risk of PH-postTB during screening. However, due to small sample size our correlation estimates may be biased, thus we need a larger sample size to have a better understanding of the relationship between PH symptoms. Further data in other post-TB populations are needed to decide if a case could be made for screening for PH in all post-TB patients, to identify PH earlier in the disease process before right ventricular failure ensues.

Strengths and limitations

To our knowledge, this is the first study that assessed for PH more than 1 year after an acute TB episode, and approached subjects in the community, using a prespecified random sampling framework. However, death, loss to follow-up and inability to recruit due to concerns around staff personal safety, could have introduced selection bias, while the demographics of our population, particularly in relation to smoking and HIV status, may not be applicable to all post-TB population groups. Although TTE is the most commonly utilized screening method for PH, we acknowledge that right heart catheterization is the gold standard for accurately diagnosing PH and that our estimates may be subject to the well described measurement errors for TTE. Finally, our protocol was written and study initiated before the publication of a reduction in pressure thresholds for PH, and therefore future studies should consider the updated guidelines, as this may influence PH prevalence.

CONCLUSION

In conclusion, screen probable PH-postTB was a common finding in our community-based adult population. These findings warrant further study of PH-postTB, including prospective cohort studies both with TTE and right heart catheterization, both to confirm these estimates and to better elucidate disease mechanisms. Importantly, long-term outcomes including health-care resource utilization and mortality warrant exploration as do potential treatment options. This report provides further impetus for research into PH-postTB which may be one of the most important and underappreciated causes of Group 3 PH worldwide.

AUTHOR CONTRIBUTIONS

Elizabeth Louw and **Brian Allwood**: were involved in the conceptualization, study design, data collection and drafting of the original manuscript. **Lovemore Sigwadhi**: did data analysis and figures. **Nicola Baines**: did project administration and data curation. **Coenraad Koegelenberg, Elvis Irusen, Steven Nathan, Richard Channick, Anton Doubell, Gerald Maarman, Muhammad Osman**: contributed to the review and editing of final manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ETHICS STATEMENT

This study was approved by the Human Research Ethics Committee of Stellenbosch University (REF N18/08/091) and was conducted in accordance with the Declaration of Helsinki. All patients included gave written informed consent.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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