Pulmonary hypertension in adults completing tuberculosis treatment

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Background. Pulmonary hypertension (PH) after tuberculosis (TB) is typically not included among the chronic lung diseases causing PH (group 3 PH), with few data available to support the inclusion.
Objectives. To determine the prevalence of PH in an adult population completing TB treatment.
Methods. This single-centre, cross-sectional study only included patients with their first documented episode of TB, and who were in the second half of treatment or had recently completed treatment. PH was assessed using transthoracic echocardiography. Questionnaires were completed, and spirometry and a 6-minute walk test were performed.
Results. One hundred patients were enrolled, with a mean age of 37.1 years, of whom 58% were male and 46% HIV positive. The median time since initiation of TB treatment was 22 weeks. The mean (standard deviation) measured right ventricular systolic pressure (RVSP) was 23.6 (6.24) mmHg. One participant had PH (defined as RVSP ≥40 mmHg; 95% confidence interval (CI) 0.0 - 3.0) and a further 3 had possible PH (RVSP ≥35 and <40 mmHg), with a combined PH prevalence of 4% (95% CI 0.2 - 7.8). Airflow obstruction on spirometry was found in 13.3% of 98 patients, while 25.5% had a reduced forced vital capacity. There was no association between RVSP or PH/possible PH and sex, age, HIV status, systemic hypertension, spirometry measurements or 6-minute walking distance. Smoking status was associated with RVSP, but not with the presence of PH/possible PH.
Conclusion. There was a significant prevalence of PH in this preliminary study of predominantly young patients completing treatment for a first episode of TB. Larger and more detailed studies are warranted.
Keywords. Post-tuberculosis, pulmonary hypertension, echocardiography, tuberculosis, cor pulmonale.

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Study synopsis
What the study adds. Of 100 adult patients with their first episode of tuberculosis (TB) who underwent echocardiograms near the end of treatment completion to determine the prevalence of pulmonary hypertension (PH), 1 (1%) had PH and a further 3 (3%) had possible PH. There was no association between sex, age, HIV status, lung function or 6-minute walking distance and the presence of PH. The study adds to the growing awareness of the association of TB with pulmonary vascular disease. It shows that even in a young population with a first episode of TB treated in an ambulatory setting, there is a significant prevalence of PH on treatment completion.
Implications of the findings. Given that 10.6 million people acquire TB annually, the absolute global burden of cases with PH is likely to be high, but is underappreciated to date. Further work is urgently needed in this field.

Pulmonary hypertension (PH), now defined as a mean pulmonary artery pressure (PAP) >20 mmHg, is estimated to affect ~1% of the global population.[1] PH occurring in the context of chronic lung diseases (CLDs) is classified as group 3 PH or CLD-associated PH (CLD-PH), and is the second most common cause of PH after left heart disease, accounting for ~8% of all PH cases.[2,3] The most recent guidelines cite chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) as common causes of CLD-PH, yet omit post-tuberculosis (TB) lung disease as a cause.[1,2,4]

There are an estimated 155 million survivors of TB alive today,[5] mainly living in low- and middle-income countries, and pulmonary vascular complications after TB have been named as one of the post-TB clinical syndromes.[6] However, very little is known about PH either occurring during active TB or developing after TB treatment completion, and the pathogenesis thereof. The development of right ventricular (RV) failure following TB was documented in the 1950s, yet disappeared from the literature for almost 5 decades.[7,8] More recently, a study from China estimated that 39% of CLD-PH cases could be attributed to previous TB,[9] and it has been our anecdotal clinical experience that the majority of cases of CLD-PH in South Africa (SA) are due to previous TB.[10] One study described elevated PAP in 9.5% of 777 recently diagnosed hospitalised patients with pulmonary TB,[11] and another found PH in 72 of 76 post-TB patients who presented with chronic symptoms.[12] However, both studies had significant selection bias, thereby limiting extrapolation of the findings to TB patients in general.

Raised PAP in the context of other CLD (e.g. COPD and ILD) heralds a poor prognosis, prompting a shift in the PH literature towards early diagnosis of CLD-PH.[2] Whether this poor prognosis is true of post-TB PH is not known. However, limited data suggest that this may indeed be the case, with a small single-centre study concluding that the median survival following an episode of TB was 10 months, if the echocardiographic estimates of PAP were raised.[13]

Previous TB may yet prove to be one of the most important causes of CLD-PH globally, given the high burden of TB in low- and middle-income countries, but many important questions remain unanswered. The aim of this study was to determine the prevalence of PH, assessed using echocardiography, in an adult population completing ambulatory TB treatment, and to assess associated risk factors.

Methods

This was a single-centre, cross-sectional study of adults attending an outpatient community TB clinic in Khayelitsha, Cape Town, SA. All participants were at least 18 years old and had their first episode of microbiologically confirmed pulmonary TB. They attended for a single study visit near treatment completion, after at least 5 months of anti-TB therapy and not longer than 3 months after treatment cessation. Patients were excluded if they had any known pre-existing heart disease.

The primary outcome was the presence of PH on echocardiography. The secondary outcomes were the association of PH with spirometric measurements, 6-minute walking distance (6MWD) and comorbidities.

All participants completed symptom questionnaires, did a 6-minute walk test and underwent spirometry according to the American Thoracic Society/European Respiratory Society guideline.[14] Transthoracic echocardiograms were conducted by a single trained echocardiographer and reviewed by a single cardiology consultant following the British Society of Transthoracic Echocardiography guideline.[15] The RV systolic pressure (RVSP) was estimated using the maximum velocity (Vmax) of tricuspid regurgitation (TR) and applying the modified Bernoulli equation to determine the pressure difference between the right-sided chambers and adding the estimated right atrial pressure (RAP). The RAP was estimated using the diameter changes of the inferior vena cava during sniffing.[15] The tricuspid annular plane systolic excursion (TAPSE) and RV wall motion were recorded. PH was diagnosed if the RVSP was ≥40 mmHg in the absence of RV outflow obstruction (including pulmonary stenosis), and when the other features suggesting PH were present (reduced TAPSE, RV dilation, septal wall motion abnormality). 'Possible PH' was defined as an RVSP ≥35 and <40 mmHg. An RVSP <35 mmHg was considered normal. In patients without TR, pulmonary regurgitation (PR) was used to estimated RVSP. In the absence of both TR and PR, the RVSP was considered normal if the RAP was not elevated, the right atrium was not dilated and the RV Tei index was <0.4.

Sample size calculations estimated that 42 participants were required to detect a 10% proportion of participants with PH with a power of 0.9 and a significance level of 0.05 on a presumed population prevalence of 1%. To detect a prevalence <10%, we aimed to recruit 100 participants. Statistical analysis was performed for the outcome variables (RVSP and presence of PH and possible PH) using standard parametric and non-parametric measures of comparison. Fisher's exact test was used to explore the effect of predictor variables on the presence of definite and possible PH. Associations of echocardiography findings and predictor variables were initially assessed visually and then by median regression analysis. Significance was determined at a p-value <0.05. Analysis was conducted using Stata 15 (2017) (StataCorp, USA).

Ethical approval to conduct the study was obtained from the Stellenbosch University Human Ethics Research Committee (ref. no. N16/01/11). All participants provided written informed consent.

Results

Demographics

A total of 100 patients were recruited between April and November 2016. The mean age was 37.1 years (range 18 - 73), and 58% were male; 46% were HIV positive, with a median (interquartile range) CD4 count of 142 (56 - 253) cells/μL for the 30 participants whose count was known. The time from initiation of TB treatment to recruitment was a median of 22 weeks (14 - 37 weeks minimum to maximum). All the participants were black Africans. Two participants had systemic hypertension and one had diabetes, no participant reported a history of underlying heart disease or venous thromboembolism, and 54% of participants were never smokers (Table 1).

Echocardiography results

It was possible to estimate the RVSP in 72 participants. The remainder did not have a TR or PR jet, and the RVSP was assumed to be normal. The mean (standard deviation (SD)) RVSP was 23.6 (6.24) mmHg. RAP was estimated in 99 participants: in 92 (92.9%) it was <5 mmHg, in 5 (5.1%) 5 - 10 mmHg, and in 2 (2.0%) >10 mmHg. TAPSE of <17 mm was found in 3 of 98 participants (3.1%) (Fig. 1).

Table 1. Demographics and clinical characteristics of the study participants (*N*=100)

Variable	*n* (%)*
Age (years), mean (SD)	37.1 (12.4)
Male sex	58 (58)
Black African	100 (100)
Comorbidities	
HIV	
Negative	53 (53)
Unknown	1 (1)
Positive	46 (46)
On ART	46
CD4 count known	30
Nadir CD4 count (cells/μL), median (IQR)	142 (56 - 253)
Hypertension	2 (2)
Diabetes mellitus	1 (1)
Previous venous thromboembolism	0
Known heart disease†	0
Previous episode of TB†	0
BMI (kg/m²), mean (SD)	24.3 (5.2)
Smoking status	
Never	54 (54)
Ex-smoker	31 (31)
Current	15 (15)

SD = standard deviation; ART = antiretroviral therapy; IQR = interquartile range; TB = tuberculosis.
*Except where otherwise indicated.
†An exclusion criterion.

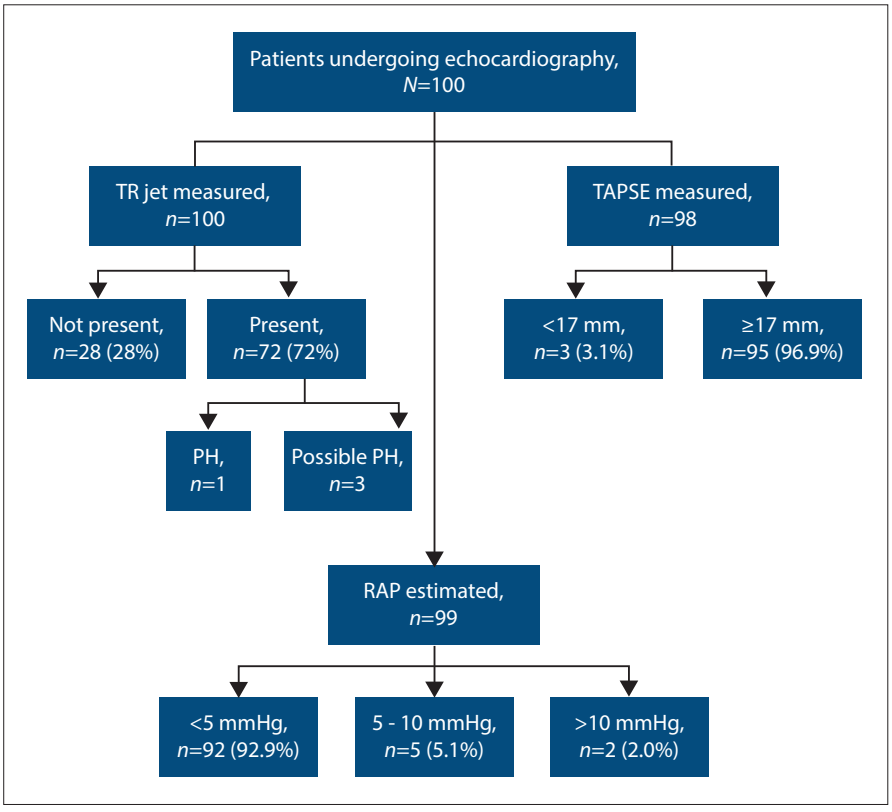

*Fig. 1. Overview of echocardiography findings (*N*=100). (TR = tricuspid regurgitation; TAPSE = tricuspid annular plane systolic excursion; PH = pulmonary hypertension; RAP = right atrial pressure.)*

One participant was found to have PH, with an estimated RVSP of ≥40 mmHg (95% confidence interval (CI) 0.0 - 3.0), while a further 3 had possible PH with an estimated RVSP between ≥35 and <40 mmHg, giving a combined PH prevalence (possible and probable) of 4% (95% CI 0.2 - 7.8). One of the participants with possible PH was found to have a restrictive muscular ventriculoseptal defect, and a second a secundum atrioseptal defect without haemodynamic effect.

Additional unexpected echocardiography findings were concentric left ventricular hypertrophy secondary to hypertension (*n*=1 participant) and a congenital abnormality of the mitral and aortic valves (*n*=1).

Spirometry and 6MWD results

Acceptable spirometry was performed by 98 patients. The mean (SD) forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were 87.8% (20.8%) predicted and 93.4% (18.9%) predicted, respectively. The mean (SD) FEV_1/FVC ratio was 78.5 (9.3). Thirteen participants (13.3%) had an FEV_1/FVC ratio <0.7 and would be considered to have airflow obstruction, while 29 (29.6%) and 4 (4.1%) had an FEV_1 <80% predicted and <50% predicted, respectively. A reduced FVC (<80% predicted) was found in 25 (25.5%) participants, with 4 (4.1%) having an FVC <60% predicted. The mean (SD) 6MWD was 499.5 (97.4) m for the 96 participants who completed the test (Table 2).

Univariate and multivariate analysis

There were no associations between the presence of PH or possible PH and sex, age, smoking status, HIV status or systemic hypertension (p>0.05 for all) (Supplementary Table 1, available online at https://www.samedical.org/file/2067). Multivariate regression was therefore not undertaken.

There was no association visually between RVSP and time since initiating TB treatment, sex, age, BMI, 6MWD or lung function parameters (Supplementary Fig. 1, https://www.samedical.org/file/2067). Visual analysis revealed that ever smoking may have influenced RVSP (Supplementary Fig. 2, https://www.samedical.org/file/2067). Owing to the skewed data, median regression was used. Thirty participants had missing values on some of the covariates. In the developed model, ever smoking was statistically

significantly associated with RVSP (coefficient 4.14; 95% CI 0.39 - 7.90) when adjusted for age, time since initiating of TB treatment, percentage of predicted FEV_1, percentage of predicted FVC, and body mass index (Table 3).

Discussion

The prevalence of PH in 100 patients who were currently receiving or had recently completed TB treatment was significant (1 confirmed and 3 possible cases) after a median of 22 weeks of treatment. Almost half of the patients were HIV positive (*n*=46), and 46 were current or ex-smokers. Other comorbidities were rare. Pulmonary function was generally preserved in this group, with the mean FEV_1 and FVC percentage of predicted being 88% and 93%, respectively. There were no associations between estimated pulmonary pressures (RVSP) or PH/possible PH and sex, age, BMI, 6MWD or lung function, although smoking status was significantly associated with RVSP.

These findings differ from two previous studies, where PH was present in from 10% up to 95% of TB patients,[11,12] and our clinical experience, where anecdotally the prevalence of PH after TB is high. However, the study from Iran[11] had a high prevalence of participants with opium addiction (18.7%), and both this and the study from India[12] suffered from significant selection bias. The prevalence of PH in the present study is particularly interesting given the high proportion of patients with HIV. HIV is a well described cause of group 1 PH (pulmonary arterial hypertension), with a cross-sectional study from a referral HIV centre in Ethiopia estimating the prevalence of PH to be 14%,[16] yet in our study the prevalence of PH was lower, and showed no associations with HIV status.

On face value, our findings support the possibility that the prevalence of PH may have been overestimated in previous studies for the majority of ambulatory patients with TB. However, when extrapolating from both the local and global incidence of TB, even this lower-than-expected prevalence rate may suggest impressive numbers of new cases of PH. This is supported by the finding that in 39% of patients with CLD-PH from China, TB was named as the cause.[9] It is plausible that this study, and our own clinical experience, may reflect referral bias. However, it is also possible that the development of PH may be delayed until long after completion of TB treatment and was therefore not detected by our study design. Certainly, we know that in a proportion of patients, lung function changes evolve during the year after treatment completion.[17] For example, 1 year after treatment completion, 1 in 5 of 305 patients in Malawi demonstrated a decline in FEV_1, and 1 in 3 reported residual symptoms.[18] Although our study showed no association between time since initiation of treatment and pulmonary pressures, it is possible that this time interval would be too short to detect these changes. Another SA study of 20 patients, evaluated at a median of 30 months after TB diagnosis, demonstrated declining TAPSE and RV function with increased time from diagnosis, supporting the hypothesis that PH may evolve with increasing time following TB treatment completion.[19]

It is also possible that co-factors may increase the likelihood of PH after TB. We demonstrated a significant association between smoking status and RVSP, but not PH. Given that PH may evolve over time, and that PAP is a continuous variable, this finding should be explored further. The contribution of smoking to PH in the context of COPD is poorly understood, but may be related to vascular dysfunction.[20,21] In contrast, however, the previously mentioned Iranian study found no significant difference in smoking status between those with PH and those without.[11] Further work is needed to determine whether smoking is indeed an independent risk factor or effect modifier in the context of TB.

We excluded patients with previous TB, which may be an important risk factor for the development of PH. Certainly, recurrent TB is an important risk factor for post-TB lung disease.[22] The importance of significant structural lung damage in the development of PH after TB is not yet known, but was suggested by Ahmed *et al.*,[23] who found abnormal chest radiographs in all of 14 patients with PH and previously treated TB, implying that significant structural diseases may be a prerequisite for subsequent development of PH.

Our study benefited from the recruitment of a patient cohort who were currently completing or had completed ambulatory TB treatment, which was representative of the local TB patient population, with a high prevalence of HIV and few comorbidities. By only including participants with their first episode of TB, the possible effects of previous TB were minimised. Other common causes of PH were excluded; however, radiographic imaging was not included as part of this study.

Table 2. Spirometry and 6MWD results (*N*=98)

Variable	*n* (%)*
FEV_1 (L), mean (SD)	2.46 (0.70)
FEV_1 (% predicted), mean (SD)	87.8 (20.8)
FEV_1 <80% predicted	29 (29.6)
FEV_1 <50% predicted	4 (4.1)
FVC (L), mean (SD)	3.14 (0.80)
FVC (% predicted), mean (SD)	93.4 (18.9)
FVC <80% predicted	25 (25.5)
FVC <60% predicted	4 (4.1)
FEV_1/FVC ratio, mean (SD)	78.5 (9.3)
FEV_1/FVC <0.7	13 (13.3)
6MWD (m), mean (SD)	499.5 (97.4)
Missing	2 (2.0)

6MWD = 6-minute walking distance; FEV_1 = forced expiratory volume in 1 second; SD = standard deviation; FVC = forced vital capacity.
*Except where otherwise indicated.

Table 3. Results of median regression for predictor variables associated with RVSP

Variable	Adjusted coefficient estimate (95% CI)	*p*-value
Ever smoker	4.14 (0.39 - 7.90)	0.03*
Age	0.09 (–0.03 - 0.22)	0.15
Time since TB treatment initiation	0.04 (–0.01 - 0.09)	0.10
Female sex	0.61 (–3.21 - 4.43)	0.75
FVC (% predicted)	–0.04 (–0.22 - 0.15)	0.71
FEV1 (% predicted)	0.04 (–0.15 - 0.22)	0.69
BMI	0.27 (–0.08 - 0.61)	0.13

RVSP = right ventricular systolic pressure; CI = confidence interval; TB = tuberculosis; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; BMI = body mass index.
*Significant result ($p<0.05$).

The study was limited by being a single-centre study with a small sample size and a small number of identified PH cases, although the calculated sample size was exceeded. We estimated pulmonary pressures using echocardiography, which is an effective tool for this purpose; however, we did not perform the gold-standard right heart catheterisation, and our estimates may have been influenced by the well-described measurement errors of echocardiography.[24] To limit some of these errors, including between-operator variability, a single echocardiographer performed all scans in this study. It is, however, also possible that our study suffered from random or unknown selection biases, for example with more symptomatic patients less likely to agree to participate.

The prevalence of PH in our study findings must also be interpreted against the prevalence of other causes of PH, where the prevalence of group 1 PH (pulmonary arterial hypertension) is estimated at 48 - 55 cases per million population (~0.005%), while for advanced COPD with chronic respiratory failure or referred for transplant, PH is reported in between 1% and 5% of cases, similar rates to our young population.[4] These prevalence data suggest that a figure of ~4% for individuals newly ill with TB is not insubstantial. To date there have been no prospective studies on the long-term effects of TB causing PH in high-prevalence settings. It is therefore important to replicate this study in other high-prevalence settings and develop prospective cohorts to study the progression of post-TB lung, PH and other cardiovascular diseases over time following completion of TB treatment.

Conclusion

In this preliminary study that recruited a young population completing treatment for the first episode of TB with a high HIV co-infection rate, there was a significant prevalence of PH, which must be interpreted against the backdrop of the very high TB burden in southern Africa (meaning that the absolute burden of cases with PH is likely to be high). Further work to confirm these findings in other populations is needed, as well as prospective cohort studies to assess the evolution of PH over time after TB treatment, and potential influences of other factors, most importantly smoking and recurrent TB.

Declaration. BWA and EI are members of the editorial board.

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Author contributions. BWA, EI, GW: conceptualised the study. SMan, SMat, SLA, GM: assisted with patient recruitment, lung function and other tests, and data quality. LH: performed all echocardiograms. AP: quality controlled all echocardiograms. MS: data analysis and statistics. All authors: manuscript preparation.

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Conflicts of interest. None.

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