Occult Pulmonary Hypertension in patients with previous Tuberculosis: A pilot study

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine.

Johannesburg, 9 March 2021

DECLARATION

I, Anisa Miri, hereby declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine. This research report is submitted in the publishable format as recognized by the Faculty of Health Sciences. I further declare that this work has not been submitted before for any degree or examination at this or any other University.

_____

9 March 2021

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS RESEARCH

Published in the African Journal of Thoracic and Critical Care Medicine:
Kalla I, Miri A, Seedat F. Occult pulmonary arterial hypertension in patients with previous pulmonary tuberculosis. Afr J Thoracic Crit Care Med 2020; 26(4): 133-137.

DEDICATION

With gratitude to God.

For my parents,

Rosa and Jamal Miri

ETHICAL CONSIDERATIONS

Permission for this prospective study was obtained from Prof. J. Wing (Head of Internal Medicine, Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital), Ms. G. Bogoshi (Chief Executive Officer, Charlotte Maxeke Johannesburg Academic Hospital), and the Human Research Ethics Committee of the University of Witwatersrand (Clearance number M180275).

ABSTRACT

Introduction

Pulmonary tuberculosis (PTB) has a large worldwide burden and despite successful treatment can lead to permanent lung damage and pulmonary hypertension (PH). PH in the absence of significant lung damage is also seen to occur, leading respiratory physicians to question whether pulmonary TB may cause pulmonary arterial hypertension (World Health Organization – WHO class 1 PAH) due to a TB Associate's arteritis of the pulmonary artery, an entity not otherwise described.

Methods

We undertook a pilot study in which 20 individuals with previously treated pulmonary TB and no other underlying risk factors for the development of PH underwent electrocardiograph (ECG), chest radiography (CXR), lung function tests and echocardiography (ECHO). Data from these non-invasive investigations was evaluated in determining findings suggestive of PH.

Results

At a median duration of 30 months from diagnosis of TB, no patients had ECHO findings suggestive of PH (PAP $\geq$ 40 mmHg). However, there was a trend towards a negative correlation between the time from diagnosis and right ventricular dysfunction assessed by measuring a tricuspid annular plane systolic excursion (TAPSE; r = -0.5136, p=0.0205). Furthermore, 7 individuals (35%) had one or more ECG features supporting PH and 17 individuals (85%) demonstrated at least one CXR feature of PH respectively.

Conclusion

Further studies are needed in order to examine the entity of PAH secondary to previously treated PTB. Although our study did not demonstrate echo findings supporting PH, ECG and CXR modalities were suggestive. Therefore, larger cohorts utilizing more sensitive modalities such as CT chest are required.

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ABBREVIATIONS

AAD	Ascending aorta diameter
BMI	Body mass index
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
COPD	Chronic obstructive pulmonary disease
CPA	Chronic pulmonary aspergillosis
CT	Computed tomography
CXR	Chest radiography
DLCO	Diffusion capacity for carbon monoxide
ECG	Electrocardiogram
ECHO	Echocardiography
ETPB	Extra-pulmonary tuberculosis
FEV1:FVC	Forced expiratory volume: Forced vital capacity ratio
FNA	Fine needle aspiration
HIV	Human immunodeficiency virus
HPVC	Hypoxic pulmonary vasoconstriction
ILD	Interstitial lung disease
IQR	Interquartile range
mPAD	Mean pulmonary artery diameter
MTB	Mycobacterium tuberculosis
OPD	Outpatient department
OSA	Obstructive sleep apnoea
PA	Pulmonary artery
PAD	Pulmonary artery diameter
PAH	Pulmonary arterial hypertension
PAPm	Mean pulmonary artery pressure
PASP	Pulmonary artery systolic pressure
PAWP	Pulmonary artery wedge pressure
PH	Pulmonary hypertension
PTB	Pulmonary tuberculosis
PVR	Pulmonary vascular resistance
RAP	Right atrial pressure
RHC	Right heart catheterization

RV	Right ventricle
RVH	Right ventricular hypertrophy
RVSP	Right ventricle systolic pressure
SAMJ	South African Medical Journal
SD	Standard deviation
TAPSE	Tricuspid annular plane systolic excursion
TB	Tuberculosis
TRV	Tricuspid regurgitant velocity
WU	Wood units

CHAPTER 1: PROTOCOL AND EXTENDED LITERATURE REVIEW

1. BACKGROUND

1.1 Introduction

Pulmonary hypertension (PH) is a major cause of morbidity and mortality and has many known aetiologies.[1] International guidelines recommend early detection and specific treatment for this disease however many of these are not easily accessible in a South African context, both within the private and public healthcare system.[2]

Lung disease due to a variety of causes is a recognized entity that may lead to PH, namely group III PH. Destroyed lungs secondary to previous pulmonary tuberculosis (PTB) disease has been implicated in this category.[3] Over recent years, experienced respiratory physicians in this field have recognized an additional entity that may be contributory, where it has been observed that previously treated PTB patients present with PH that is out of keeping with the degree of lung parenchymal changes observed. This has led some centres with a high tuberculosis (TB) burden to prompt studies in order to investigate this association further. [4-6]

Given the high TB burden in South Africa, and the implications that this entity may have on expanding what we know about the long-term effects of treated PTB, this study aims to explore this suspected association. This in turn may have further implications on prevention and identification strategies going forward.

1.2 TB disease

1.2.1 The burden of TB disease

TB is ranked amongst the top 10 leading causes of death worldwide and is the leading cause of death from a single infectious agent.[7] It is estimated that in 2017 alone, 10 million people contracted TB disease. [7] Of these, 91% were HIV negative, and two thirds were living in eight countries: India, China, Indonesia, the Philippines,

Pakistan, Nigeria, Bangladesh and South Africa. [7] In 2016, 438 000 incident cases were reported in South Africa alone, at a rate of 781 cases per 100 000.[7]

Although strategies have been implemented globally to minimize the incidence of disease and great advancements have been made, there is concern that the WHO 2035 goal of ending the global TB epidemic may not be achieved. [8] In South Africa alone, estimates by extrapolation show that incidence rates would need to decrease to 83 cases per 100 000 by 2035 for this to be achieved.[9] The South African National TB Program aims to decrease incidence and mortality through a number of prevention and treatment services.

1.2.2. Risk Factors for TB Disease

Many risk factors have been identified in the occurrence of TB disease in individuals and are separated by impaired immunity (host factors) and increased exposure to infectious persons (environmental factors). Those that fall under impaired immunity include Human Immunodeficiency Virus (HIV), malnutrition, chronic renal failure and haemodialysis, diabetes mellitus, silicosis, substance abuse (cigarette smoking, alcohol and drug use) and treatment with immunosuppressive agents. [7, 10]

In high burden TB areas, increased exposure to household contacts with active TB and poor socio-economic settings that lead to crowding and poor ventilation lead to increased risk of developing TB disease.[11] Individuals working in hospitals, correctional facilities, nursing homes and homeless shelters have also been shown to be at increased risk.[12-14]

1.2.3. TB Disease manifestations

TB infection may manifest as pulmonary or extra-pulmonary disease, the latter of which involves the pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones or meninges. HIV co-infection is associated with an increase in cases of extra-pulmonary TB (EPTB) whilst PTB is more prevalent in HIV non-infected individuals [15]. Radiographic features also differ between HIV infected and non-infected

groups. Diffuse infiltrates and lymphadenopathy are a more common finding in HIV infected individuals whereas cavitatory disease and upper lobe involvement is more prevalent in those without HIV. [16-18]

1.2.4. Complications of pulmonary TB

PTB may have no resulting long-term complications, yet despite effective therapy complications may also occur and involve anatomical areas of the lung including the airway, mediastinum, lung parenchyma and pulmonary vasculature. Well documented complications involving the airways and lung parenchyma include fibrosis, bronchiectasis, chronic pulmonary aspergillosis (CPA), and chronic obstructive pulmonary disease (COPD).[19] In a small prospective study, 64% of participants with previously treated PTB were shown to have fibrotic bands[20], whilst bronchiectasis was evident in 19 – 64% of people who died from TB in several post mortem studies.[21] An aspergilloma was reported in 22% of patients with previous PTB.[22] In a South African study, airway obstruction was found in 68% of individuals with previously treated TB[23], whilst a second South African study examining airway obstruction following TB infection demonstrated airway obstruction in 18.4% of subjects following one episode of TB, 27.1% after two episodes and 35.2% after three or more episodes of TB.[24] A more recent study in Mexico showed a 34.3% incidence of post TB airway obstruction.[3] Other less documented complications of PTB affect the pulmonary vasculature and these include vasculitis of the pulmonary arteries and veins, bronchial artery enlargement associated with post-TB bronchiectasis and Rasmussen's aneurysms.[25]

Regarding the pathology of the involvement of vessels within the lungs, three varying mechanisms have been described.[26] One involves obliterative changes that may occur in pulmonary arteries, another is an endarteritis obliterans in vessels with no specification of origin, and lastly the formation of small pedunculated aneurysms of Rasmussen which traverse walls of tuberculous cavities.

Speculation on the significance of the development of endarteritis were related to the probable benefit in controlling the activity of the *Mycobacterium tuberculosis* (MTB) bacilli. Reducing the oxygen delivery to the MTB bacillus would hinder its

activity.[26]

1.3. Pulmonary hypertension

1.3.1. PH definition

Lung parenchymal destruction following treated PTB may lead to PH and later right heart failure. PH was defined until recently as an increase in mean pulmonary artery pressure (PAPm) equal to or greater than 25mmHg at rest assessed by right heart catheterization (RHC)[1], and now considered greater than 20mmHg.[27] PH is categorized into groups according to similar clinical presentation, hemodynamics and treatment strategies.[1] This classification of PH is reviewed in Appendix C. Group III PH is PH secondary to lung disease and/or hypoxemia. Patients with previous PTB who have established lung disease may present with this group of PH.

1.3.2. Pathogenesis of group III PH

Hypoxic pulmonary vasoconstriction (HPVC) with remodeling of the pulmonary vascular bed occurs in this group of PH.[28] HPVC is a normal regulatory mechanism that limits blood flow to hypoxic alveoli in a compensatory mechanism of preserving ventilation-perfusion.[28] Initial changes related to vascular remodeling include distal neomuscularization of the arterioles, intimal thickening and medial hypertrophy.[29] At a later stage, abnormal collage matrix is deposited within the adventitia. This obliterative remodeling leads to fewer peripheral blood vessels and subsequently to increased peripheral vascular resistance of PH.[29]

1.3.3. Pathogenesis of group I PH

One of the previously mentioned complications of pulmonary TB includes direct involvement of TB on the pulmonary vasculature, on the basis of a vasculitis. When this occurs in the pulmonary arterioles, pulmonary arterial hypertension may occur, specifically group 1 pulmonary hypertension, also known as pulmonary arterial hypertension (PAH), which is a result of pre-capillary pulmonary hypertension. PAH is characterized by vasoconstriction, cell proliferation, fibrosis and

micothrombosis.[30, 31] Hypertrophy and hyperplasia is observed on pathological examination of the layers that comprise the vascular walls of small pulmonary arterioles, which lead to a progressive increase in pulmonary vascular resistance.[30]

On a cellular level, endothelial cells abnormally proliferate in response to certain stimuli.[32] Hypoxia, inflammation, infections and genetic susceptibility are a few of the causes that have been implicated.[32]

1.3.4. PH incidence

There is scanty data on the worldwide incidence of PH. A multinational cohort study was undertaken to assess the epidemiology of patients with PH in Africa and found that 16% had PAH, 69% had PH due to left heart disease and 11% due to lung disease and/or hypoxia.[33] The Heart of Soweto Study in South Africa found that of the patients investigated for PH, 20% were due to PAH, 31% due to left heart disease and 26% due to chronic lung disease.[34]

1.3.5. PH diagnosis

Clinical symptoms may raise suspicion of PH and are mainly as a result of right ventricular dysfunction. These non-specific symptoms include shortness of breath, fatigue, weakness, angina and syncope, and infrequently, non-productive cough.[1] They are typically experienced upon exertion. Other symptoms related to mechanical complications include haemoptysis, which occurs as a result of ruptured hypertrophied bronchial arteries.[1]

Ancillary investigations may support the diagnosis of PH but normal results are not exclusionary. These include electrocardiography (ECG), chest radiography (CXR) and pulmonary function tests.

Electrocardiogram features suggestive of PH include P pulmonale, right axis deviation, right ventricular hypertrophy (RVH), RV strain and right bungle branch block. These findings are more commonly found in severe PH. RV hypertrophy has an insufficient sensitivity of 55% and specificity of 70%, whilst RV strain is more

sensitive.[1]

CXR assists in assessing lung disease as a cause of PH (Group III PH) or pulmonary venous congestion due to left heart disease (Group II PH). It may also assist in identifying PAH with the following suggestive features: central pulmonary arterial dilatation, pruning of peripheral pulmonary vessels, enlarged right atrium and elevated cardiac apex.[1]

Pulmonary function tests assess the underlying airway or parenchymal lung disease contributing to PH. Patients with PAH have mild to moderate reduction of lung volumes, and may have normal or decreased lung diffusion capacity for carbon monoxide (DLCO).[1] COPD as a cause of group III PH is diagnosed as evidenced by irreversible airflow obstruction and increased residual volumes.[1]

Contrast-enhanced computed tomography (CT) imaging is a useful tool in assessing vascular, cardiac, parenchymal and mediastinal pathology. Findings may suggest PH (pulmonary artery (PA) or RV enlargement) and identify the cause of PH (lung disease or chronic pulmonary thromboembolic disease). An increased PA diameter (≥29mm), increased pulmonary: ascending aorta diameter (≥1.0) and a segmental artery:bronchus ratio >1:1 in three or four lobes also raise suspicion of PH.[1, 35]

In diagnosing PH, transthoracic echocardiography (ECHO) is the first line of investigation performed. Pulmonary artery pressure (PAP) findings on ECHO may raise the probability of PH, as well as assess left ventricular dysfunction as the cause.[1]

RHC remains gold standard in the diagnosis of pulmonary hypertension.[1] This modality confirms the diagnosis of PAH. It assesses the severity of hemodynamic impairment. PAH is characterized by the presence of pre-capillary PH, defined by a pulmonary artery wedge pressure (PAWP) ≤15 mmHg and pulmonary vascular resistance (PVR) > 3 Wood units (WU) in the absence of other causes of pre-capillary PH [1].

1.4. PH in patients with previous PTB

In a study undertaken in India in 2016, *Bhattacharyya et al.* looked at a group of 40 patients with previous PTB who were found to have PH. This group was subdivided into smokers and non-smokers. Their observations found that the smokers group demonstrated a COPD picture on spirometry and had a poor quality of life (based on the COPD assessment test).[5] This group belonged to a relatively higher age group with lower PAP's. The non-smokers group demonstrated a restrictive pattern in spirometry. In comparing small airway disease between the two groups, there was distinct small airway obstruction in the smokers group, but not in the non-smokers group. Radiological differences between the two groups were insignificant. These findings led the authors to conclude that perhaps a distinct entity entitled 'tuberculosis associated pulmonary hypertension' exists that is not otherwise explained by the commonly associated obstructive airway disease as a sequelae of PTB.[5]

Verma et al. subsequently noted that in high TB burden countries such as India, patients who have been previously treated for PTB have been seen to present in right heart failure, and postulated this may be secondary to PH caused by destruction of the vascular bed due to , a vasculitis and endarteritis, leading to reduction in cross-sectional area of the pulmonary vasculature.[6] These patients are seen to commonly present with respiratory symptoms out of keeping with their radiological findings, and are often misdiagnosed as relapse of PTB and subsequently initiated on TB therapy, or are prescribed bronchodilators without further adequate work up. *Verma et al* subsequently concluded that further studies need to be undertaken to identify this form of PH associated with previous PTB.

One small cross-sectional study in Iran identified PH in 14 of 30 patients who had previous sputum-positive PTB and presented with shortness of breath.[36] A diagnosis of PH was considered based on ECHO findings of a pulmonary artery systolic pressure (PASP) $\geq$ 40mmHg. Of significance, the mean age of these patients was 43 years, and the diagnosis of PH was made on average 9 years after cure of PTB, demonstrating the development of PH well beyond the immediate post-treatment period and cure of active TB. The study was designed to exclude other causes of PH, such as HIV (group I PH) and cardiac lesions (group II). 3 patients (21%) were current or previous smokers. There were however significant radiological

abnormalities amongst this group – 7 patients (50%) demonstrated fibrocavitatory disease, 5 patients (36%) demonstrated fibrosis, 1 patient (7%) demonstrated bullae and fistula and 1 patient (7%) demonstrated fibrothorax. The aetiology of the PH observed in this study is therefore most likely to be group III related. It would be difficult given the extensive disease processes on CXR to infer the contribution of PAH.

Another study carried out in India assessed 264 patients with previously cured PTB.[37] Other causes of PH were excluded, such as HIV infection, history of smoking and established asthma or COPD. CXR, spirometry and transthoracic ECHO were performed on each patient. CXR findings showed 119 patients (45%) with minimal fibrotic changes, 100 patients (38%) had involvement of more than 2 lobes and 45 patients (17%) had severe fibrotic and/or cavitatory changes. Spirometry findings showed 86.8% of patients with obstructive airway disease and 13.2% with normal values. Notably, 28.7% if of those patients who demonstrated obstructive airway disease also had a concomitant restrictive pattern. 76 patients of the cohort had an ECHO, less than the initial number due to both logistical reasons and limiting investigations performed on those who demonstrated clinical signs of right heart failure. 4 of these patients had normal ECG's and ECHO's, whilst the remaining 72 showed peaked P waves on ECG and elevated right ventricular systolic pressures (RVSP) above 30 mmHg. This study therefore likely identified overt PH in those with significant lung disease, hence group III PH. Those patients who had minimal fibrotic changes on CXR and who had not manifested as overt RHF were not studied, therefore the presence of PH in these patients was not determined.

Along with India and Iran, South Africa carries a large burden of TB disease therefore common complications are frequently seen and more rare complications have been noted amongst the respiratory community. In a correspondence piece to the South African Medical Journal in 2018.[4] *Allwood et al.* state that significant destruction of the pulmonary vasculature in the absence of extensive parenchymal disease following PTB is an unexplored entity, and may result in post TB associated PH. They further note that the prevalence of PH in individuals who have previously completed TB treatment and have minimal parenchymal sequelae has not been studied. The author's state there is a paucity of information regarding the association between treated PTB

and PH and propose further research be undertaken to study this link.

1.5 Summary

Despite worldwide efforts to curb the incidence of TB disease, it still remains a significant health concern across the world and particularly in, South Africa a high TB burden setting. Furthermore, successfully addressing PTB does not conclude once treatment is completed. Complications of the treated disease are many and will continue to pose a burden on the quality of life of these individuals as well as healthcare systems, specifically due to the difficulty in treatment of PH.

Through mechanisms of destruction to the lung parenchyma, group III PH has been implicated subsequent to PTB disease. Clinical experts in the field have further noted the presence of PH in those with minimal lung changes, heightening the suspicion of the development of TB secondary due to another mechanism. PAH has been implicated here, where TB causes a vasculitis involving pulmonary arterioles that may lead to pre-capillary hypertension and hence PH.

Given the high burden of TB disease in a South African context, it is necessary to gain a better understanding of the long-term cardiopulmonary effects of PTB infection and in particular, due to the paucity of data available, to assess if there is a correlation between previous PTB and the development of a TB arteritis and consequent PAH. Earlier detection of PAH may have implications for initiating earlier therapy and in delaying disease progression, whilst additional guidance is needed regarding methods for screening. To our knowledge, there is little data, and none in the South African population, that has examined the development of PAH, in particular occult PAH, following prior PTB infection despite respiratory physician opinion that a significant association exists. Therefore, this study aims to investigate the occurrence of occult PAH, on the basis of direct involvement of the pulmonary artery from TB infection and in the absence of significant parenchymal lung disease, in adult patients who were previously diagnosed with PTB, and better characterize this association.

2. OBJECTIVES

To determine the spectrum of occult PAH in adult patients with previously diagnosed

and treated PTB.

SPECIFIC AIMS

In a population of patients with at least one prior episode of pulmonary TB:

1. To describe the following parameters and stratify them by the occurrence of PAH:
    - Demographics
    - Details regarding prior TB infection
        - Number of episodes
        - Modality of diagnosis
        - Duration since TB therapy
    - Assess the presence of any of the following respiratory symptoms: dyspnea, cough, sputum expectoration and haemoptysis.

2. To determine the presence of markers of PH as well as the severity of the underlying lung disease using various investigative modalities:
    - Electrocardiogram.
    - Spirometry with concomitant DLCO.
    - Chest Radiograph.
    - Transthoracic echocardiography.

3. To determine the prevalence of and classify the PAH in terms of severity.

4. To correlate the occurrence of PAH with factors related to prior TB infection and associated risk factors:
    - Number of prior pulmonary TB infections.
    - Duration since prior TB diagnosis.
    - Respiratory symptoms.
    - Smoking.
    - Airflow limitation.
    - Degree of post TB fibrosis.

3. METHODOLOGY

1. Study Design

A prospective descriptive cross-sectional study.

2. Study population and sample

I. Location and duration

The study will take place at the Charlotte Maxeke Johannesburg Academic Hospital. If adequate numbers of participants are not reached early in the study, provision will be sought to extend to other hospitals.

II. Population

The study will recruit patients admitted to or attending the outpatient departments (OPD) of Charlotte Maxeke Johannesburg Academic Hospital with one or more previous episode of pulmonary TB. Majority of patients who fit the inclusion and exclusion criteria will likely be found in the Infectious Diseases (ID) OPD. Patients' records kept in the clinic and radiographs on the picture archiving and communication system will be screened the day prior to the patients visit to determine which patients would meet inclusion criteria. Following this these patients will be enrolled the following day in the study. The TB Registry will also be used to identify potential participants. If the numbers are not met from this clinic alone, patients will be sought from other OPD's or alternatively admitted patients in the wards in the department of internal medicine.

III. Inclusion Criteria

- Age older than 18.
- Patient reports at least one previous episode of treated pulmonary TB diagnosed via radiological or microbiological investigations.

IV. Exclusion Criteria

- Patients unable or unwilling to give written informed consent.
- Patients currently on TB therapy or suspected with active pulmonary TB by treating clinician.
- Hypoxic patients as defined by a room air saturation level of less than 88% to be measured using a portable pulse oximeter [38].
- Known patients with pulmonary arterial hypertension.

- Known patients with a collagen vascular or connective tissue disorder.
- Known patients with liver cirrhosis or portal hypertension.
- Known patients with chronic bilharzia infection.
- Known patients with structural, ischemic, valvular or congenital heart disease
- Known patients with the following respiratory diseases:
  - Chronic obstructive pulmonary disease (Gold C or with FEV1 less than 50% predicted).
  - Interstitial lung disease.
  - Obstructive sleep apnea or sleep disordered breathing according to the NoSAS score [39] – see Appendix II.
  - Severe bronchiectasis according to the FACED Score[40] – see Appendix III.
- Known patients with current or previous pulmonary embolus or deep vein thrombosis.
- HIV Positive patients.

3. Sample size and duration

   This pilot study will aim to enrol 20-30 patients within the time period. The anticipated recruitment period will be 10 months. These patients will be recruited from patients admitted to or attending outpatient clinics at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). If the target sample size is not reached within this period, the study will still proceed based on the numbers obtained. The study may be extended in the future to include a larger sample size.

4. Description of methods and technique

   I. <u>Identifying patients with previous pulmonary TB</u>

   Following a historical enquiry and assessing the records of both past, present and new patients admitted to or attending the out patient clinics of

the CMJAH, those who have had at least one episode of previously treated pulmonary TB will be identified. These patients will be approached and counselled on the study and written informed consent obtained. Through an interview, information pertaining to the patient demographics, the time of diagnosis of pulmonary TB, the mode of diagnosis and the duration of treatment will be obtained. They will also be asked about any respiratory symptoms.

II. Investigations

This study has been discussed with the departments of Pulmonology and Cardiology at CMJAH, who have agreed to provide support in the performance of echocardiography and lung function tests. An electrocardiogram will be obtained to determine supportive evidence of pulmonary hypertension. Echocardiography will be performed by echocardiography technologists and fellows in cardiology. Spirometry with a DLCO will be performed and a chest radiograph will be evaluated to delineate evidence of PH (and post TB fibrosis). Transthoracic echocardiography will be performed to evaluate pulmonary arterial pressures and other predictive markers of PH. As in other studies that have examined PH in TB, we will consider pulmonary hypertension as peak systolic pulmonary artery pressure $\geq$ 40 mmHg as measured by transthoracic echocardiography.[36, 41] Severity will be graded according to the following: mild: 40-45mmHg, moderate: 46-60mmHg and severe >60mmHg.[41]

Below is a schematic diagram illustrating methodology of recruitment and investigation.

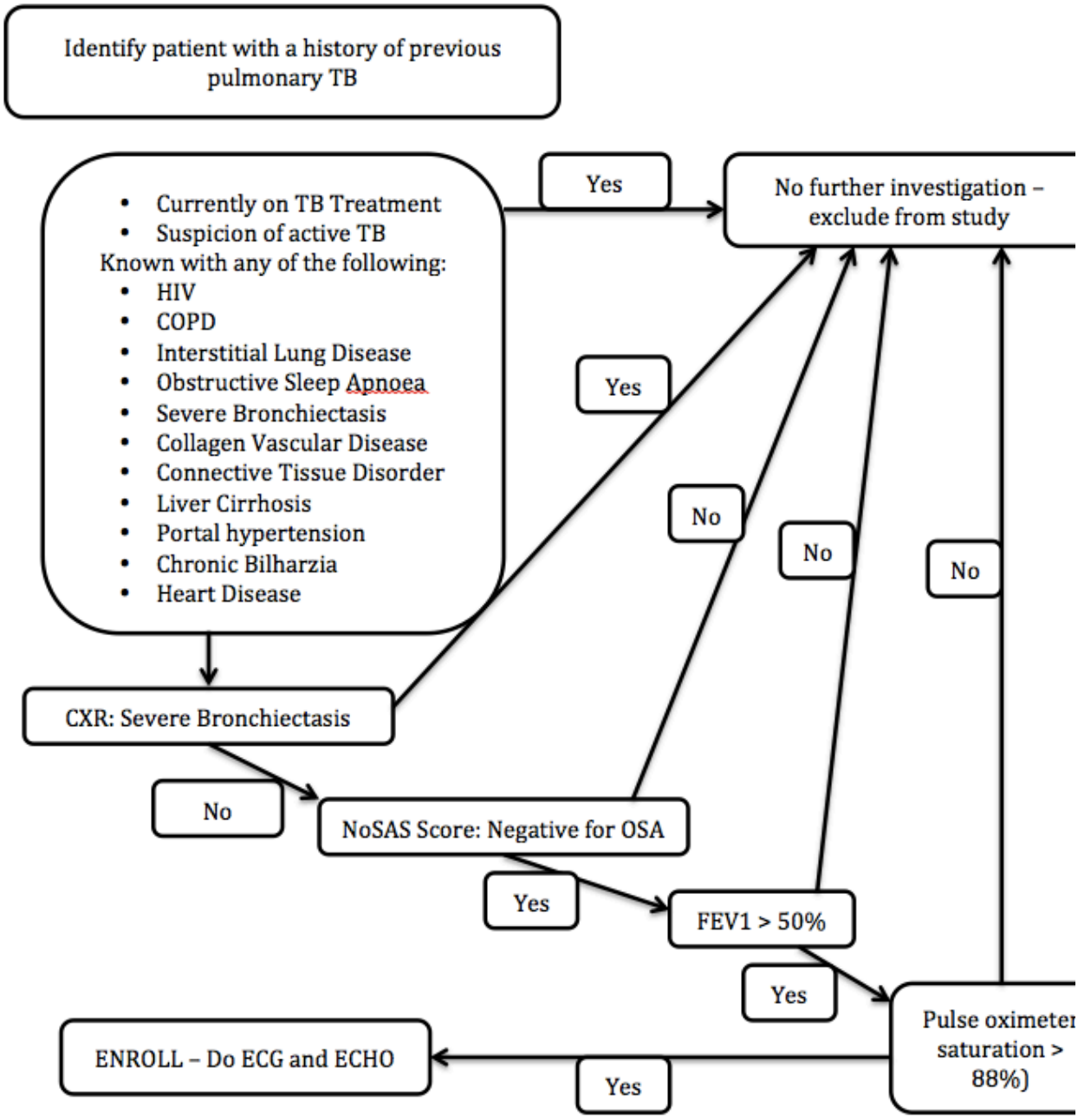

Figure 1: Methodology of Recruitment and Investigation

4. STATISTICAL ANALYSIS

Aims 2 and 3 will be analysed using descriptive statistics in the form of parametric (using means and standard deviations) and non-parametric (using medians and interquartile range) measures; furthermore, categorical variables will be analysed using frequency tables and percentages. For aims 1, 2 and 3 comparisons using the unpaired t-test for parametric data and Mann-Whitney test for non-parametric variables will be applied. The Pearson correlation for parametric and Spearman

correlation will be used for aim 4 and Linear regression will be performed if the outcome is continuous variable or Logistic regression if the outcome is categorical. An appropriate statistical package will be utilized and a statistician consulted for assistance.

5. ETHICS

The study protocol will be submitted to the Human Resource Ethics Committee for approval. Consent for use of patient records will be sought from the Academic Head of Internal Medicine and CEO's/Superintendent of the Charlotte Maxeke Johannesburg Academic Hospital. Individual patient consent will be obtained from the patients included in the study. Each data sheet will be assigned a study number, which will not include patient name or hospital number so to ensure confidentiality. Data will only be made available to the supervisors, the researcher and statistician.

7. TIMING

The study will commence once approval is received. The following is a Gantt chart illustrating the timeline of the study:

2018	Jan	Feb	Mar	Apr	May	June	July	Aug	Sep	Oct	Nov	Dec
Literature Review												
Preparing protocol												
Protocol Assessment												
Ethics Application												
Data collection												

2019	Jan	Feb	Mar	Apr	May	June	July	Aug	Sep	Oct	Nov	Dec
Data												

collection												
Data analysis												
Write up of report												

Figure 2: Timeline

7. FUNDING

Anticipated funding will be to cover photocopying of data sheets and for potential travel costs of patients if requested to come to the hospital for the interview and/or investigations at a time outside of their scheduled outpatient appointments - the primary researcher will fund these. Neither the hospital nor the patients will be required to bear any costs related to this study.

8. LIMITATIONS

Given the prospective nature of this study and the time limitation, the anticipated sample size may not be reached, which may have implications on the significance of the findings. This is however a pilot study thus it is anticipated that findings may prompt future further investigations. Echocardiography is operator-dependent and several cardiologist and technologists are expected to perform this investigation for the purpose of this study, thus creating operator-dependent differences in findings. The diagnosis of PAH will be based on the absence of any other aetiology to explain PH and will be confirmed by elevated pulmonary pressures measured by echocardiography. Echocardiographic criteria will be based on those used in other studies (see methodology) examining PH, however, a right heart catheterization will not be performed.

9. REFERENCES

1. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). European heart journal. 2016;37(1):67-119.
2. Essop MR, Galie N, Badesch DB, Lalloo U, Mahomed AG, Naidoo DP, et al. Management of pulmonary hypertension. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2015;105(6):437-9.
3. de la Mora IL, Martinez-Oceguera D, Laniado-Laborin R. Chronic airway obstruction after successful treatment of tuberculosis and its impact on quality of life. Int J Tuberc Lung Dis. 2015;19(7):808-10.
4. Allwood BW, Maarman GJ, Kyriakakis CG, Doubell AF. Post-pulmonary tuberculosis complications in South Africa and a potential link with pulmonary hypertension: Premise for clinical and scientific investigations. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2018;108(7):12339.
5. Bhattacharyya P, Saha D, Bhattacherjee PD, Das SK, Bhattacharyya PP, Dey R. Tuberculosis associated pulmonary hypertension: The revelation of a clinical observation. Lung India : official organ of Indian Chest Society. 2016;33(2):135-9.
6. Verma AK. Tuberculosis and pulmonary hypertension: Commentary. Lung India : official organ of Indian Chest Society. 2016;33(2):232-3.
7. Glaziou P, Floyd K, Raviglione MC. Global Epidemiology of Tuberculosis. Seminars in respiratory and critical care medicine. 2018;39(3):271-85.
8. Tao NN, Li YF, Wang SS, Liu YX, Liu JY, Song WM, et al. Epidemiological characteristics of pulmonary tuberculosis in Shandong, China, 2005-2017: A retrospective study. Medicine. 2019;98(21):e15778.
9. Naidoo P, Theron G, Rangaka MX, Chihota VN, Vaughan L, Brey ZO, et al. The South African Tuberculosis Care Cascade: Estimated Losses and Methodological Challenges. The Journal of infectious diseases. 2017;216(suppl_7):S702-s13.
10. Baker MA, Lin HH, Chang HY, Murray MB. The risk of tuberculosis disease among persons with diabetes mellitus: a prospective cohort study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(6):818-25.
11. Becerra MC, Appleton SC, Franke MF, Chalco K, Arteaga F, Bayona J, et al. Tuberculosis burden in households of patients with multidrug-resistant and extensively drug-resistant tuberculosis: a retrospective cohort study. Lancet (London, England). 2011;377(9760):147-52.
12. Stead WW, Lofgren JP, Warren E, Thomas C. Tuberculosis as an endemic and nosocomial infection among the elderly in nursing homes. The New England journal of medicine. 1985;312(23):1483-7.
13. Sharma D, Sharma J, Deo N, Bisht D. Prevalence and risk factors of tuberculosis in developing countries through health care workers. Microbial pathogenesis. 2018;124:279-83.
14. Dolla C, Padmapriyadarsini C, Pradeep Menon A, Muniyandi M, Adinarayanan S, Sekar G, et al. Tuberculosis among the homeless in Chennai city,

South India. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2017;111(10):479-81.
15. Lee JY. Diagnosis and treatment of extrapulmonary tuberculosis. Tuberculosis and respiratory diseases. 2015;78(2):47-55.
16. Henn L, Nagel F, Dal Pizzol F. Comparison between human immunodeficiency virus positive and negative patients with tuberculosis in Southern Brazil. Memorias do Instituto Oswaldo Cruz. 1999;94(3):377-81.
17. Hadadi A, Tajik P, Rasoolinejad M, Davoudi S, Mohraz M. Pulmonary Tuberculosis in Patients with HIV/AIDS in Iran. Iranian journal of public health. 2011;40(1):100-6.
18. Hongthiamthong P, Riantawan P, Subhannachart P, Fuangtong P. Clinical aspects and treatment outcome in HIV-associated pulmonary tuberculosis: an experience from a Thai referral centre. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 1994;77(10):520-5.
19. Shah M, Reed C. Complications of tuberculosis. Current opinion in infectious diseases. 2014;27(5):403-10.
20. Long R, Maycher B, Dhar A, Manfreda J, Hershfield E, Anthonisen N. Pulmonary tuberculosis treated with directly observed therapy: serial changes in lung structure and function. Chest. 1998;113(4):933-43.
21. Jordan TS, Spencer EM, Davies P. Tuberculosis, bronchiectasis and chronic airflow obstruction. Respirology (Carlton, Vic). 2010;15(4):623-8.
22. Chakaya J, Kirenga B, Getahun H. Long term complications after completion of pulmonary tuberculosis treatment: A quest for a public health approach. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases.3:10-2.
23. Willcox PA, Ferguson AD. Chronic obstructive airways disease following treated pulmonary tuberculosis. Respiratory medicine. 1989;83(3):195-8.
24. Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. Thorax. 2000;55(1):32-8.
25. Kim HY, Song KS, Goo JM, Lee JS, Lee KS, Lim TH. Thoracic sequelae and complications of tuberculosis. Radiographics : a review publication of the Radiological Society of North America, Inc. 2001;21(4):839-58; discussion 59-60.
26. Cudkowicz L. The blood supply of the lung in pulmonary tuberculosis. Thorax. 1952;7(3):270-6.
27. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. European Respiratory Journal. 2019;53(1):1801913.
28. Klinger JR. Group III Pulmonary Hypertension: Pulmonary Hypertension Associated with Lung Disease: Epidemiology, Pathophysiology, and Treatments. Cardiology clinics. 2016;34(3):413-33.
29. Vender RL. Chronic hypoxic pulmonary hypertension. Cell biology to pathophysiology. Chest. 1994;106(1):236-43.
30. Pietra GG, Capron F, Stewart S, Leone O, Humbert M, Robbins IM, et al. Pathologic assessment of vasculopathies in pulmonary hypertension. Journal of the American College of Cardiology. 2004;43(12 Suppl S):25s-32s.
31. Farber HW, Loscalzo J. Pulmonary arterial hypertension. The New England journal of medicine. 2004;351(16):1655-65.

32. Montani D, Günther S, Dorfmüller P, Perros F, Girerd B, Garcia G, et al. Pulmonary arterial hypertension. Orphanet journal of rare diseases. 2013;8:97.
33. Thienemann F, Dzudie A, Mocumbi AO, Blauwet L, Sani MU, Karaye KM, et al. The causes, treatment, and outcome of pulmonary hypertension in Africa: Insights from the Pan African Pulmonary Hypertension Cohort (PAPUCO) Registry. International journal of cardiology. 2016;221:205-11.
34. Stewart S, Mocumbi AO, Carrington MJ, Pretorius S, Burton R, Sliwa K. A not-so-rare form of heart failure in urban black Africans: pathways to right heart failure in the Heart of Soweto Study cohort. European journal of heart failure. 2011;13(10):1070-7.
35. Tan RT, Kuzo R, Goodman LR, Siegel R, Haasler GB, Presberg KW. Utility of CT scan evaluation for predicting pulmonary hypertension in patients with parenchymal lung disease. Medical College of Wisconsin Lung Transplant Group. Chest. 1998;113(5):1250-6.
36. Ahmed AEH, Ibrahim AS, Elshafie SM. Pulmonary Hypertension in Patients with Treated Pulmonary Tuberculosis: Analysis of 14 Consecutive Cases. Clinical Medicine Insights Circulatory, Respiratory and Pulmonary Medicine. 2011;5:1-5.
37. Akkara SA, Shah AD, Adalja M, Akkara AG, Rathi A, Shah DN. Pulmonary tuberculosis: the day after. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2013;17(6):810-3.
38. Using Pulse Oximeters World Health Organisation. 2011.
39. Guichard K, Marti-Soler H, Micoulaud-Franchi JA, Philip P, Marques-Vidal P, Vollenweider P, et al. The NoSAS score: A new and simple screening tool for obstructive sleep apnea syndrome in depressive disorder. Journal of affective disorders. 2017;227:136-40.
40. Martinez-Garcia MA, de Gracia J, Vendrell Relat M, Giron RM, Maiz Carro L, de la Rosa Carrillo D, et al. Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score. The European respiratory journal. 2014;43(5):1357-67.
41. Strange G, Playford D, Stewart S, Deague JA, Nelson H, Kent A, et al. Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. Heart (British Cardiac Society). 2012;98(24):1805-11.

Occult pulmonary arterial hypertension in patients with previous pulmonary tuberculosis

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Background. Pulmonary tuberculosis (TB) still causes a significant public healthcare burden. Despite successful treatment, TB can lead to permanent lung damage and pulmonary hypertension (PH). PH can also occur in the absence of significant lung damage, leading clinicians to question whether pulmonary TB may cause pulmonary arterial hypertension (PAH), an entity that has not been otherwise described.
Objectives. To determine the prevalence of PAH in patients previously treated for TB.
Methods. We recruited 20 participants who were previously treated for TB and had no other underlying risk factors for the development of PH. The participants underwent electrocardiography (ECG), chest radiography, lung function tests and echocardiography (ECHO). Data from these non-invasive investigations were evaluated to determine findings that were suggestive of PH.
Results. At a median duration of 30 months from diagnosis of TB, no participant had echocardiography findings that were suggestive of PH (pulmonary artery pressure (PAP) ≥40 mmHg). However, there was a negative correlation between the time from diagnosis and right ventricular dysfunction assessed by measuring a tricuspid annular plane systolic excursion (r=–0.5136; p=0.0205). Furthermore, one-third of the participants (n=7) had one or more ECG features supporting PH and 85% of the participants (n=17) demonstrated at least one chest X-ray (CXR) feature of PH.
Conclusion. Although our study did not demonstrate ECHO findings supporting PH, ECG and CXR modalities were suggestive. Therefore, future studies consisting of larger cohorts and including the use of other sensitive modalities such as computed tomography are warranted. Moreover, these studies will need to determine whether the entity of PAH secondary to previously treated pulmonary TB exists.

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Tuberculosis (TB) is ranked amongst the top 10 leading causes of death worldwide and is the leading cause of death from a single infectious agent.[1] South Africa (SA) has a high burden of TB, with ~438 000 new cases reported in 2019.[2] The Department of Health in SA has implemented strategies that have been successful in curbing the incidence of TB.[3]

Despite successful treatment, TB may cause significant long-term cardiorespiratory complications that are well known, including fibro-cavitary changes, bronchiectasis, chronic pulmonary aspergillosis and chronic obstructive pulmonary disease.[4] These complications may have further sequelae such as the development of pulmonary hypertension (PH) and right heart failure, which substantially impacts quality of life and further burdens the healthcare system.[5]

Pulmonary hypertension is defined as an increase in mean pulmonary artery pressure (PAP) ≥20 mmHg at rest as assessed by right heart catheterisation (RHC) as gold standard.[6,7] Other modalities such as echocardiography may be used to determine the probability of PH.[6] This disease is associated with significant morbidity and mortality.[8] Therefore, it is crucial that those suspected to be at risk of disease are identified and be put on treatment as early as possible.

An under-recognised cause of PH associated with previously treated TB is the development of a vasculitis of the pulmonary artery.[9] This may lead to an increase in pulmonary arterial vascular resistance and subsequently PH.[10] Other mechanisms that have been described to lead to the development of PH include obliterative changes of the pulmonary arteries and an endarteritis obliterans in the vessels following TB,[11] similar to those noted in the development of pulmonary arterial hypertension (PAH).

Specific targeted therapy has recently been developed for PAH based on its underlying pathophysiology. These include endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, prostacyclin analogues and prostacyclin receptor agonists.[6] Early and appropriate administration of these drugs has been shown to be efficacious in alleviating symptoms, improving the haemodynamic profile and delaying the time to worsening of clinical symptoms.[12] Many of these therapies are not currently available in the SA public healthcare sector due to their costs.

Previous studies have demonstrated that PAH can develop in patients with minimal lung complications in countries with a high burden of TB.[13,14] In fact, Allwood *et al.*[14] noted that significant destruction of the pulmonary vasculature, in the absence of extensive parenchymal disease following TB, is an unexplored entity and may result in post-TB associated PAH.[14] They suggested that this paucity in the literature underscores a need for future studies to resolve this challenge. The outcomes of these studies will have serious implications on the burden of TB disease, the need for early detection of PAH and

the need to dispense appropriate treatment in order to minimise disease morbidity. The aim of this study was to investigate whether PAH was present in participants who were previously treated for TB.

Methods

Participants who were previously treated for TB were recruited and enrolled into this pilot prospective cohort study between October 2018 and April 2019. The study was undertaken in the Department of Infectious Diseases at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a quaternary hospital in Gauteng Province, SA. Participants were identified from the TB registry kept in the Outpatient Department or from those who attended follow-up visits after completing their TB treatment.

Participants with active TB and those with known aetiologies of PH such as HIV, chronic obstructive pulmonary disease, interstitial lung disease, obstructive sleep apnoea, autoimmune diseases, connective tissue disorders, collagen vascular disorders, liver cirrhosis, chronic bilharzia, heart disease and current or previous pulmonary embolus or deep vein thrombosis were excluded from the study. A chest X-ray (CXR) was subsequently performed to assess the presence of parenchymal lung disease. Participants who had severe bronchiectasis were risk stratified using the FACED score developed by Martinez-Garcia *et al.*[15] The score uses the forced expiratory volume in one second (FEV_1), age, chronic microbial colonisation, radiological extent and dyspnoea to stratify patients with non-cystic bronchiectasis. Patients with a FACED score ≥5 were excluded from the study.

A structured questionnaire was used to record demographics, details of TB diagnosis (date, method and duration of therapy) and TB drug sensitivity. Each participant underwent an electrocardiogram (ECG), pulmonary function test (spirometry and diffusing capacity of lung for carbon monoxide (DLCO)), echocardiography (ECHO) and CXR to determine features that were indicative of PAH. The data were interpreted by a pulmonologist in the Division of Pulmonology at CMJAH. A diagnosis of PH was made based on a peak systolic pulmonary artery pressure (PASP) ≥40 mmHg on ECHO.[6] The gold standard for the diagnosis of PAH is RHC. However, RHC is a highly invasive procedure that is infrequently performed in our setting due to resource constraints. Therefore, to ensure the safety of participants and to preserve resources, RHC was not performed.

This study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (ref. no. M180275). All participants provided written informed consent.

Frequencies, median and interquartile range were used to describe demographic characteristics, clinical features and investigations (Tables 1 and 2). We explored pairwise associations between numeric variables to determine correlation with each other and with the outcomes of the tricuspid annular plane systolic excursion (TAPSE) and PASP. We plotted linear fit prediction plots with confidence intervals to further explore statistically significant pairwise associations of importance (Fig. 1). Statistical analysis was performed using the SPSS software, version 12 (SPSS Inc., USA).

Results

We recruited and enrolled 22 participants who were previously treated for smear-positive TB into the study. However, we excluded two participants who had severe bronchiectasis. The median age of the remaining 20 participants was 33 years old (interquartile range (IQR) 29 - 41.5). The majority of the participants (60%) were female and black African (Table 1). All participants had microbiologically confirmed TB at diagnosis, with 80% (n=16) by sputum, 15% (n=3) by bronchial washings and 5% (n=1) by computed tomography (CT) guided fine needle aspirate (FNA) of a lung nodule. The median duration after initial TB diagnosis was 30 months (IQR 14 - 42). No participants had a past or current history of smoking tobacco.

A few participants (15%; n=3) complained of a dry persistent non-productive cough and no complaints of dyspnoea, sputum expectoration or haemoptysis were reported.

Pulmonary function tests showed a median forced expiratory volume in one second: forced vital capacity (FEV_1:FVC) ratio of 83% (IQR 73 - 87). We also found that in 15% (n=3) of the participants, the DLCO was reduced after an average of 23 months following diagnosis of TB. All the participants had room air saturation measurements that were above 95% by pulse oximetry (Table 2). More than one-third of the participants (35%; n=7) had one or more features of PH on ECG while the majority of the participants (85%; n=17) demonstrated at least one CXR feature suggestive of PH (Table 2). The majority of the patients (60%) had some degree of broncho-vascular distortion and pleuro-parenchymal

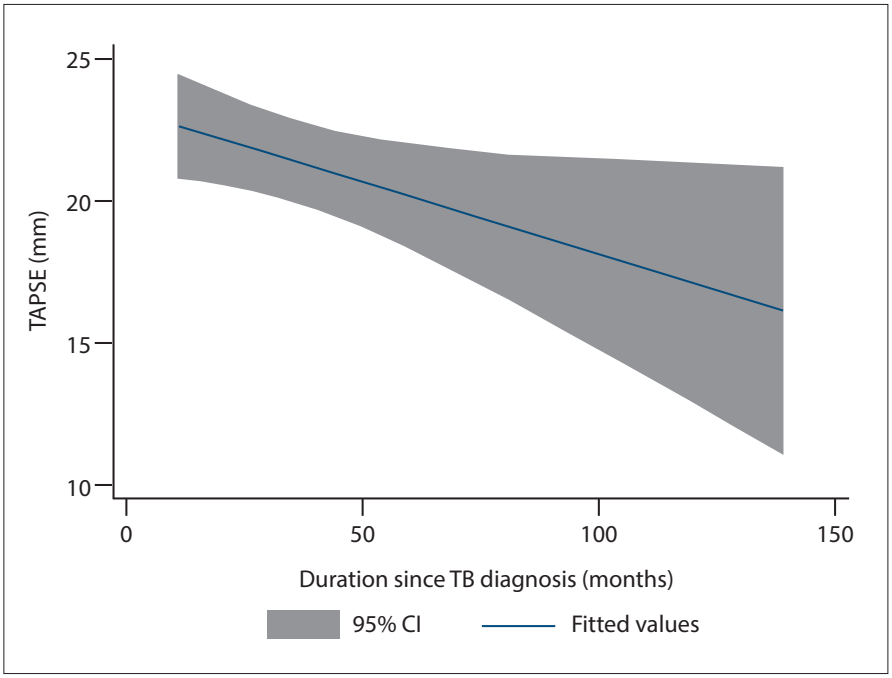

Fig. 1. Linear prediction plot showing association between duration since TB diagnosis and tricuspid annular plane systolic excursion (TAPSE). (CI = confidence interval; TB = tuberculosis.)

Table 1. Characteristics of patients with previous TB (*N*=20)

Patient characteristics	Mean (SD)*	*n* (%)
Demographic characteristics		
Overall age in years	36.65 (12.83)	
Median (IQR)	33 (29 - 41.5)	
Self-reported race		
Asian		1 (5)
Black		12 (60)
Coloured		1 (5)
Indian		5 (25)
White		1 (5)
Gender		
Male		8 (40)
Female		12 (60)
Clinical features		
Details regarding prior TB infection		
Duration since TB diagnosis (months)	35.65 (31.02)	
Median (IQR)	30 (14 - 42)	
Mode of TB diagnosis		
Sputum		16 (80)
Bronchial washings		3 (15)
CT-guided FNA lung nodule (CXR suggestive of active TB)		1 (5)
Current presence of respiratory symptoms		
Cough		3 (15)
Dyspnoea		0
Sputum expectoration		0
Haemoptysis		0
Comorbidities and risk factors		
Smoking		0
Hypertension		1 (5)
Diabetes		2 (10)
Malignancy		0
Screening for sleep-disordered breathing		
Neck circumference >40 cm		0
Overweight (BMI 25 - 30)		1 (5)
Obesity (BMI >30)		0
Snoring		0
Age >55		2 (5)
Male sex		8 (40)

SD = standard deviation; IQR = interquartile range; FNA = fine-needle aspiration; CXR = chest X-ray; BMI = body mass index.
*Unless otherwise specified.

Table 2. Clinical investigations

Findings on ECG	Median (IQR)	*n* (%)
P		0
Right-axis deviation		1 (5)
S wave in standard lead 1		3 (15)
Q wave in standard lead 3		2 (10)
T wave in standard lead 3		1 (5)
R wave in ventricular lead 1		1 (5)
RVH		0
RV strain		1 (5)
RBBB		0
Findings on chest X-ray		
Elevated cardiac apex		10 (50)
Enlarged right atrium		10 (50)
Enlarged pulmonary arteries		15 (75)
Pruning of peripheral pulmonary vessels		5 (25)
Pleuro-parenchymal bands		12 (60)
Volume loss		2 (10)
Tracheal deviation		0
Spirometry		
FEV_1	2.77(2.29 - 3.31)	
FVC	3.41 (2.82 - 3.96)	
Ratio	82.85 (73.10 - 86.85)	
DLCO (%Pred)	99.5 (84.5 - 108.5)	
Low DLCO		3 (15)
Room air saturation	96 (95.5 - 97.0)	
Echocardiography		
LVIDd (mm)	43.5 (41.5 - 48.5)	
LVIDs (mm)	28 (27.5 - 30)	
LVEF (%)	60 (56 - 64)	
RWMA		0
Left atrium (mm)	27.5 (23 - 31)	
Ascending aorta (mm)	23 (21 - 26.5)	
E/a	1.24 (1 - 1.50)	
E/e	6 (5.19 - 8.30)	
Diastolic dysfunction		3 (15)
Aortic regurgitation		1 (5)
Aortic stenosis		0
Mitral regurgitation		2 (10)
Mitral stenosis		0
Tricuspid regurgitation		5 (25)
TAPSE (mm)	21 (19 - 23)	
TAPSE <16 mm		0
PASP (mmHg)	18 (8.5 - 24.5)	
RAP (mmHg)	5 (3 - 9.5)	
IVC (mm)	14 (13 - 18)	
NT-proBNP	26 (16 - 66)	

ECG = electrocardiography; IQR = interquartile range; P = pulmonale; R = right-axis deviation; RVH = right ventricular hypertrophy; RV = right ventricular; RBBB = right bundle branch block; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; DLCO = diffusing capacity of lung for carbon monoxide; LVIDd = left ventricular internal diameter end diastole; LVIDs = left ventricular internal diameter end systole; LVEF = left ventricular ejection fraction; RWMA = regional wall motion abnormality; TAPSE = tricuspid annular plane systolic excursion; PASP = pulmonary hypertension echocardiography; RAP = right arterial pressure; IVC = inferior vena cava; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

bands on CXR and the rest had no radiological complications of TB (Table 2). We found no participants that displayed ECHO criteria supportive of PH based on PASP at a median of 30 months after TB diagnosis (Table 3). However, the overall trend of TAPSE values was observed to decline over time after the initial TB diagnosis (Table 2).

Discussion

In this pilot study, we examined PAH in HIV-negative participants that were previously diagnosed with TB. We found CXR and ECG changes that were suggestive of PAH in some participants after a

Table 3. Radiological features of the lung scarring chest X-ray

	n (%)
Right lung	
Right upper lobe/zone	10 (50)
Right mid-zone	1 (5)
Right lower lobe/zone	4 (20)
Left lung	
Left upper lobe/zone	1 (5)
Left mid-zone	1 (5)
Left lower zone	1 (5)
Diffuse fibro-cavitary changes	1 (5)
No fibro-cavitary changes	8 (40)
Fibro-cavitary changes limited to one lobe	6 (30)
Fibro-cavitary changes in two lobes	3 (15)
Fibro-cavitary changes in three lobes	2 (10)

median duration of 30 months after TB diagnosis. However, no ECHO features of PAH were noted in all participants. A decline in TAPSE was observed over time after TB diagnosis, suggesting a possible decline in right ventricular function.

CXR is readily used as a screening tool for PAH, particularly in low-resource settings and is also able to assess lung parenchymal changes.[16] CXR has a high sensitivity (96.9%) and specificity (99.1%) for detection of PAH when pre-test probability is 50% or more.[17] Miniati *et al.*[17] suggested that CXR findings that are suggestive of PAH are sufficient to warrant further investigation by RHC and that a normal CXR does not exclude the presence of PH. The severity of PH, however, cannot be correlated with CXR changes.[16] We showed in this study that 85% of the participants had CXR features that were suggestive of PH. Although the pre-test probability in these patients was low, these findings still indicated a possible need for further investigations, which would include more definitive investigations such as chest computed tomography (CT) scan and RHC for the confirmation of PAH. This would offer this subgroup of patients novel therapies for PAH under a trial scenario to observe outcomes.

ECG is also another cost-effective screening tool that is not sufficiently sensitive or specific for the diagnosis of PH. For instance, a previous study showed that ECG can be used to detect right ventricular hypertrophy and right-axis deviation in patients with PAH 87% and 79% of the time, respectively.[18] Another study conducted by Al-Naamani *et al.*[17] demonstrated a positive predictive value that was >80% in specific ECG criteria, namely R/S amplitude in V1 >1 and right-axis deviation of QRS axis >110^0.[19] The absence of ECG features does not exclude the presence of PAH.[18] Our study found right-axis deviation in one participant and a dominant R wave in V1.

Transthoracic ECHO is used as a screening tool for suspected PH in individuals with suggestive signs and symptoms. It determines the probability of PH and has a sensitivity of 83%;[20] however, detection of mild PH is limited.[21] PASP is estimated from the peak tricuspid regurgitant jet velocity and the right ventricular size and function is measured by TAPSE.[22] The accuracy of transthoracic ECHO in estimating PASP has been questioned as it may frequently underestimate PASP.[23] This has been attributed to inaccuracies in the estimation of right atrial pressure and poor Doppler imaging of the trans-tricuspid regurgitant jet.[23]

The measurement of the tricuspid regurgitant velocity (TRV) by echocardiography improves the probability of detecting PAH. An elevated TRV (>3.4 m/s) suggests a high probability of PAH. We did not include TRV in the analysis for this study, and this is a potential limitation of the study.

The trend of a decreasing TAPSE over time observed in our study highlighted the potential development of PAH over time from initial TB diagnosis. Perhaps the lack of ECHO findings that were suggestive of PAH in this study was due to PAH developing later than the median time of 30 months (IQR 14 - 42). A study undertaken by Humbert *et al.*[24] found a 27-month delay between onset of symptoms and diagnosis of PAH, with 75% of patients having New York Heart Association functional class III at time of diagnosis.[24] This suggested that these individuals may need further prospective follow-up of RV function as well as the performance of more detailed ECHO measures such as TRV to determine if PAH is present.

CT is becoming more accepted as an initial test in the evaluation of PH.[16,25] A main pulmonary artery diameter (PAD) ≥29 mm has an 87% sensitivity in the diagnosis of PH.[21] The size of the pulmonary artery measured on CT is positively correlated with the severity of PH.[26] A mean PAD (mPAD) and mPAD: ascending aorta diameter (AAD) ratio >1 has been shown to have a high correlation (r=0.51 and r=0.53, respectively; p<0.001) with PAP. When an increased mPAD is accompanied by a segmental artery-to-bronchus ratio that is >1:1 in 2 or 4 pulmonary lobes, sensitivity in the diagnosis of PH is 100%.[26] A mPAD:AAD ratio >1 has a sensitivity of 70.8% and a specificity of 76.5% for the diagnosis of PH. The positive predictive value of mPAD: AAD ratio >1 for the diagnosis of PH is 96%.[27] CT is further useful in identifying other causes of PH such as pulmonary vasculature, lung parenchyma and cardiovascular structures.[28]

One of the major limitations of this pilot study was the small number of participants that were recruited and enrolled in the study. Identifying participants who were previously treated for TB and had no underlying risk factors for the development of PAH is difficult in a quaternary hospital where most patients suffer from several co-existing pathologies. A more detailed ECHO evaluation of PAH combined with CT may be of value in future studies. Finally, the duration from time of TB diagnosis to enrolment may have been too short to identify the occurrence of PAH. Therefore, this period should be extended in future studies to ensure that sufficient time is provided for PAH to develop.

Conclusion

Although we did not determine ECHO findings that were suggestive of PAH in the HIV-negative participants that were previously treated for TB, we did find the presence of CXR and ECG features which were suggestive of PH and the possible presence of PAH. This provides enough evidence to prompt further studies with larger sample sizes, a more heterogeneous post-TB population and inclusion of more in-depth ECHO analysis to evaluate RV function in combination with radiological studies such as CT to examine the occurrence of PAH after TB.

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Author contributions. AM conducted the study, interpreted the data and wrote the manuscript. ISK and FS conceptualised the study, assisted with data interpretation and revised the manuscript. All the authors approved the final manuscript for publication.

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1. Mello FCQ, Silva DR, Dalcolmo MP. Tuberculosis: Where are we? J Bra de Pneumol 2018;44(2):82. https://doi.org/10.1590/s1806-37562017000000450
2. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990 - 2019: A systematic analysis for the global burden of disease study 2019. Lancet 2020;396(10258):1204-1222.
3. Glaziou P, Floyd K, Raviglione MC. Global epidemiology of tuberculosis. Semin Respir Crit Care Med 2018;39(3):271-285. https://doi.org/10.1101%2Fcshperspect.a017798
4. Shah M, Reed C. Complications of tuberculosis. Curr Opin Infect Dis 2014;27(5):403-410. https://doi.org/10.1097/QCO.0000000000000090
5. Akkara SA, Shah AD, Adalja M, Akkara AG, Rathi A, Shah DN. Pulmonary tuberculosis: The day after. Int J Tuberc Lung Dis 2013;17(6):810-813. https://doi.org/10.5588/ijtld.12.0317
6. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37(1):67-119. https://doi.org/10.1093/eurheartj/ehv317.
7. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53(1):1801913. https://doi.org/10.1183/13993003.01913-2018
8. Chang WT, Weng SF, Hsu CH, et al. Prognostic factors in patients with pulmonary hypertension – a nationwide cohort study. J American Heart Assoc 2016;5(9). https://doi:10.1161/JAHA.116.003579
9. Kim HY, Song KS, Goo JM, Lee JS, Lee KS, Lim TH. Thoracic sequelae and complications of tuberculosis. Radiographics 2001;21(4):839-858. https://doi.org/10.1148/radiographics.21.4.g01jl06839.
10. Montani D, Günther S, Dorfmüller P, et al. Pulmonary arterial hypertension. Orphanet J Rare Dis 2013;8:97. https//doi.10.1186/1750-1172-8-97
11. Cudkowicz L. The blood supply of the lung in pulmonary tuberculosis. Thorax 1952;7(3):270-276. https://doi.org/10.1136%2Fthx.7.3.270
12. Montani D, Chaumais MC, Guignabert C, et al. Targeted therapies in pulmonary arterial hypertension. Pharmacol Ther 2014;141(2):172-191.
13. Verma AK. Tuberculosis and pulmonary hypertension: Commentary. Lung India 2016;33(2):232-233. https://doi.org/10.1016/j.pharmthera.2013.10.002
14. Allwood BW, Maarman GJ, Kyriakakis CG, Doubell AF. Post-pulmonary tuberculosis complications in South Africa and a potential link with pulmonary hypertension: Premise for clinical and scientific investigations. S Afr Med J 2018;108(7):12339. https://doi.org/10.7196/samj.2018.v108i7.13359
15. Martínez-García MÁ, De Gracia J, Relat MV, et al. Multidimensional approach to non-cystic fibrosis bronchiectasis: The FACED score. Eur Respir J 2014;43(5):1357-1367. https://doi:10.1183/09031936.00026313
16. Ascha M, Renapurkar RD, Tonelli AR. A review of imaging modalities in pulmonary hypertension. Annals Thorac Med 2017;12(2):61-73. https://doi.org/10.4103/1817-1737.203742
17. Miniati M, Monti S, Airo E, et al. Accuracy of chest radiography in predicting pulmonary hypertension: A case-control study. Thromb Res 2014;133(3):345-351. https://doi.org/10.1016/j.thromres.2013.12.019
18. Forfia PR, Trow TK. Diagnosis of pulmonary arterial hypertension. Clin Chest Med 2013;34(4):665-681. https//doi.10.1016/j.ccm.2013.09.001.
19. Al-Naamani K, Hijal T, Nguyen V, Andrew S, Nguyen T, Huynh T. Predictive values of the electrocardiogram in diagnosing pulmonary hypertension. Int J Cardiol 2008;127(2):214-218. https://doi.org/10.1016/j.ijcard.2007.06.005
20. Janda S, Shahidi N, Gin K, Swiston J. Diagnostic accuracy of echocardiography for pulmonary hypertension: A systematic review and meta-analysis. Heart 2011;97(8):612-622. https://doi.org/10.1136/hrt.2010.212084
21. Sirajuddin A, Donnelly EF, Crabtree TP, et al. ACR appropriateness criteria suspected pulmonary hypertension. J Am Coll Radiol 2017;14(5s):S350-S361. https://doi.org/10.1016/j.jacr.2017.01.040
22. Ahmed M, Dweik RA, Tonelli AR. What is the best approach to a high systolic pulmonary artery pressure on echocardiography? Cleveland Clin J Med 2016;83(4):256-260. https://doi.org/10.3949/ccjm.83a.14186
23. Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009;179(7):615-621. https://doi.org/10.1164%2Frccm.200811-1691OC
24. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: Results from a national registry. Am J Resp Crit Care Med 2006;173(9):1023-1030. https://doi.org/10.1164/rccm.200510-1668oc
25. Mahammedi A, Oshmyansky A, Hassoun PM, Thiemann DR, Siegelman SS. Pulmonary artery measurements in pulmonary hypertension: The role of computed tomography. J Thorac Imaging 2013;28(2):96-103. https://doi.org/10.1097/rti.0b013e318271c2eb
26. Tan RT, Kuzo R, Goodman LR, Siegel R, Haasler GB, Presberg KW. Utility of CT scan evaluation for predicting pulmonary hypertension in patients with parenchymal lung disease. Medical College of Wisconsin Lung Transplant Group. Chest 1998;113(5):1250-1256. https://doi.org/10.1378/chest.113.5.1250
27. Ng CS, Wells AU, Padley SP. A CT sign of chronic pulmonary arterial hypertension: The ratio of main pulmonary artery to aortic diameter. J Thorac Imaging 1999;14(4):270-278. https://doi.org/10.1097/00005382-199910000-00007
28. Altschul E, Remy-Jardin M, Machnicki S, et al. Imaging of pulmonary hypertension: Pictorial essay. Chest 2019;156(2):211-227. https://doi:10.1016/j.chest.2019.04.003

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CHAPTER 3: APPENDICES

3.1 Appendix A – Ethics approval certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr A Miri

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180275

NAME: (Principal Investigator)	Dr A Miri
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Helen Joseph Hospital
PROJECT TITLE:	Occult pulmonary arterial hypertention in patients with previous pulmonary tuberculosis
DATE CONSIDERED:	23/02/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr I Kalla
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	05/06/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **February** and will therefore be due in the month of **February** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

20/06/2018
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

3.2 Appendix B – Data collection sheets

1) Participant Information Sheet

Study Number_____

Information Form for the study:
Occult Pulmonary Arterial Hypertension in patients with previous Pulmonary Tuberculosis

Dear Sir/Madam,

My name is Dr. Anisa Miri. I am a doctor specializing in Internal Medicine at the University of the Witwatersrand. As part of my training, I am required to complete a research project, which I am inviting you to participate in.

The aim of this research is to assess the presence of pulmonary artery hypertension in individuals who have previously had one episode of pulmonary tuberculosis. One of the possible long-term complications of pulmonary tuberculosis is the development of pulmonary hypertension (a high blood pressure in the artery connecting the heart and the lungs), however this is usually diagnosed at a late stage of the disease. This research will provide us with information about how frequently this complication occurs before symptoms arise and, if significant, may suggest that we identify this specific complication sooner in order to institute earlier treatment. This particular study is for research purposes only; therefore, the findings will not change your specific therapy. However it may improve the quality of care for patients in the future.

There is no risk to you in participating in this study. Your involvement in this research is completely voluntary; furthermore, any information obtained will remain confidential and will not be able to be traced back to you. If you choose to participate, you will be asked a few brief questions related to your diagnosis of pulmonary tuberculosis and any symptoms you may currently experience. You will also be asked to undergo four specific tests, namely: an electrocardiogram (ECG), chest radiograph or X-ray, a lung function test (Spirometry) and transthoracic echocardiography

(ECHO), which is a sonar of the heart. None of these investigations are invasive and will not subject you to any pain or complications.

By agreeing to participate in this research project and signing this form, you are agreeing to allow me to access your medical records that are relevant to this project, as well as to perform the investigations mentioned above and to use the data captured.

There is neither payment nor cost involved, should you agree to participate in the study.

If you choose to not participate in this study, you will not be penalized in any way. At any stage during the study you may choose to withdraw. A decision not to participate will have no influence over the care you receive from your doctor or the clinic you are attending.

If you require any further information about the study at any time, you may contact me on telephone no. 082 372 2438, or by e-mail on anisan.miri@gmail.com. You also have the option of contacting my supervisor, Dr Ismail Kalla, on telephone no. 011 854 2634, or by e-mail on iskalla786@gmail.com.

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.

If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for reading this Information Sheet.
Date: June 2018

2) Participant Consent Sheet

PARTICIPANT CONSENT SHEET

Project Title

Occult Pulmonary Arterial Hypertension in patients with previous Pulmonary Tuberculosis

1. I have been given a Participant Information Sheet which explains the nature and processes involved in this study, which is attached hereto;
2. I was given time to read it, or had it read to me, in the language I best understand;
3. I was given time to ask any questions I wanted to and found any answers given to me to be reasonable and satisfactory;
4. I believe I fully understand why the study is being conducted and what the intended outcomes will be;
5. I understand that there will be no immediate benefit to me, should I agree to participate, nor will I receive any payment; conversely, participation will not cost me nothing but my time;
6. I understand that, even if I initially consent to take part in the study, I may subsequently withdraw at any time and would not be required to give any reasons; if that happened, any data collected about me for the purposes of the study would immediately be destroyed, unless I give consent for it to be retained
7. I have been given a range of contact details, listed below. If I require further information or become concerned about any aspect of this study I am free to speak to any of these contacts.

Contact details:

Dr Anisa Miri, Principal Investigator, telephone no. 082 372 2438, or by e-mail anisan.miri@gmail.com

Dr Ismail Kalla, Supervisor, on telephone no. 011 854 2634, or by e-mail at iskalla786@gmail.com

Professor CB Penny, Chairperson of the Human Research Ethics Committee (Medical) at the University of Witwatersrand, on telephone no. 011 717 2301, or by e-mail at Clement.Penny@wits.ac.za.
Ms. Z Ndlovu or Mr Rhulani Mkansi, Committee Secretariat, telephone nos.: 011 717 2700 or 1234, or by e-mail at: Zanele.Ndlovu@wits.ac.za or Rhulani.Mkansi@wits.ac.za

Name of Participant: _____

Date: _____

Place: _____

Signature or mark _____

Witnessed by:

Name of Witness: _____

Signature: _____

Date: _____

3) Data Sheet

Occult pulmonary arterial hypertension in patients with previous pulmonary tuberculosis

1. DEMOGRAPHICS

Patient ID (Study number)_____

DOB: _____/_____/_____

Age: _____

Gender: M / F

Ethnicity: Black / White / Colored / Indian / Other

2. PREVIOUS PULMONARY TB DIAGNOSIS

1st EPISODE

Date of diagnosis of previous pulmonary TB_____

Method of diagnosis: Sputum / Radiological / Empiric / Unsure

Rifampicin Sensitive: Yes/No/Unsure

Treatment taken: Yes/ No

Detail treatment taken: Rifafour / Other: Name drugs_____

Duration of Therapy in months: _____

Completed treatment: Yes / No

2nd EPISODE if present & repeated for any additional episodes:

Date of diagnosis of previous pulmonary TB: _____

Method of diagnosis: Sputum / Radiological / Empiric

Rifampicin Sensitive: Yes/No/Unsure

Treatment taken: Yes/ No

Detail treatment taken: Rifafour / Other: Name drugs_____

Duration of Therapy in months: _____

Completed treatment: Yes / No

3. CURRENT PRESENCE OF RESPIRATORY SYMPTOMS

Cough	Yes / No
Expectoration	Yes / No IF YES, COLOUR _____
Dyspnea	Yes / No IF YES, MMRC 0 / 1 / 2 / 3/ 4
Haemoptysis	Yes / No IF YES • VOLUME _____ • HISTORY OF BRONCHIAL ARTERY EMBOLIZATION Yes / No

4. CO – MORBIDITIES AND RISK FACTORS

Smoker	Yes / No If YES, pack years _____
Hypertension	Yes / No
Diabetes	Yes / No
Malignancy	Yes / No
HIV	Yes / No IF YES • Duration of ART _____ • ART Regimen History_____ _____ • CD4 _____ • VL _____

Screening for Sleep Disordered Breathing (NoSAS Score)

1) Neck circumference > 40 cm: Yes / No (If yes, 4 points)
2) Obesity
   - BMI 25kg/m^2 to < 30kg/m^2: Yes / No (If yes, 3 points)
   - BMI ≥ 30 kg/m^2: Yes / No (If yes, 5 points)
3) Snoring: Yes / No (If yes, 2 points)
4) Age > 55 years: Yes / No (If yes, 4 points)
5) Sex: M / F (If male, 2 points0

Final NoSAS Score _____

5. ECG FINDINGS

P - pulmonale: Yes / No

Right axis deviation: Yes / No

S1: Yes / No

Q3: Yes / No

T3: Yes / No

R wave in V1: Yes / No

Right ventricular hypertrophy: Yes / No

Right ventricular strain (T wave inversion in V1 – V3) : Yes / No

Right bundle branch block: Yes / No

6. CHEST X-RAY

Features of pulmonary hypertension:

- ➔ Elevated Cardiac apex: Yes / No
- ➔ Enlarged Right atrium: Yes / No
- ➔ Enlarged pulmonary arteries: Yes / No
- ➔ Pruning of peripheral pulmonary vessels: Yes / No

Evidence of Fibrosis (Circle if present) → Yes / No

➔ Zone

- Right – Upper / Middle / Lower
- Left – Upper / Middle / Lower

➔ Percentage: _____

Detail additional other findings → Yes / No

Volume loss – Location and Percentage _____

Other e.g.: Tracheal deviation _____

7. SPIROMETRY

FEV1	
FVC	
FEV1/FVC	
DLCO	

Restrictive Lung Disease: Yes / No Obstructive Lung Disease: Yes / No

Low DLCO: Yes / No

8. ROOM AIR SATURATION LEVEL

% Saturation:_____

9. ECHOCARDIOGRAPHY

LVIDd (mm)	
LVIDs (mm)	
LVEF (%)	
Regional wall motion abnormalities	Yes / no
Left atrium (mm)	
Ascending aorta (mm)	
E/a	
E/e	
Diastolic dysfunction	Yes / no
Aortic regurgitation	Yes / no
Aortic stenosis	Yes / no
Mitral regurgitation	Yes / no
Mitral stenosis	Yes / no
Tricuspid regurgitation	Yes / no
TAPSE (mm)	
PASP (mmHg)	
RAP (mmHg)	
IVC (mm)	

3.3 Appendix C – Classification of Pulmonary Hypertension (2015 ESC/ ERS Guidelines for the diagnosis and treatment of pulmonary hypertension)

1 – Pulmonary arterial hypertension	**1. Idiopathic** **2. Heritable** **3. Drugs and toxins induced** **4. Association with other disease** o **Connective tissue disease** o **HIV Infection** o **Portal hypertension** o **Congenital heart disease** o **Schistosomiosis**
2 – Pulmonary hypertension due to left heart disease	**1. Left ventricular systolic dysfunction** **2. Left ventricular diastolic dysfunction** **3. Valvular disease** **3. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies** **4. Other**
3 – Pulmonary hypertension due to lung disease and/or hypoxia	**1. Chronic obstructive pulmonary disease** **2. Interstitial lung disease** **3. Other pulmonary diseases with mixed restrictive and obstructive pattern** **4. Sleep-disordered breathing** **5. Alveolar hypoventilation disorders** **6. Chronic exposure to high altitude** **7. Developmental lung disease**
4 – Chronic thromboembolic	**1. Chronic thromboembolic pulmonary**

pulmonary hypertension and other pulmonary artery obstruction	**hypertension** **2. Other pulmonary artery obstruction**
5 – Pulmonary hypertension with unclear and/or multifactorial mechanisms	**1. Haematological disorders** **2. Systemic disorders** **3. Metabolic disorders** **4. Others**

3.4 Appendix D - Turnitin Report

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