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IDIOPATHIC PULMONARY FIBROSIS IN SOWETO, SOUTH AFRICA: A DESCRIPTIVE STUDY

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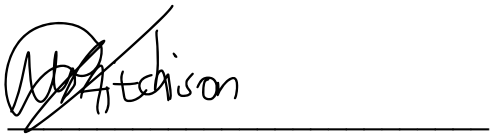
A research report submitted to the Faculty of Science, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine (Internal Medicine).

Johannesburg, 5 October 2021

DECLARATION

I, Wesley Mark Aitchison, student number 0702495A, declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Medicine (Internal Medicine) at the University of the Witwatersrand, Johannesburg. This research report is submitted in the publishable format as recognized by the Faculty of Health Sciences. It has not been submitted before for any degree or examination at any other University.



Fifth day of October 2021 in Johannesburg

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS RESEARCH REPORT

The author intends to publish this research report in a peer reviewed journal.

ETHICAL CONSIDERATIONS

Permission for this study was granted before data collection commenced by Dr JML Tsitsi (Head of Department: Internal Medicine, Chris Hani Baragwanath Academic Hospital), the Medical Advisory Committee, hospital management, as well as the Human Resource Ethics Committee (Medical) at the University of the Witwatersrand (clearance number M180302). It was also submitted via National Health Research Database website (reference GP_201902_015).

ABSTRACT

Background: Idiopathic Pulmonary Fibrosis (IPF) is a specific form of age-related fibroproliferative interstitial pneumonia that is chronic, progressive, and carries a poor prognosis, with median survival just 2.5-3.5 years from diagnosis. At present, there are very limited South African data available regarding the incidence, presentation, and risk factors in this population.

Objectives: This study sought to describe the cohort of patients that attended the respiratory outpatient services at a tertiary-level hospital in South Africa during the period 2007-2016. To the best of the authors' knowledge, this the first such descriptive study performed in Africa.

Methods: This was a retrospective, descriptive record review, that included patients ≥ 18 years of age who fulfilled 2011 ATS/ERS/JRS/ALAT diagnostic criteria for IPF.

Results: Data from 74 patients were used for analysis in this study, of which 60.8% were female. The mean age (SD) was 64.4 (10.9) years, and the majority (79.7%) were Black. Over half of the patients (40/74, 54.1%) were current or previous smokers, although there was no correlation between smoking history and age or baseline pulmonary function testing. All patients reported dyspnoea, which was mMRC grade 3 or 4 in 80% of patients. HRCT chest was reported as radiological UIP in 72 patients (97.3%), and three patients underwent lung biopsy, all of which showed a UIP pattern. Fifty-eight patients (78.4%) had spirometry results available, with median FVC 67.3% of predicted; this was significantly higher in females. Median TL_{CO} was 39% predicted. Twenty-five patients (33.8%) received corticosteroids, of whom five (6.8%) received the prednisone-azathioprine-NAC regime. Three patients (4.1%) received nintedanib; two of whom showed slowing of decline in lung function, although no significant symptomatic improvement was reported. Mean duration of follow up was 13.3 months, although 85.1% of patients were lost to follow up.

Conclusion: Despite a fairly small sample size and retrospective nature, this study contributes to the body of literature on IPF, and highlights the need for additional studies in developing countries, particularly in Africa. Of particular concern is the late presentation and advanced disease noted in this cohort of patients.

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NOMENCLATURE & ABBREVIATIONS USED

ABG	Arterial Blood Gas analysis
ALAT	Latin American Thoracic Association
ATS	American Thoracic Society
CFA	Cryptogenic Fibrosing Alveolitis
CHBAH	Chris Hani Baragwanath Academic Hospital
COPD	Chronic Obstructive Pulmonary Disease
CPFE	Combined Pulmonary Fibrosis and Emphysema
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GAP	Gender-Age-Physiology
GORD	Gastro-oesophageal Reflux Disease
HIV	Human Immunodeficiency Virus
HRCT	High Resolution Computed Topography (of the chest)
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
JRS	Japanese Respiratory Society
LTDOT	Long Term Domiciliary Oxygen Therapy
mMRC	Modified Medical Research Council Dyspnoea Scale
NAC	N-acetylcysteine
PFT	Pulmonary Function Testing
PHT	Pulmonary Hypertension
PPIs	Proton Pump Inhibitors
PR	Pulmonary Rehabilitation
RV	Residual Volume
TB	Tuberculosis
TLC	Total Lung Capacity
TL_{CO}	Transfer factor of the Lung for Carbon Monoxide
UIP	Usual Interstitial Pneumonia

CHAPTER 1 - PROTOCOL & LITERATURE REVIEW

1.1. EXPANDED LITERATURE REVIEW

1.1.1. INTRODUCTION

Idiopathic Pulmonary Fibrosis (IPF) is a specific form of age-related fibroproliferative interstitial pneumonia that is chronic, progressive, and carries a poor prognosis. The aetiology is uncertain, and few treatment options are available at present. The disease affects only the lungs, with progressive decline in lung function associated with worsening dyspnoea[1,2].

1.1.2. EPIDEMIOLOGY

Although rare, IPF is the most common of the idiopathic interstitial pneumonias, accounting for 20–30% of interstitial lung diseases[3,4], and is up to five times more common than cystic fibrosis or amyotrophic lateral sclerosis, yet attracts a miniscule amount of research funding compared to these other rare diseases[5]. The annual incidence of IPF is estimated to be 4.6–16.3 cases per 100 000 people, and appears to be increasing[2], although marked differences exist in incidence between different countries, with some studies estimating an incidence of 28 cases per 100 000[6]. The incidence in individuals 75 years and older may be closer to 80 per 100 000 people[7]. An international IPF registry would aid in more accurate data[8], which may also prompt increased research interests.

At present, there are very limited South African data available regarding the incidence, presentation, and risk factors in this population, and none since the introduction of the 2011 ATS/ERS/JRS/ALAT diagnostic criteria[9]. There are only two reported studies of IPF in South Africa, performed when IPF was known by its previous name, Cryptogenic Fibrosing Alveolitis (CFA)[10,11]. Since these studies were undertaken before current definitions of IPF had been established, it is possible that diseases other than IPF, including other idiopathic interstitial pneumonias that may present very similarly to IPF, were included. These will therefore be excluded from this study. In addition, High Resolution Computed Topography (HRCT) was not available at that time but now forms an important aspect of diagnosis. One of the studies included only Black patients (51 patients)[11], while the other consisted mostly

of White and Coloured patients, with only two Black patients (42 patients in total)[10]. It is now accepted that the diagnosis of IPF in patients aged less than 50 years is rare[9], whereas these studies both included patients below 50 years of age, and even included patients as young as 25 years of age[10,11], suggesting that some of these patients may have had interstitial lung disease that would not meet the current diagnostic criteria for IPF.

IPF increases in incidence and prevalence with increasing age, with patients typically presenting in their sixth and seventh decades of life[9]. Males are more commonly affected than females, although there is evidence to suggest that males may be overdiagnosed while females may be underdiagnosed[12,13]. Racial differences vary between studies, with some showing increased mortality in Black patients[14], and others showing decreased mortality in this group[15].

1.1.3. Risk Factors & Pathogenesis

The exact aetiology of IPF is unknown, but several potential risk factors have been identified: smoking, exposure to metal and wood dust, gastro-oesophageal reflux disease, certain viral infections, exposure to livestock, certain occupations, and various genetic predispositions[16–17]. The pathogenesis of IPF is complex and poorly understood, and is thought to be initiated by an unknown inciting factor or exposure in a genetically susceptible individual, with dysfunction of fibroblasts and epithelial cells, succeeded by progressive fibrosis[16–20]. Such fibrosis is histologically and radiologically characterised by the presence of a pattern of usual interstitial pneumonia (UIP), although UIP is not specific to IPF.[1]

Smoking, in particular, has been shown to be a strong risk factor for the development of IPF and has also been shown to aggravate fibrosis in animal models[21,22]. Smokers may develop IPF at a younger age, with acute exacerbations being more common and bearing a higher mortality rate compared to non-smokers[23,24]. Smoking also increases cardiovascular risk and mortality, as well as lung cancer risk, further contributing to the poor prognosis observed in IPF[22,25]. Smoking appears to induce accumulation of inflammatory cells within the small airways and lung interstitium, and induces the production of transforming growth factor beta, which is pro-fibrotic, stimulates the production of collagen, and reduces particle clearance by alveolar macrophages[22,26].

Familial cases of IPF have been described, in which patients often present at a younger age. Familial pulmonary fibrosis, a disease with autosomal dominant inheritance with variable penetration, accounts for less than 5 percent of patients with IPF. Affected individuals may present with different interstitial lung diseases, even within the same family[27], and half of family members without clinical disease show evidence of alveolitis on gallium-67 scanning[28]. Another rare cause of UIP is Hermansky-Pudlak syndrome, an autosomal recessive disorder characterized by oculocutaneous albinism and platelet abnormalities[29]. Mutations in genes responsible for maintaining telomere length have also been identified and linked to pulmonary fibrosis, as well as bone marrow and liver dysfunction. Telomere shortening has been found in about one quarter of non-familial IPF cases[30–33]. Telomerase mutations and smoking can also induce telomere shortening[22,34]. In addition to the above, several mutations that have been associated with IPF include genes encoding surfactant proteins A2 and C, mucin 5B, desmoplakin, A-kinase anchoring protein 13, and more[35–40]. Micro-RNA alterations have also been observed, resulting in increased fibroblast and myofibroblast proliferation and collagen deposition, as well as reduced senescence and apoptosis[41–43].

Inflammation appears to precede fibrosis in some animal models, with a dominance of alveolar macrophages, neutrophils, eosinophils, and lymphocytes observed in alveolitis and early fibrosis[20,44]. In particular, the alveolar macrophage is believed to play a key a role in the pathogenesis of pulmonary fibrosis given its ability to effect mesenchymal cellular proliferation and collagen deposition by secretion of pro-inflammatory and pro-fibrotic cytokines[17,45,46]. There is, however, some doubt about the role of inflammation in IPF, given that anti-inflammatory therapy such as corticosteroids has minimal effect on disease progression, IPF patients do not generally demonstrate inflammatory changes, even in early disease, and fibrosis can be induced without inflammation in animal models[46–49]. Dysfunction of epithelial cells and aberrant fibroblast activation in the presence of little or no inflammation has been observed, likely caused by loss of cellular homeostasis and a shift in fibroblast subpopulations. This results in excessive deposition of connective tissue matrix, disruption of the basement membrane, and abnormal epithelial-mesenchymal cellular interactions[18,19,49–51]. There is also evidence to suggest that coagulation abnormalities may contribute to pathogenesis and mortality in IPF, and may arise from a pro-thrombotic state[52–54].

It is well established that there is progressive and unremitting fibrosis, despite the debate regarding whether or not inflammation is truly antecedent to the fibrotic process in IPF[2]. Fibrosis involves the alveolar epithelium, wall, and lumen as well as the lung parenchyma, although the exact mechanism by which this occurs is not well understood. It is believed that repeated subclinical injury results in disruption of the basement membrane and loss of type I epithelial cells, resulting in mesenchymal cells and fibroblasts entering the alveoli, and subsequent collagen deposition, contraction, and fibrosis[18,42,55,56]. These fibroblasts appear to have an increased ability to proliferate, are somewhat resistant to various antiproliferative substances, and have an increased propensity to differentiate into myofibroblasts[57–59]. Myofibroblasts, which produce significant amounts of collagen and have contractile properties, are derived from differentiated fibroblasts as well as from epithelial mesenchymal transformation[59,60].

Pro-inflammatory and pro-fibrotic cytokines, growth factors, and other mediators are central to this process and are increased, including transforming growth factor beta, fibroblast growth factor, connective tissue growth factor, platelet derived growth factor, insulin-like growth factor, tumour necrosis factor alpha, and various interleukins. Similarly, anti-inflammatory and anti-fibrotic substances are decreased, including interferon gamma and anti-inflammatory interleukins[61–64].

1.1.4. Presentation & Diagnosis

Typical symptoms on presentation include gradual onset of dyspnoea on exertion and non-productive cough, usually progressing over several months. Extrapulmonary manifestations such as fever or arthralgia are rare. Thorough history-taking including family history, exposure to medications, fumes, dusts, and radiation, and symptoms of connective tissue disease are critically important to establish other possible aetiologies of ILD. Clinical features include bibasal, fine inspiratory crackles (often termed “Velcro” crackles), and digital clubbing (in 25–75% of patients). If presenting late, patients may have features of pulmonary hypertension, cor pulmonale, and right heart failure[1,2,65,66].

Workup for patients with possible IPF is initially aimed at excluding other diagnoses, thereby confirming the diagnosis of IPF. This is based on a multi-disciplinary approach including clinical, radiological, and pathological investigations. The diagnosis of IPF requires the exclusion of other known causes of ILD, and a typical

UIP pattern on HRCT in patients not subjected to lung biopsy (see Table 3.1.). In patients subjected to lung biopsy, both radiological and histological findings are used to make the diagnosis of IPF (see Table 3.2.), although lung biopsy is not required in all patients[9].

Laboratory investigations are aimed at excluding connective tissue diseases, and usually include an antinuclear antibody and rheumatoid factor. Additional testing such as anti-topoisomerase and anti-cyclic citrullinated peptide antibodies may also be performed depending on the clinical circumstance[1,9]. At present, there are no specific serological or breath biomarkers that are diagnostic of IPF. Some biomarkers have been identified that are of prognostic significance, as well as for disease severity and activity monitoring; however, none are in routine clinical use[67–70].

Plain chest X-ray usually reveals reduced lung volumes, with an increase in reticular markings. HRCT is now essential for the diagnosis of IPF. A definite UIP pattern requires all of the following: subpleural and basal predominance of the disease, reticular infiltrates, honeycombing with or without traction bronchiectasis, and absence of features inconsistent with UIP. None of these findings are specific for the diagnosis of IPF and need to be interpreted within the patient's clinical context. Ground glass opacifications should be absent or minimal, but may be present, particularly in the setting of acute exacerbations[1,9,71].

As with most interstitial lung diseases, pulmonary function tests in patients with IPF usually show a restrictive pattern, with a reduced FVC and normal to high FEV_1:FVC ratio, low RV and TLC, and a reduced TL_{CO}, which typically declines with disease progression[1,72,73]. Bronchoalveolar lavage, although not generally recommended as part of the diagnostic workup unless an alternative diagnosis is suspected or HRCT findings are not consistent with UIP, may reveal an increase in polymorphonuclear leukocytes and eosinophils as well as increased IgG levels[1,9,74,75]. Surgical lung biopsy is usually reserved for patients with clinical, laboratory, or HRCT findings not consistent with IPF, and is recommended in preference to transbronchial lung biopsy[9]. UIP on surgical biopsy is characterised by patchy lung involvement, dense fibrosis with remodelling of lung architecture and honeycombing, fibroblastic foci, and typical subpleural and para-septal distribution. There should also be absence of features suggestive of other diseases or aetiologies. As with radiological findings, the

presence of UIP on histopathology is not specific to IPF and the clinical context is of utmost importance (see also Table 3.2.)[9,76,77].

1.1.5. MANAGEMENT & PROGNOSIS

While expert centres for rare pulmonary diseases do exist, particularly in developed countries, the majority of IPF patients are managed at general or tertiary level hospitals, whether in developed or developing countries[78–80]. Treatment options for IPF are limited, with previously-used treatment regimens being shown to be ineffective or even harmful. The Gender-Age-Physiology (GAP) index (see Table 3.4.) incorporates gender, age, and PFT results (FVC and TL_{CO}) provides a staging system (stages I to III) which then predicts mortality at one, two, and three years respectively[81]. This can be used to assist in decision-making regarding treatment options, as well as to guide patient and family expectations.

Supportive care including pulmonary rehabilitation, vaccination, and long-term domiciliary oxygen therapy are currently recommended, and form a critical component of the management of IPF[1]. Many patients with IPF have reported feeling that they had not received adequate information about their diagnosis, prognosis, and treatment options[82]. Education on these aspects is thus also an important part of IPF management, and similarly, smoking cessation should be encouraged at all times[47]. This may require extensive counselling, as well as various pharmacological therapies, including nicotine replacement therapy, bupropion, nortriptyline, or nicotine receptor antagonists such as varenicline. Other therapies currently not proven to be beneficial for this purpose include e-cigarettes, hypnotherapy, and acupuncture[83]. Early involvement of palliative care teams may be beneficial in alleviating suffering, and assisting with patient and family expectations and preparations[84,85].

Pulmonary rehabilitation (PR) is currently defined as “a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviours”[86]. In the context of ILD, exercise training appears to improve symptoms, exercise capacity, functional status, and quality of life, with the degree of improvement inversely related to the baseline function. Although longer treatment courses seem to have greater benefit, this benefit appears in the short term only and

is absent six months after the intervention[87–91]. In IPF specifically, mostly only small studies have been carried out, but seem to show improvement in dyspnoea, exercise capacity, and quality of life, but not overall health status[91–94].

In the past, various therapies including warfarin, azathioprine-prednisone-N-acetylcysteine (NAC), and cyclophosphamide were each used to treat IPF. Warfarin used in IPF without another indication for anticoagulation is associated with increased mortality[95]. In the past, the combination of azathioprine, prednisone, and NAC was recommended as a treatment regimen for select patients with IPF, and was thought to be safe, despite its efficacy not being well documented[47,96]. Subsequently, it was demonstrated that patients treated with this regimen had worse outcomes in terms of risk of death and hospitalisations, and is thus no longer recommended[97,98]. Other immunomodulatory agents such as cyclophosphamide, colchicine, interferon gamma 1b, and NAC have also not shown meaningful benefit[99,100]. Agents used to treat pulmonary hypertension such as sildenafil and endothelin receptor antagonists have also failed to show benefit in IPF[101,102].

Currently, the only conditionally recommended pharmacological therapies are pirfenidone and nintedanib, while anti-acid agents may be considered in appropriate patients[1,2,97]. Pirfenidone, an anti-fibrotic drug that appears to act by inhibiting the effect of transforming growth factor beta and platelet derived growth factor[103,104], is available in South Africa for approximately R40 000 per month on maintenance dosing[105,106]. Pirfenidone improves all-cause mortality, progression of IPF, and decline in FVC and six-minute walk test distance; however, it does not reduce acute exacerbations of IPF[107]. The drug is taken three times daily, and common adverse effects include nausea, photosensitivity/rash, and abdominal pain or discomfort[105]. Nintedanib, a multi-site tyrosine kinase inhibitor, prevents fibrosis by inhibiting, amongst others, platelet-derived growth factor receptor, fibroblast growth factor receptor, and vascular endothelial growth factor receptor. It is taken twice daily, and common adverse effects include diarrhoea (in 62% of patients), nausea, and abdominal pain or discomfort[108]. It is currently available on Section 21 in South Africa, but is due to be launched shortly[1,109]. Nintedanib slows rate of decline in FVC as well as time to first acute exacerbation, but has only a small effect on overall survival[108].

These drugs are both very costly, and do seem to improve overall quality of life[1,110]. There does not appear to be a significant difference between pirfenidone and nintedanib in terms of reduction in rate of FVC decline or mortality when compared[111]. Additionally, trials involving these agents did not extend beyond one year, and did not include patients with very early or very severe disease, therefore bringing into question their utility outside of these parameters[1,111]. While it appears safe to use these two agents in combination, the therapeutic benefit thereof remains unknown[112]. Multiple novel agents, including pamrevlumab and recombinant pentraxin-2, are currently being investigated with some promise[113]. Several traditional Chinese medicines have been found to improve symptoms and prognosis, although there is currently insufficient evidence to make recommendations in this regard[80]. Given the high prevalence of gastro-oesophageal reflux in IPF and the subsequent risk of recurrent micro-aspiration, anti-acid therapy, particularly proton pump inhibitors (PPIs), has been shown to be associated with a lower radiological fibrosis score, less reduction in FVC, and prolonged survival, although more recent evidence has suggested no benefit[114–118].

In selected patients, lung transplantation may improve functional status and survival significantly, and patients younger than 60 years of age may have increased benefit from bilateral lung transplant rather than unilateral lung transplanation[119–124]. Patients who have been diagnosed with IPF should generally be referred for transplantation when they have any of the following: TL_{CO} <40% predicted, FVC <80% predicted, any dyspnoea or functional limitation due to their lung disease, and haemoglobin oxygen saturation of ≤88% (at rest or on exertion). Furthermore, these patients should be listed for transplant when they have pulmonary hypertension on echocardiography or right heart catheterisation; hospitalisation for acute exacerbation, pneumothorax, or worsening respiratory function; or during six months of follow-up with a decline in FVC of ≥10%, decline in TL_{CO} of ≥15%; or six-minute walk test distance <250 metres, oxygen desaturation <88%, or decline in distance >50 metres within six months[125]. In South Africa, access to experienced transplant centres and donor organs limits the referral and subsequent transplant of IPF patients[1].

The management of comorbidities and complications of IPF are crucial for holistic patient management and may impact quality of life and outcomes. GORD and pulmonary hypertension have been discussed above. Most comorbidities such as

diabetes mellitus, hypothyroidism, cardiovascular conditions, obstructive sleep apnoea, and chronic obstructive pulmonary disease (COPD) require early identification and management. When managing lung cancer, an important consideration is that surgery, chemotherapy, and radiation therapy may all increase the risk of acute exacerbations. Patients with IPF are at an increased risk of venous thromboembolism. This also requires early identification and treatment, and must be considered in acute exacerbations (discussed below). Depression and anxiety are common in patients with IPF, and may require both psychotherapy and pharmacotherapy[126].

The clinical course of IPF is somewhat heterogeneous, with median survival just 2.5–3.5 years from diagnosis, although up to one quarter of patients may live beyond 10 years[2,127]. Up to 20% of patients experience acute exacerbations, which carry a mortality rate of at least 50%, even in developed countries[5]. The median survival following an acute exacerbation is only three to four months[128]. While some studies have shown increased frequency of acute exacerbations and mortality in smokers, others have found the opposite[26,79,128,129].

1.1.6. Acute Exacerbations of IPF

Acute exacerbations of IPF, currently defined as “any acute respiratory event, typically less than one month in duration, characterized by new bilateral ground-glass opacification/consolidation not fully explained by cardiac failure or fluid overload” (see also Table 3.3), have no proven effective therapies, and generally carry a very poor prognosis[130]. Factors associated with acute exacerbations may include severity of IPF, pneumonia and other infections, micro-aspiration, pulmonary embolism, invasive procedures (including surgery and bronchoscopy), and coronary artery disease[115,131–134]. Patients usually present with worsening dyspnoea or exertion tolerance and cough, and clinically may be tachypnoeic, with fine basal crackles in keeping with ILD. HRCT reveals bilateral ground glass infiltrates or consolidation on a background of UIP. Laboratory investigation is directed toward ruling possible precipitants in or out, and may include blood and sputum cultures, C-reactive protein, procalcitonin, troponin, D-dimer, pro-BNP, and other testing depending on the clinical circumstance[130,135].

There is a lack of evidence for most therapies, but corticosteroids are generally recommended, and antimicrobial therapy is used where infection is the known or

suspected precipitant. Treatment is largely supportive and palliative, and mechanical ventilation is not recommended in view of the high mortality rate and poor long-term prognosis[47,130,136,137]. Therapies including anticoagulation (including thrombomodulin alpha), immunosuppressants, and biologics have hitherto shown no benefit when used in acute exacerbations of IPF[136,138]. While nintedanib may help prevent acute exacerbations, there is minimal evidence regarding continuing or adding either nintedanib or pirfenidone during an acute exacerbation[130,139]. It is currently recommended to continue treatment in patients on these agents, but not to initiate them during an acute exacerbation[1].

1.1.7. Conclusion

IPF is a devastating interstitial lung disease affecting the elderly, and despite vast improvements in the understanding of the pathophysiology of the disease, there remains little widely available treatment beyond supportive and palliative measures. Newer agents that show some benefit are currently very costly and therefore not accessible for many patients. IPF carries a poor prognosis, particularly following acute exacerbations. Little is known about the epidemiology and risk factors in South African populations specifically; such data may be valuable to improve diagnosis and care offered to such patients in the future.

1.2. Study Protocol

1.2.1. Aim

This study aims to describe, using data from available records, the cohort of patients that attend or have attended the respiratory outpatient services at Chris Hani Baragwanath Academic Hospital (CHBAH). To the best of the authors knowledge, this is the first such study in South Africa and indeed Africa, using the 2011 definition of IPF.

1.2.2. Objectives

1. To describe the demographics, presentation symptoms, and clinical features of patients in the sample population.
2. To determine any identifiable risk factors and associations present in this population, including laboratory studies performed.

3. To determine the presentation and subsequent lung functions, including but not limited to forced vital capacity, total lung capacity, and transfer factor of the lung for carbon monoxide (TL_{CO}) in this population.
4. To determine treatment regimens used in this population, and the effect (if any) on symptoms and lung function.
5. Where documented, to determine mean time from symptom development to death, as well as from diagnosis to death, in patients who have died, and to thereby demonstrate if diagnosis was delayed.

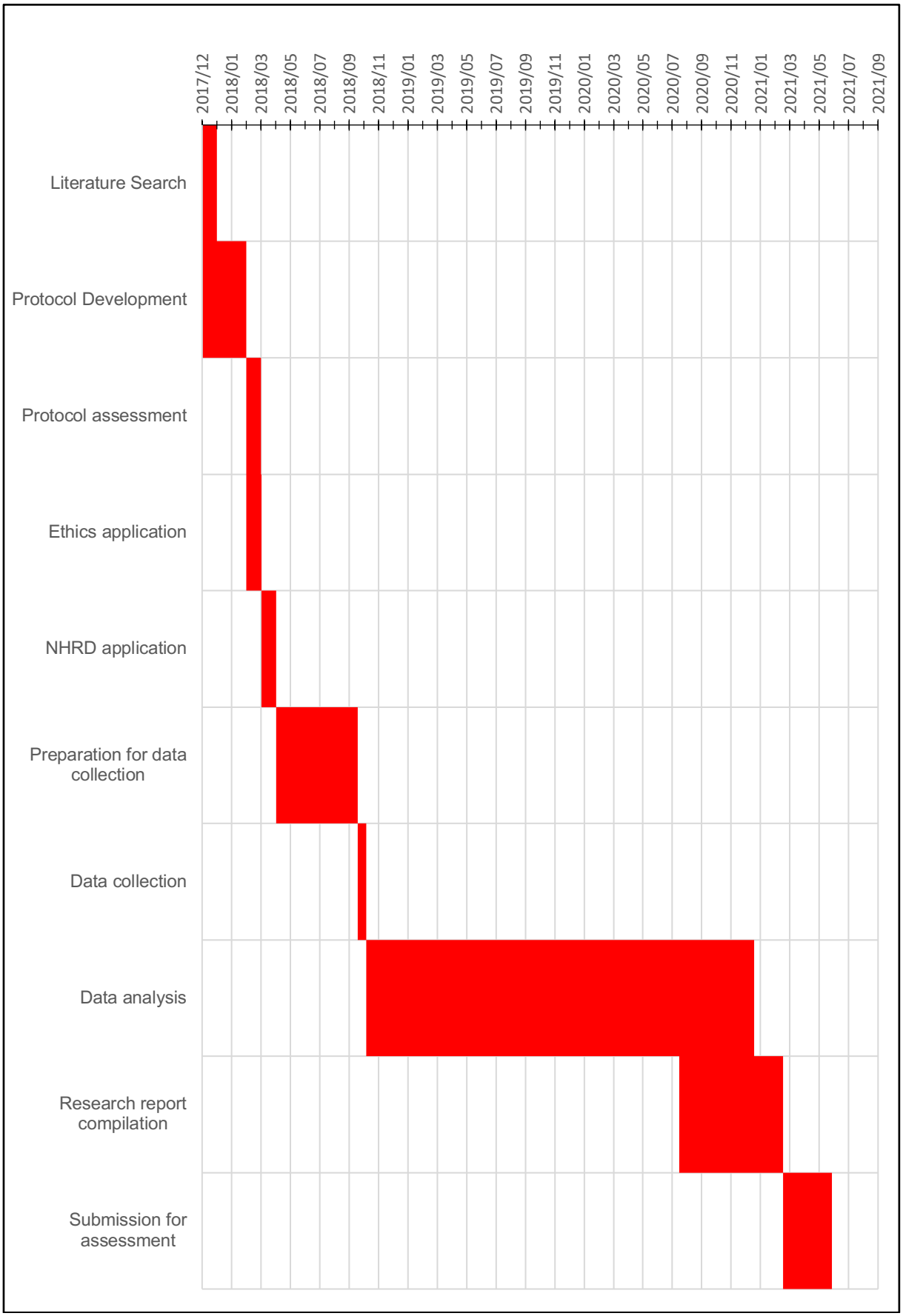
1.2.3. METHODS

a. ***Study design***: Retrospective, descriptive record review for the 10-year period 2007–2016
b. ***Study population***:
   The sample size for this study was estimated to be 100 predominantly Black patients, in keeping with the demographics of the hospital population.
   Inclusion criteria:
   - Aged ≥ 18 years
   - Diagnosis of IPF according to the 2011 ATS/ERS/JRS/ALAT diagnostic criteria[47] (see Appendix A)
   - Evaluation by the Division of Pulmonology at Chris Hani Baragwanath Academic Hospital

   Exclusion criteria:
   - Files in which it is documented that the patient requested their information not be used for studies
c. ***Data collection***: The following data was captured from patient records: demographics, clinical, laboratory and radiologic findings, lung function tests, treatment, date of last follow-up visit and, where applicable and available, date of death. Data was captured by the investigator on a data collection sheet (see Appendix C) using files kept in the respiratory outpatient clinic at CHBAH. No information that could be used to identify patients was captured. These data were then be transcribed into electronic format using a specially-designed, password-protected database for analysis.
d. ***Data analysis***: Using the aforementioned database, data was analysed using various statistical software programmes. Patient demographics and clinical characteristics of the cohort group were summarised using descriptive

statistics. Normal distribution was represented by means and standard deviation. Skewed distribution was represented by medians and interquartile ranges. Risk and demographic factors, clinical features, and results of special investigations, including pulmonary function testing, were analysed using the Chi-squared test for nominal variables and logistic regression for quantitative variables. Where outcome variables are not nominal (for example, decline in FEV_1 over time or relationship between mMRC grade and TL_{CO}), the Mann-Whitney test and Spearman rank test were used, respectively. Similarly, duration of various treatment modalities received and effect thereof upon pulmonary function tests, symptoms and clinical features, survival, and adverse events were analysed using the Spearman rank test or linear regression depending on the outcome being sought. Where applicable (depending on data availability), survival data and effect of treatment on survival will be analysed using Kaplan Meier plots, log-rank testing, and Cox proportional hazards regression analysis. The assistance of a statistician was sought to assist with these analyses. A p-value of <0.05 was considered statistically significant.

e. ***Funding***: All expenses were covered by the principal investigator, which include paper, stationery, and printing. There were no cost implications for patients, the hospital, or the Department of Health.
f. ***Ethics approval***: This research application was submitted to the University of the Witwatersrand HREC for ethical approval (M180302). Approval was granted by the Head of the Division of Pulmonology, Head of Department of Internal Medicine, as well as the Hospital MAC; see attached in Appendix E.
g. ***Intentions:*** This study was conducted for purposes of submission for a Master of Medicine degree, as well for publication in a peer reviewed medical journal.
h. ***Limitations:*** Being retrospective, this study relied upon existing records, in which poor record keeping and missing patient information or documentation limited the availability of all data for all patients.
i. ***Timeline:*** See Gantt chart on next page.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Ethics application
NHRD application
Preparation for data collection
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Data analysis
Research report compilation
Submission for assessment

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CHAPTER 2 - PROPOSED MANUSCRIPT

2.1. BACKGROUND

Idiopathic Pulmonary Fibrosis (IPF) is a specific form of age-related fibroproliferative interstitial pneumonia that is chronic, progressive, and carries a poor prognosis[1]. Although rare, IPF is the most common of the idiopathic interstitial pneumonias[2,3]. The annual incidence of IPF is estimated to be 4.6–16.3 cases per 100 000 people, and appears to be increasing[4].

At present, there are very limited South African data available regarding the incidence, presentation, and risk factors in this population, and none since the introduction of the 2011 ATS/ERS/JRS/ALAT diagnostic criteria (see Table 3.1)[5]. As such, this study aimed to describe the cohort of patients that attend or have attended the respiratory outpatient services at a South African tertiary-level hospital.

2.2. METHODS

2.2.1. STUDY DESIGN & SETTING

A retrospective, descriptive record review was undertaken at the Respiratory Outpatients Department at Chris Hani Baragwanath Academic Hospital. This tertiary-level academic institution in Soweto, South Africa is affiliated with the University of the Witwatersrand.

2.2.2. DATA COLLECTION & SAMPLE SELECTION

Data from patient records was collected, including demographics, clinical, laboratory and radiologic findings, lung function tests, treatment, date of last follow-up visit and, where applicable and available, date of death. A pre-existing database of patients was used to identify patients suspected or diagnosed with IPF during the study period (2007–2016); 115 such patients were identified. The following criteria were then applied:

Inclusion criteria: patients aged ≥ 18 years who had been evaluated by the Division of Pulmonology at Chris Hani Baragwanath Academic Hospital and met the 2011 ATS/ERS/JRS/ALAT diagnostic criteria for IPF[6] (see Appendix A).

Exclusion criteria: files in which it is documented that the patient requested their information not be used for studies.

Descriptive statistics were used to described baseline demographics and clinical profile of study participants. Categorical variables were described using frequencies and percentages, while skewed continuous variables were described using the median and interquartile range. Bivariate analysis for categorical variables was assessed using the Pearson's Chi squared test, otherwise Fisher's exact for sparse data. The Wilcoxon rank-sum test was used to evaluate equality of medians between groups where applicable. Linear regression models determined factors associated with decline in predicted FVC and FEV_1 values (%) over time. The statistical analyses were performed using Microsoft Excel with XLSTAT add-in.

2.2.3. MEASURE OUTCOMES

1. To describe the demographics, presentation symptoms, and clinical features of patients in the sample population.
2. To determine any identifiable risk factors and associations present in this population, including laboratory studies performed.
3. To determine the presentation and subsequent lung functions, including but not limited to forced vital capacity, total lung capacity, and transfer factor of the lung for carbon monoxide (TL_{CO}) in this population.
4. To determine treatment regimens used in this population, and the effect (if any) on symptoms and lung function.
5. Where documented, to determine mean time from symptom development to death, as well as from diagnosis to death, in patients who have died, and to thereby demonstrate if diagnosis was delayed.

2.3. Results

2.3.1. Patient Characteristics

Of the 115 patients identified for inclusion, three (2.6%) were excluded due to lack of records, and a further 38 (33.0%) were excluded as they did not meet the 2011 ATS/ERS/JRS/ALAT diagnostic criteria[6], thus resulting in 74 patients' data being used for analysis. The demographic and clinical characteristics of these patients at presentation are summarised in Table 2.1. The mean (range, SD) age was 64.4 years (33–86, 10.9), and 45 patients were female (60.8%). Difference in age between males and females was not statistically significant (p=0.17). Fifty-nine (79.7%) of the patients were of Black ethnicity. Mean BMI amongst females was 26.8kg/m^2, versus 24.6kg/m^2 amongst males (p=0.07). Mean time from symptom onset to diagnosis was 17.4 months (range 1.6–86.4 months), and was not significantly different between females and males (17.0 vs 18.0 months, p=0.41), nor between Black and non-Black ethnic groups (18.6 vs 12.9 months, p=0.09).

One patient (1.4%) was HIV-positive on anti-retroviral therapy, although HIV status was not determined in 38.7%. Forty patients (54.0%) were either current or previous smokers. Males were significantly more likely to be current or previous smokers than females (75.8% vs 40.0%, p=0.007). White patients were significantly more likely to be current or previous smokers than Black patients (87.5% vs 49.2%, p=0.007). Current smokers had greater mean pack years than previous smokers, although this difference was not statistically significant (50.4 vs 28.0, p=0.08), nor was it significantly different between males and females (34.5 vs 24.6 p=0.08). Hypertension was the most common comorbidity, present in 35 patients (47.3%), followed by diabetes mellitus in nine patients (12.1%).

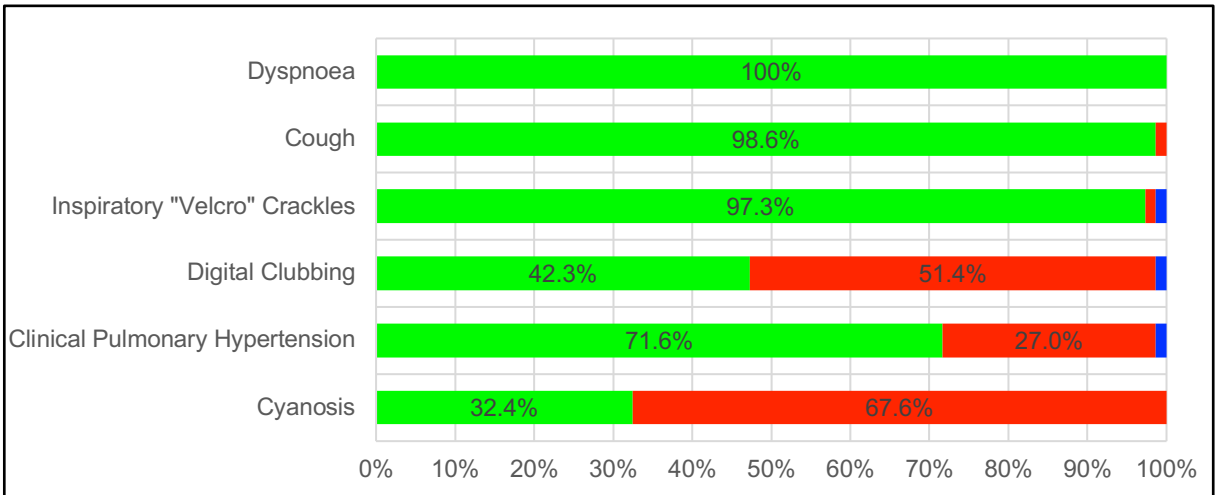
2.3.2. Features at Presentation and Risk Factors

A summary of symptoms and clinical signs at presentation is presented in Figure 2.1. All patients reported dyspnoea on presentation, most patients (79.7%) presented with either mMRC dyspnoea score 3 or 4. Cough was present in all but one patient. Seventy-two patients (97.3%) had inspiratory "Velcro" crackles on presentation, while 35 patients (42.3%) had digital clubbing.

Table 2.1. Demographic and Clinical Characteristics at Presentation (n=74)

Variable	n (%)
Sex	
Female	45 (60.8%)
Male	29 (39.2%)
Age	
Mean, SD (Range)	*64.4, 10.9 (33–86)*
<60	18 (24.3%)
60–70	31 (41.9%)
≥70	25 (33.8%)
Ethnicity	
Black	59 (79.7%)
White	8 (10.8%)
Indian	6 (8.1%)
Coloured	1 (1.4%)
HIV status	
Positive	1 (1.4%)
Negative	45 (60.8%)
Unknown	28 (37.8%)
Smoking status	
Never smoked	32 (43.2%)
Current smoker Pack years: *Mean (SD)*	5 (6.8%) *50.4 (27.1)*
Previous smoker Pack years: *Mean (SD)*	35 (47.3%) *28.0 (16.7)*
Unknown	2 (2.7%)
Body Mass Index (kg/m^2)	
<18.5	4 (5.4%)
18.5–24.9	20 (27.0%)
≥25.0	26 (35.1%)
Undocumented	24 (32.4%)
Tuberculosis (TB) history	
Never had TB	57 (77.0%)
Current pulmonary TB	7 (9.5%)
Previous pulmonary TB	10 (13.5%)
Documented Exposures	
Construction/Dust	2 (2.7%)
Mining/Asbestos	4 (5.4%)
Paint and/or cleaning chemicals	3 (4.1%)
Comorbidities	
Hypertension	35 (47.3%)
Other Comorbidities	
Asthma Cardiomyopathy/Ischaemic Heart Disease Diabetes Mellitus Gastro-Oesophageal Reflux Disease Lung Cancer Pulmonary Thrombo-Embolic Disease Others *(aortic stenosis, aortic aneurysm, atrial fibrillation, chronic kidney disease, epilepsy, fatty liver disease, gout, hypothyroidism, osteoarthritis, prostate cancer)*	1 (1.4%) 7 (9.5%) 9 (12.1%) 2 (2.7%) 1 (1.4%) 2 (2.7%) 13 (17.6%)
None known	25 (33.8%)
Abbreviations: SD standard deviation, HIV Human Immunodeficiency Virus	

Figure 2.1. Symptoms and Signs at Presentation
(n=74)



	Dyspnoea	Cough	Inspiratory "Velcro" Crackles	Digital Clubbing	Clinical Pulmonary Hypertension	Cyanosis
Yes	74	73	72	35	53	24
No	0	1	1	38	20	50
Unknown	0	0	1	1	1	0

The chest radiograph findings of 70 patients were documented, of which 70 (100%) showed bilateral reticular infiltrates. Two patients (2.7%) also had radiographic hilar lymphadenopathy, while an additional two patients (2.7%) had features of bronchiectasis documented. Neither of these patients were known to have had previous TB. One patient (1.4%) had a parenchymal mass visible on chest radiography and HRCT chest, suspected of being primary lung cancer. HRCT chest was reported as radiological UIP in 72 patients (97.3%), while two patients (2.7%) were reported as radiological nonspecific interstitial pneumonia (NSIP). One patient had a history of asbestos exposure, and although a diagnosis of IPF was favoured over asbestosis, the latter cannot be conclusively excluded. Three patients (4.1%) underwent lung biopsy, two of which were performed on the patients reported to have NSIP on HRCT. All three lung biopsies showed UIP.

Baseline pulmonary function testing (PFT) (where available/documented) is shown in Table 2.2. Fifty-eight patients (78.4%) had spirometry results documented. Percentage of predicted FVC was significantly higher amongst females (median 72.0 vs 62.0, p=0.04), as was percentage of predicted FEV_1 (median 83.0 vs 61.0, p=0.026). FEV_1/FVC ratio was not significantly different between males and females (median 83.3 vs 84.9, p=0.89). Results of full pulmonary function testing were available in 32 patients (43.2%), which revealed no significant differences in

percentage of predicted values in TLC, RV, or TL_{CO} between males and females. There was also no significant correlation between pack year history and baseline pulmonary function tests (see Figure 2.2).

Using available data, the Gender-Age-Physiology (GAP) score[7] (see Appendix B) could be calculated for 32 patients. The scores and corresponding stages are presented in Figure 2.3. The majority of females were GAP stage II on presentation (14 patients, 63.6%), while five male patients (50%) were stage II (p=0.24).

Echocardiographic findings were documented in 19 patients (25.7%), although only 14 of these included pulmonary artery pressures (PAP), and 18 recorded left ventricular ejection fraction (LVEF). PAP was elevated in all 14 patients (range 34–110, median 53.5 mm Hg), and clinical features of pulmonary hypertension were recorded in 13 of these patients (92.9%). There was no significant difference between PAP in males and females (p=0.37). The median EF was 65.5% (interquartile range 61–67.8%). Two patients had a LVEF <50%; these patients both had documented cardiomyopathies.

Room air arterial blood gases were recorded in 32 patients (43.2%); the results of these can be found in Table 2.3. On formal laboratory testing, 56 patients (75.7%) had full blood count results documented, which revealed a mean haemoglobin concentration of 14.0 g/dL in females and 15.5 g/dL in males. Urea, electrolytes, and creatinine were available in 59 patients (79.7%); these results were also not significantly different between males and females. Serological studies including anti-nuclear antibody (ANA), rheumatoid factor (RF), and serum angiotensin converting enzyme (ACE) were used to screen for alternate causes of ILD. ANA positivity was found in six patients (8.1%), all of whom were female, with no patients have a titre greater than 1:160. Given the increasing prevalence of ANA positivity with age in the general population, this is not an unexpected finding[8].

Table 2.2. Baseline Pulmonary Function Tests amongst patients diagnosed with IPF

Variable	All	Females	Males	p-value
FVC (L) (median, range)	1.8 (1.3–2.1) [n=58]	1.6 (1.2–2.0) [n=35]	2.1 (1.8–2.4) [n=23]	
FVC (% predicted)				
Median (IQR)	*67.3 (54.0–89.0)*	*72.0 (55.0–96.0)*	*62.0 (52.9–73)*	0.040*
<80% [n (%)]	39 (67.2%)	20 (57.1%)	19 (82.6%)	
≥80% [n (%)]	19 (32.8%)	15 (42.9%)	4 (17.4%)	
FEV_1 (L) (median, range)	1.5 (1.1–1.8) [n=57]	1.3 (1.1–1.6) [n=34]	1.7 (1.3–2.0) [n=23]	
FEV_1 (% predicted)				
Median (IQR)	*71.0 (52.0–91.0)*	*83.0 (54.0–98.0)*	*61.0 (51.3–82.0)*	0.026*
<80% [n (%)]	32 (56.1%)	15 (44.1%)	17 (73.9%)	
≥80% [n (%)]	25 (43.9%)	19 (55.9%)	6 (26.1%)	
FEV_1/FVC ratio (%)	83.6 (76.8–88.0) [n=57]	83.3 (76.8–87.0) [n=34]	84.9 (73.0–88.6) [n=23]	0.890
TLC (L) (median, range)	2.9 (2.1–3.2) [n=32]	2.6 (2.0–3.1) [n=22]	3.2 (3.0–3.9) [n=10]	
TLC (% predicted)				
Median (IQR)	*59.0 (51.0–77.0)*	*60.0 (51.0–78.0)*	*59.0 (54.0–67.0)*	0.624
<80% [n (%)]	25 (78.1%)	17 (77.3%)	8 (80.0%)	
≥80% [n (%)]	7 (21.9%)	5 (22.7%)	2 (20.0%)	
RV (L) (median, range)	1.1 (0.5–1.4) [n=32]	0.9 (0.5–1.4) [n=22]	1.3 (0.9–1.7) [n=10]	
RV (% predicted)				
Median (IQR)	*58.0 (36.5–81.5)*	*58.0 (30.0–90.0)*	*59.0 (49.0–78.0)*	0.703
<80% [n (%)]	24 (68.0%)	16 (72.7%)	8 (80.0%)	
≥80% [n (%)]	8 (32.0%)	6 (27.3%)	2 (20.0%)	
TL_{CO} (mmol/min/ mm Hg) (median, range)	7.5 (4.2–10.0) [n=31]	5.5 (4.1–8.0) [n=21]	9.5 (7.5–10.2) [n=10]	
TL_{CO} (% predicted)				
Median (IQR)	*39.0 (25.0–47.0)*	*29.0 (25.0–47.0)*	*40.5 (29.0–45.0)*	0.323
<80% [n (%)]	30 (93.8%)	21 (100.0%)	9 (90.0%)	
≥80% [n (%)]	1 (3.2%)	0 (0.0%)	1 (10.0%)	

Abbreviations: IQR inter quartile range, FVC forced vital capacity, FEV_1 forced expiratory volume in 1 second, TLC total lung capacity, RV residual volume, TL_{CO} transfer factor of the lung for carbon monoxide, *denotes statistical significance (p<0.05)

Table 2.3. Arterial Blood Gas Results at Time of Diagnosis With IPF (n=32)

	pH	pO_2 (mmHg)	pCO_2 (mmHg)	Oxygen saturation (%)	Base excess (mmol/ℓ)	$HCO3^-$ (mmol/ℓ)
Median	7.42	50.2	35.95	87	-0.3	23.5
IQR	7.40 – 7.44	47.4 – 57.5	32.0 – 40.0	81.6 – 90.0	-2.2 – 1.4	21.0 – 25.8

Figure 2.2. Correlation Coefficients Between Smoking Pack Year History and Baseline Pulmonary Function Tests

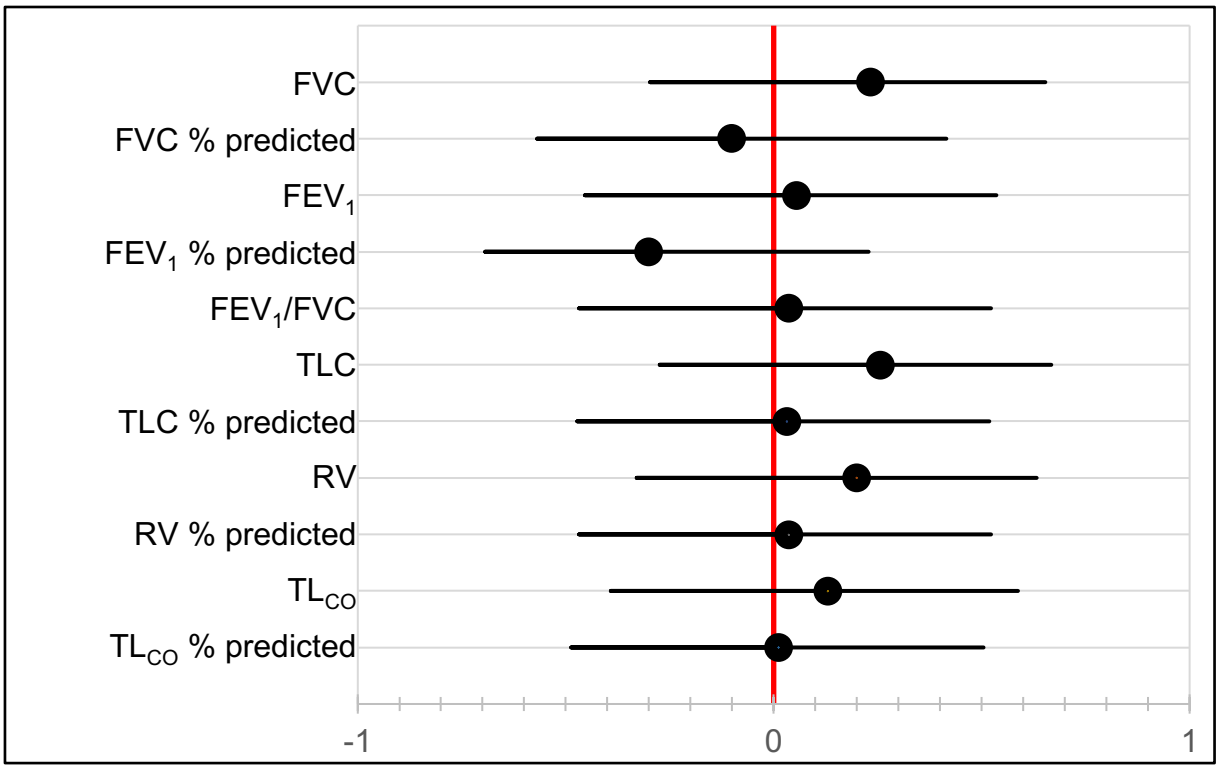
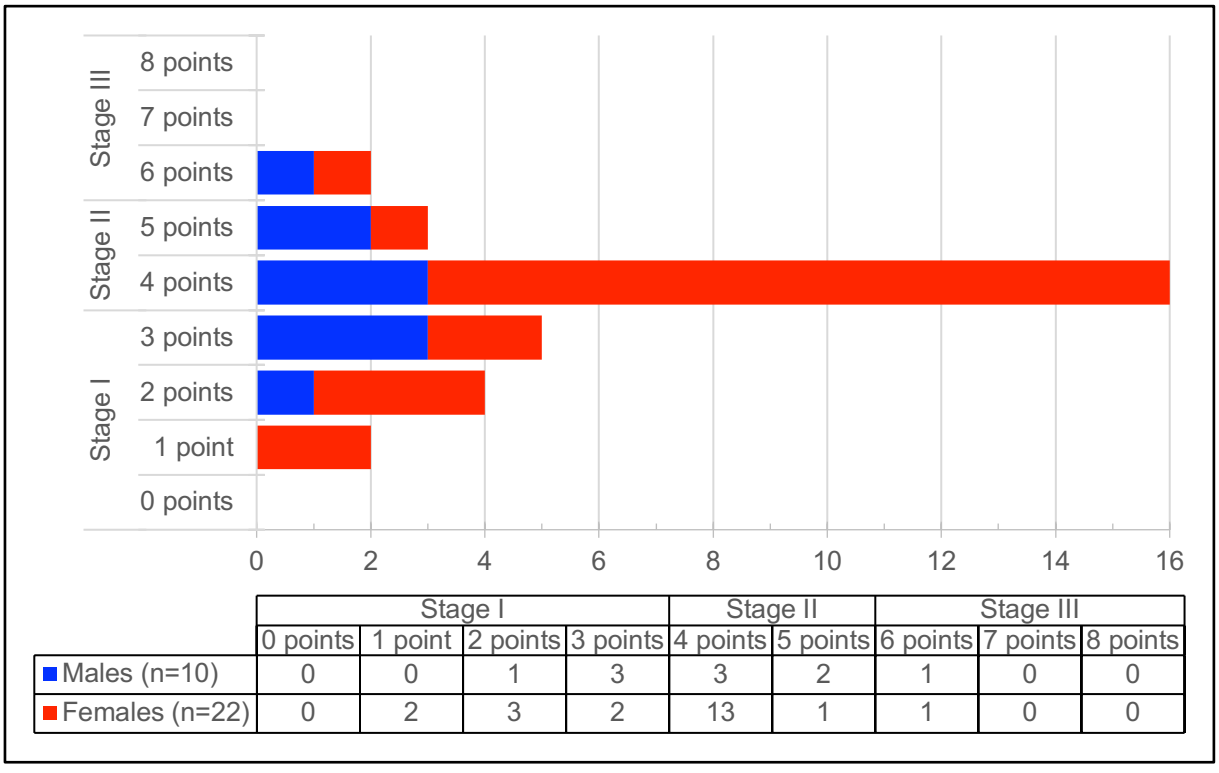


Figure 2.3. Gender-Age-Physiology (GAP) Score and Stage (n=32)



	Stage I				Stage II		Stage III		
	0 points	1 point	2 points	3 points	4 points	5 points	6 points	7 points	8 points
Males (n=10)	0	0	1	3	3	2	1	0	0
Females (n=22)	0	2	3	2	13	1	1	0	0

2.3.3. Treatment Regimens Used

Corticosteroids were used in 25 patients (33.8%), with median prednisone dosage of 30 mg daily (range 5–60 mg) and median duration of three months (range 1–32 months). Two patients (8% of those treated with corticosteroids) developed vertebral compression fractures; these patients had received steroids for ≥30 months each. One further patient (4%) developed an upper gastro-intestinal bleed after being treated for 16 months. One patient showed some symptomatic and spirometric improvement with corticosteroids, all others showed no improvement.

Ten patients (13.5%) received azathioprine, at a median dose of 75 mg daily (range 50–150 mg), and median duration of three months (range 1–33 months). These patients showed no improvement in symptoms with treatment. N-acetylcysteine (NAC) was used in five patients (6.8%); these patients all received the prednisone-azathioprine-NAC regimen, for between one and six months (median three months). All five patients were treated between 2009 and 2011. The total daily dosage range of N-acetylcysteine was 600 mg to 1800 mg. No change in condition was reported in patients receiving NAC. Proton pump inhibitors or H_1-receptor blockers were used in ten patients (13.5%). One patient received methotrexate at 7.5 mg weekly (in addition to corticosteroids).

Nintedanib was available through a compassionate use programme for a limited period and was prescribed in three patients (4.1%), for a median duration of 29 months (range 8–35 months). Dosage used was 100 mg twice daily in one patient, and 150 mg twice daily in the other two. Two patients receiving nintedanib showed slowing of decline in their lung function, although no significant symptomatic improvement was reported. No objective assessment could be made in the third patient as there were insufficient serial lung function tests performed for comment. This patient developed an acute exacerbation soon after nintedanib was initiated. One patient developed *Clostridioides difficile*-associated diarrhoea. Adverse effects did not limit the use or treatment duration of nintedanib in any of the patients. Of the patients on nintedanib, one was still alive at the time of data collection. One patient died eight months after starting nintedanib, and the other died after 4.5 years. No patients received pirfenidone. Long-term domiciliary oxygen therapy was used in 36 patients (48.6%).

2.3.4. Follow up and Outcomes

Mean duration of follow-up was 13.3 months, with females having significantly longer follow-up durations than males (17.9 vs 6.6 months, p<0.001). Indian patients had significantly shorter mean duration of follow up than Black patients (8.2 vs 12.5 months, p=0.006) and White patients (8.2 vs 14 months, p=0.02), while no significance was found between Black and White patients (p=0.27). At the time of data collection, four patients were still alive (5.4%), 63 were lost to follow-up (85.1%), and seven were known to have died (9.5%). As noted in Table 2.4, no significant differences between the different outcome groups were found in time from symptom development to first consultation or in time from symptom development to diagnosis.

Table 2.4. Outcomes and Median Time Between Symptom Development, First Consultation, and Diagnosis in Patients Diagnosed With IPF (n=74)

Outcome (at time of data collection)	**n (%)**	**Median time from symptom development to first consultation (IQR) (months)**	**Median time from symptom development to diagnosis (IQR) (months)**
Alive	4 (5.4%)	7.4 (3.2–12.5)	9.3 (3.6–24.1)
Lost to follow up	63 (85.1%)	9.8 (4.0–24.1)	11.7 (4.8–24.1)
Dead	7 (9.5%)	7.1 (4.5–24.1)	7.4 (6.3–24.1)
p-value		0.774	0.951

Baseline pulmonary function testing (PFT) was not significantly correlated with duration of follow-up (see Figure 2.4.), neither were baseline pO_2 nor pCO_2. Pack year history was also not associated with duration of follow up (HR 1.004, 95% CI 0.988–1.020). Of the seven patients known to have died, three died at home, while four died in hospital. Cause of death was documented in only one patient, which was an acute exacerbation of IPF. Too few data were available for meaningful analysis of change in full PFT over time. Factors correlated with decline in FVC over time are shown in Figure 2.5., although only 12 patients had serial PFT available for analysis. The factors most strongly correlated with decline in FVC were previous smoking history (p<0.001), current smoking (p=0.003), Black race (p=0.039), and age (p=0.044).

Figure 2.4. Correlation Coefficients Between Baseline Pulmonary Function Tests and Duration of Follow Up

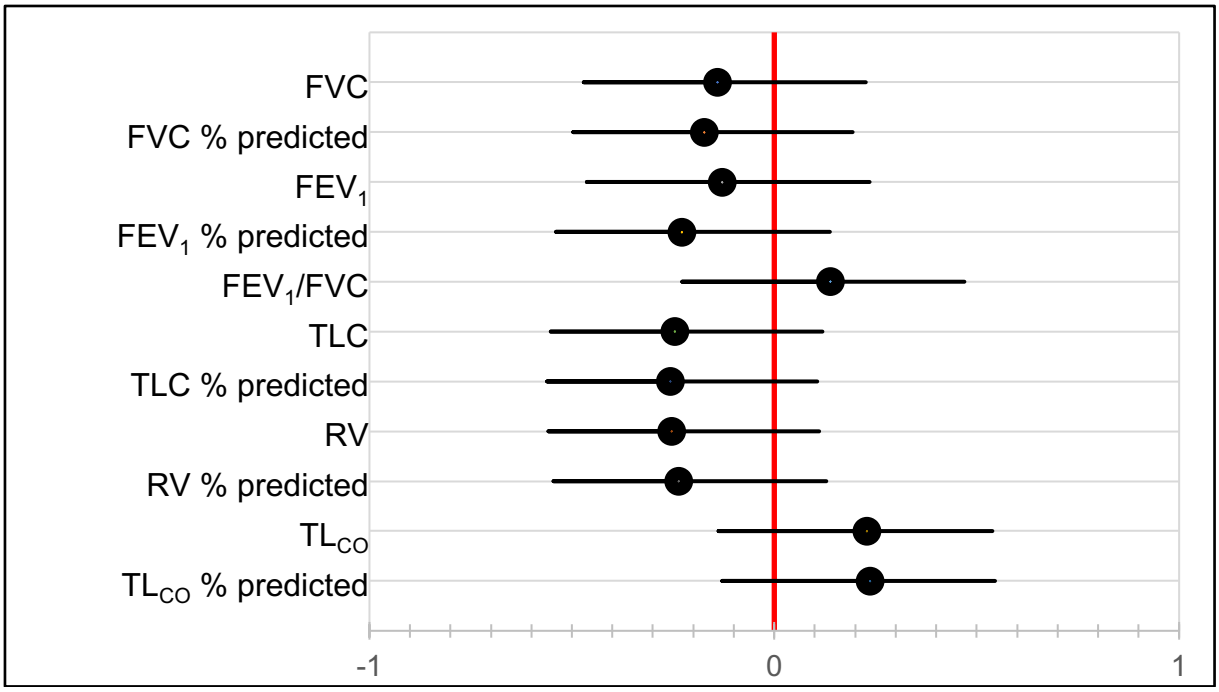
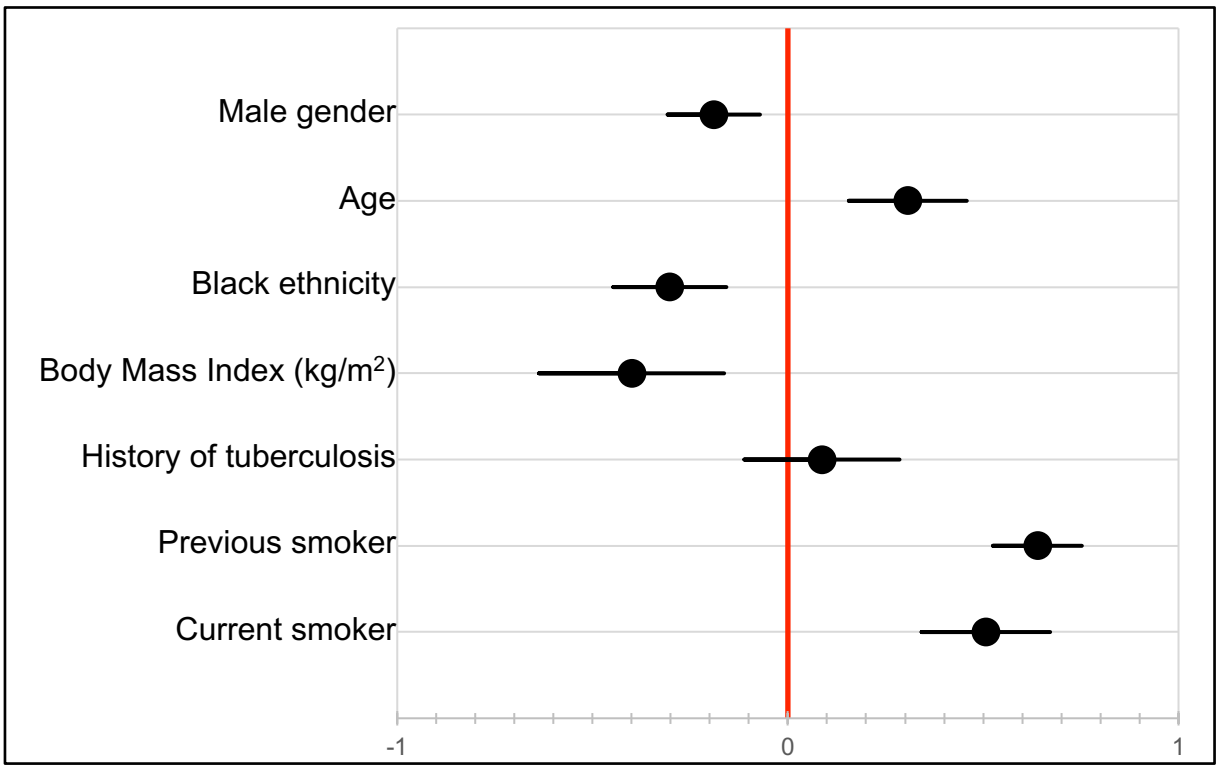


Figure 2.5. Factors Correlated with Decline in Forced Vital Capacity over time



2.4. DISCUSSION

To the best of the authors' knowledge, this is the first descriptive study of IPF in South Africa and Africa using the current definition, and included 74 patients. In keeping with existing literature (age over 60 years)[5], the median age of our patient cohort was 64.4 years. The majority of our patients were female (60.8%), which conflicts with some existing data (50% and 43.3%, respectively)[9,10]; this may, however, be due to sampling bias, cultural differences, and different health-seeking behaviour between sexes. Studies from India also found a female predominance, suggesting that epidemiology may differ in developing countries[11,12]. Our cohort was predominantly Black (79.7%); this was expected given the location and population served by CHBAH. The most common comorbidities were hypertension and diabetes mellitus, which was also expected given the age of patients in this cohort. Gastro-oesophageal reflux disease was diagnosed in only 2.7% of our patients, although antacid therapy was used in 13.5%.

In this cohort, there was no difference in age of presentation between patients with a history of previous or current smoking, and those without; this is in contrast to some evidence that has shown that smokers may develop IPF at a younger age (58.1 vs 71.4 years)[13,14]. Smoking history (previous or current) did not correlate with baseline pulmonary function tests, although it was positively correlated with more rapid decline in FVC over time (correlation coefficient of 0.64 and 0.51 in previous and current smokers respectively). Although limited by a relatively small sample size, this may either suggest that smoking is less of a risk factor in our patients, or more likely that other environmental factors such as exposure to passive smoking, biomass fuel, or environmental pollutants are important risk factors in the context of a developing country. No other risk factors could be defined in this study. Limited data prevented meaningful comparison of decline in FVC over time between races. Given conflicting existing data in this regard[15,16], this is an area requiring further study, particularly in the South African context.

Patients universally presented with dyspnoea, the majority of which were mMRC scores 3 or 4. This, in combination with 71.6% of patients having clinical features of pulmonary hypertension, suggests advanced disease at presentation. Almost all patients had cough and inspiratory crackles, while digital clubbing was present in 42.3% of patients. The mean time from symptom development to diagnosis was 17.4

months. These findings are similar to those found in existing articles from both developing and developed countries[17,18,19–21]. While baseline FVC and FEV_1 in this cohort were similar to those found by Collard *et al* (67.3 vs 67.2 and 71.0 vs 77.1, % predicted, respectively), RV, TLC, and TL_{CO} were markedly lower in our patients (58.0 vs 91.6, 59.0 vs 77.6, and 39.0 vs 52.4, % predicted, respectively).[22] This adds further evidence to the presence of advanced disease on presentation, and highlights the concern that patients in our cohort presented late.

Pharmaceutical treatment regimens used in our patients included corticosteroids, prednisone-azathioprine-NAC, and nintedanib. Long-term domiciliary oxygen therapy was used in almost half of patients. Too few data were available to analyse impact of these therapies on survival, as the majority of our patients were lost to follow up. There are several possible reasons for this, including death, disability, relocation, or socioeconomic difficulties in accessing further healthcare services. Patients in our cohort also did not receive pulmonary rehabilitation or psychological support; implementation of such services would likely be of benefit to patients.

In addition to a fairly small sample size, the major limitations of this study were the unavailability of some data, as it relied upon a retrospective review of files, as well as the high proportion of patients lost to follow-up (85.1%), which we suspect is part of the natural course of the disease. This resulted in limited data analyses, especially with regards to change in PFTs over time and survival. Additional limitations include erratic and limited drug supply, and lung function testing often being unavailable due to equipment breakdown, consumable shortages, and staffing problems.

2.5. CONCLUSION

Despite its limitations, this study contributes to the body of literature regarding IPF as the first descriptive study in Africa, and highlights the need for additional work in understanding how IPF may present and progress differently in our setting. We found a female predominance, and no correlation between smoking history and baseline PFT. Of particular concern is the advanced disease noted in this cohort of patients. These findings highlight the possibility of a different epidemiological pattern and clinical course in South African patients.

Total word count 3431

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CHAPTER 3 - APPENDICES

APPENDIX A: DEFINITIONS & DIAGNOSTIC CRITERIA

Table 3.1. Diagnostic Criteria for IPF
6

Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).
AND
The presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy.
OR
Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy (see Table 3.2 below)

Table 3.2. Combination of HRCT & surgical lung biopsy for the diagnosis of IPF
6

HRCT Pattern	**Surgical Lung Biopsy** (when performed)	**Diagnosis of IPF?** (requires multidisciplinary discussion)
UIP	UIP Probable UIP Possible UIP Non-classifiable fibrosis	Yes
	Not UIP	No
Possible UIP	UIP Probable UIP	Yes
	Possible UIP Non-classifiable fibrosis	Probable
	Not UIP	No
Inconsistent with UIP	UIP	Possible
	Probable UIP Possible UIP Non-classifiable fibrosis Not UIP	No

Table 3.3. Diagnostic Criteria for Acute Exacerbations of IPF
23

Previous or concurrent diagnosis of IPF
AND
Acute worsening or development of dyspnoea typically (but not limited to) less than one month duration
AND
Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern
AND
Deterioration not fully explained by cardiac failure or fluid overload

APPENDIX B : THE GAP STAGING SYSTEM

Table 3.4. The GAP Staging System[7]

Predictor			
Gender			
Female		0	
Male		1	
Age			
≤60		0	
61–65		1	
>65		2	
Physiology			
FVC (% predicted)			
>75		0	
50–75		1	
<50		2	
TL_{CO} (% predicted)			
>55		0	
36–55		1	
≤36		2	
Unable to perform		3	
Total Possible Points		**8**	
Stage	**I**	**II**	**III**
Points	0–3	4–5	6–8
Mortality			
One Year	5.6%	16.2%	39.2%
Two Years	10.9%	29.9%	62.1%
Three Years	16.3%	42.1%	76.8%

APPENDIX C: DATA COLLECTION SHEET

DATE OF COLLECTION: DD/MM/YY **STUDY NUMBER:**

DEMOGRAPHICS

Age: Gender: M F Ethnicity: **B** | **W** | **C** | **I** | Other:

Height: cm Weight: kg

RISK FACTORS

Smoking History:

Occupational Hx:

Other exposures documented/potential risk factors:

HIV Status: If HIV+, ARV Details:

TB History:

Co-morbidities:

PRESENTATION/BASELINE

mMRC Grade: Crackles: Cough: PHT:

Other signs/symptoms: Clubbing: Estimated duration of Sx:

Time from presentation to Dx of IPF:

CXR Findings:

HRCT Findings:

Lung biopsy:

FBC+UEC+CRP:

ANA+RF+ESR:

ABG:

Other:

Lung functions: FVC: (%) FEV1: (%) Ratio:

TLC: (%) RV: (%) DLCO: (%)

TREATMENT

	Dose	Durations Used	Response & any adverse effects
Corticosteroids			
Azathioprine			
N-acetyl-cysteine			
Warfarin			
Pirfenidone			
Nintedanib			
PPIs			
Pulm Rehab			
LTDOT			
Other 1			
Other 2			
Other 3			

FOLLOW-UP (attach additional pages if necessary)

Time from previous: mMRC: ABG:
Clinical:
Imaging:
Lung functions: FVC: (%) FEV1: (%) Ratio:
TLC: (%) RV: (%) DLCO: (%)

Time from previous: mMRC: ABG:
Clinical:
Imaging:
Lung functions: FVC: (%) FEV1: (%) Ratio:
TLC: (%) RV: (%) DLCO: (%)

Time from previous: mMRC: ABG:
Clinical:
Imaging:
Lung functions: FVC: (%) FEV1: (%) Ratio:
TLC: (%) RV: (%) DLCO: (%)

OUTCOME

Time from diagnosis to death: ☐
or lost to follow up: ☐ or still alive: ☐
Place (hospital/home) & cause of death if known: ☐

APPENDIX D: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R14/49 Dr WM Aitchison and Professor M Wong

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180302

NAME: **(Principal Investigator)**	Dr WM Aitchison and Professor M Wong
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Clinical Medicine - Pulmonology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Idiopathic Pulmonary Fibrosis in Soweto, South Africa: A descriptive study
DATE CONSIDERED:	06/04/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr SA van Blydenstein
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	17/04/2018

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 **March** and will therefore be due in the month of **March** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX E: LETTERS OF PERMISSION

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 2 Feb 2018

TITLE OF PROJECT: Idiopathic Pulmonary Fibrosis in Soweto, South Africa: a descriptive study

UNIVERSITY: Witwatersrand

Principal Investigator: WM Aitchison

Department: Internal medicine

Supervisor (If relevant): SA van Blydenstein, M Wong

Permission Head Department (where research conducted): Yes

Date of start of proposed study: Feb 2018
Date of completion of data collection: Dec 2019

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Human Research Ethics Committee of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....
Recommended
(On behalf of the MAC)
Date: 02 February 2018

.....
Approved/Not Approved
Hospital Management
Date: 06/2/18

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Department of Medicine
Chris Hani Baragwanath Academic Hospital
P.O. Bertsham
2013
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Fax: +27 11 938 1545

11 January 2017

Dr. J.M.L. Tsitsi
Head of Department of Internal Medicine
Chris Hani Baragwanath Academic Hospital

Dear Dr. Tsitsi

re: **PERMISSION FOR DR. W. AITCHISON TO CONDUCT MMED STUDY ENTITLED: IDIOPATHIC PULMONARY FIBROSIS IN SOWETO, SOUTH AFRICA: A DESCRIPTIVE STUDY**

As a supervisor of Dr. Aitchison MMed research report we would like to request your permission and the permission of the CHBAH authorities to conduct a MMed study entitled: Idiopathic Pulmonary Fibrosis in Soweto, South Africa: A Descriptive Study.

Permission will also be obtained for the University of the Witwatersrand Ethics Committee.

Yours sincerely

PROF. M.L. WONG
Head: Pulmonology Unit
Chris Hani Baragwanath Academic Hospital

Signature of approval by Dr. J.M.L. Tsitsi ..... Date 26/Jan 2018

APPENDIX F : PLAGIARISM REPORT

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