Spectrum of Diffuse Parenchymal Lung Disease with Special Reference to Idiopathic Pulmonary Fibrosis: Experience at Charlotte Maxeke Johannesburg Academic Hospital

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A research report submitted to the University of the Witwatersrand, Johannesburg,

in fulfilment for the requirements of the degree of

Master of Medicine in Internal Medicine 2017

DECLARATION

I, Ndikundisani Ananius Tshiovhe, declare that this research report is my own work, which is being submitted for the degree of Master of Medicine (in the submissible format with my protocol and extended literature review) in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

……day of ……2018

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I would like to express my sincere gratitude to my supervisor, Professor Rajen Morar, whose expertise, understanding and patience has made this project possible.

ABSTRACT

Background

Diffuse parenchymal lung diseases (DPLD) encompass a group of diseases with a wide range of causes with varied presentations and prognosis. The known causes include occupational or environmental exposure, drug induced lung diseases, hypersensitivity pneumonitis and connective tissue disease (CTD). Among the DPLD with unknown cause, idiopathic pulmonary fibrosis (IPF) is the commonest and has the worst outcome. The earlier publications from this country described cryptogenic fibrosing alveolitis. With subsequent characterisation of idiopathic interstitial pneumonia (IIP), and an increase in the burden of IPF reported worldwide, we evaluated the clinical features of patients with IPF in the South African context.

Objectives

To evaluate the clinical spectrum of DPLD encountered in Johannesburg, South Africa, and to describe the clinical profile of patients with IPF.

Methods

A retrospective record review of patient files was conducted who attended the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Respiratory Clinic in the past 5 years from January 2011 to December 2015. Patients with DPLD were identified and the diagnoses were noted. The records of patients with IPF were further analysed.

Results

We identified 132 patients with DPLD. Sarcoidosis (37.8%), IPF (21.2%), connective tissue associated diffuse parenchymal lung disease (CTD-DPLD) (14.3%), and hypersensitivity pneumonitis (HP) (9.8%) were the four most common subtypes. IPF was seen in all racial groups. Of the 28 patients with IPF in our cohort, there was a slight female predominance (1.3:1). The mean age of the patients in our study was 63.8 years and the majority were Whites. Cough (96.4%), dyspnoea (92.8%) and bilateral crackles (96.4%) were the commonest clinical features. The majority of patients (78.5%) were diagnosed by high resolution computerised tomography (HRCT) scan.

Conclusion

IPF is the second most common DPLD disease encountered after sarcoidosis at the CMJAH. IPF is seen in all racial groups in Johannesburg, South Africa, and the characteristics of patients with IPF are similar to those seen in other parts of the world.

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ABBREVIATIONS

AIP	Acute interstitial pneumonia
ANA	Anti-nuclear antibody
ARDS	Acute respiratory distress syndrome
ART	Anti-retroviral treatment
AZA	Azathioprine
BLT	Bilateral lung transplant
COP	Cryptogenic organizing pneumonia
COPD	Chronic obstructive pulmonary disease
CPFE	Combined pulmonary fibrosis and emphysema
CS	Corticosteroids
CTD-DPLD	Connective tissue disease associated DPLD
CWP	Coal worker's pneumoconiosis
DAD	Diffuse alveolar damage
DAH	Diffuse alveolar haemorrhage
DIP	Desquamative interstitial pneumonia
DLCO	Diffusion capacity for carbon monoxide
DPLD	Diffuse parenchymal lung disease
EP	Eosinophilic pneumonia
FDA	Food and drug administration
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GORD	Gastroesophageal reflux disease
GPA	Granulomatosis with polyangiitis
HIV	Human immunodeficiency virus
HRCT	High resolution computer tomography
HP	Hypersensitivity pneumonitis
IBD	Inflammatory bowel disease
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
LAM	Lymphangioleiomyomatosis
PLCH	Pulmonary Langerhans cell histiocytosis
LIP	Lymphoid interstitial pneumonia
MPA	Microscopic polyangiitis
NAC	N-acetylcysteine
NSIP	Non-specific interstitial pneumonia
PAP	Pulmonary alveolar proteinosis
PM/DM	Polymyositis/dermatomyositis
PMF	Progressive massive fibrosis
RA	Rheumatoid arthritis
RB-ILD	Respiratory bronchiolitis-associated interstitial lung disease
RV	Residual volume
SLE	Systemic lupus erythematosus
SLT	Single lung transplant
SS	Systemic sclerosis
TB	Tuberculosis

TLC	Total lung capacity
UIP	Usual interstitial pneumonia

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Conclusion

IPF is the second most common DPLD disease encountered after sarcoidosis at the CMJAH. IPF is seen in all racial groups in Johannesburg, South Africa, and the characteristics of patients with IPF are similar to those seen in other parts of the world.

CHAPTER ONE: PROTOCOL WITH EXTENDED LITERATURE REVIEW

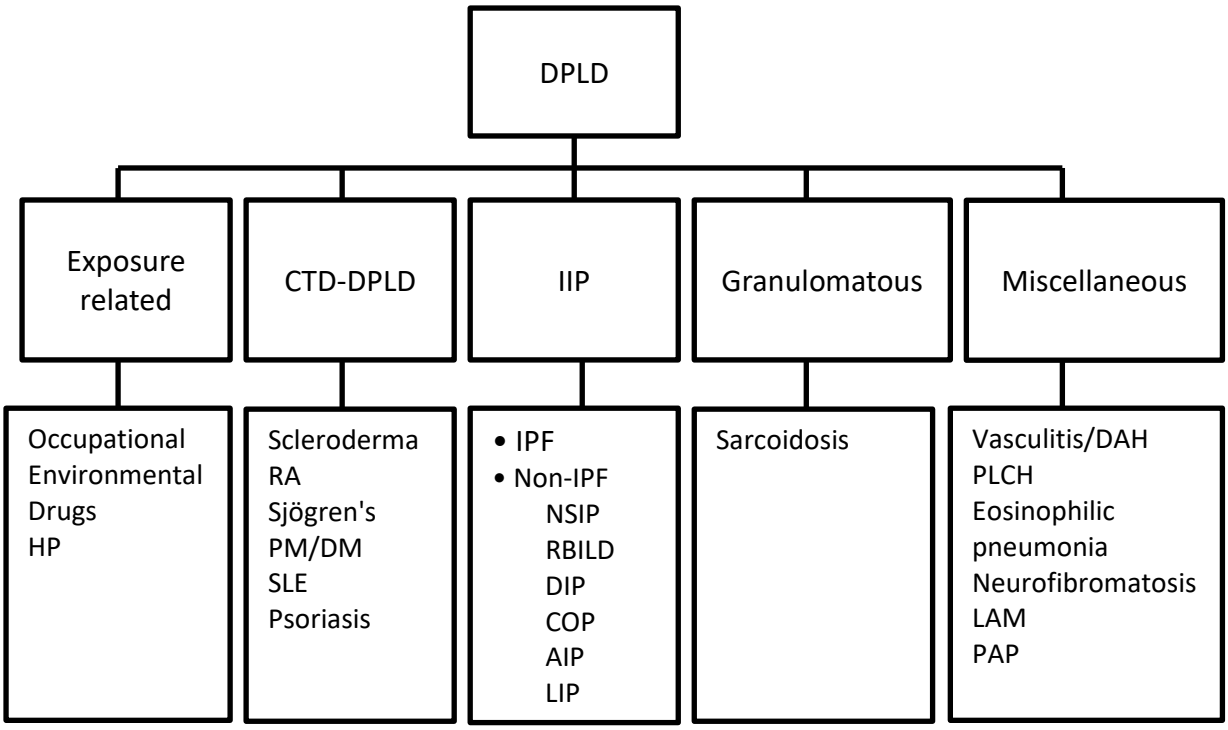
1.1 Introduction

Diffuse parenchymal lung diseases (DPLD) comprise a group of diseases with a wide range of causes that are characterized by diffuse infiltration of the lungs.(1,2) In these diseases there is inflammation and fibrosis of alveoli, distal airways and pulmonary septal interstitium causing substantial morbidity and mortality.(2,3) The fibrotic changes in the lung parenchyma are usually progressive.(5) A similar pattern of inflammation and fibrosis may result from different causes of lung injury.(3) Therefore, these categories of diseases may have similar clinical, radiological, physiologic and/or histopathological features.(6) Lung biopsy assists with differentiating between the different histopathological patterns and the overall clinical diagnosis is done through incorporation of clinical, radiological and histopathological features.(3)

1.2. Classification of DPLD

DPLD can be broadly classified into exposure related, connective tissue disease associated diffuse parenchymal lung disease (CTD-DPLD), idiopathic interstitial pneumonitis (IIP), granulomatous lung disease and other miscellaneous group of lung diseases (Figure 1, adapted from reference 7).(7,8)

Figure 1. Classification of DPLD



Adapted from reference 7

HP	Hypersensitivity pneumonitis
CTD-DPLD	Connective tissue disease associated DPLD
RA	Rheumatoid arthritis
PM/DM	Polymyositis/dermatomyositis
IIP	Idiopathic interstitial pneumonitis
IPF	Idiopathic pulmonary fibrosis
NSIP	Non-specific interstitial pneumonia
RB-ILD	Respiratory bronchiolitis-associated interstitial lung disease
DIP	Desquamative interstitial pneumonia
COP	Cryptogenic organizing pneumonia
AIP	Acute interstitial pneumonia
LIP	Lymphoid interstitial pneumonia
DAH	Diffuse alveolar haemorrhage
PLCH	Pulmonary Langerhans cell histiocytosis
LAM	Lymphangioleiomyomatosis
PAP	Pulmonary alveolar proteinosis

1.3 Clinical features of DPLD

DPLD usually presents with progressive shortness of breath, audible crackles on lung auscultation and the chest radiograph may show diffuse lung infiltrates in advanced disease.(3) Symptoms are due to the development of inflammatory and fibrotic lung changes with attenuated gaseous exchange and arterial hypoxaemia.(9) Digital clubbing and coarse “Velcro” crackles may be heard on auscultation.(9) There seem to be a correlation between long standing disease and pulmonary arterial pressures.(9) Lung function tests in most of the patients may show a restrictive pattern with reduced diffusion capacity for carbon monoxide (DLCO).(10) Reductions in DLCO are characteristic of parenchymal lung diseases and its blood supply.(3) Diagnosis of DPLD requires a combination of clinical, radiological and/or histopathological examination and discussion amongst the various disciplines.(11) Differential diagnoses include other conditions such as pulmonary oedema, infective pneumonia and malignancy.(3) Further investigations such as echocardiography may be required to exclude other possible diagnoses.(3)

1.4 Exposure and environmental related DPLD

Exposure to toxic substances, for example mining dust, may affect the lungs. The association between occupational lung disease and mining has been noted since the early 1500’s.(12) Asbestosis, silicosis and coal worker’s pneumoconiosis (CWP) are of huge public and occupational health concern.(12) Coal dust causes pneumoconiosis in the form of simple CWP and progressive massive fibrosis (PMF).(13) Controlling and preventing asbestos-related lung complications are known public health issues and several countries, including South Africa, have banned manufacturing, processing, importing or exporting of asbestos.(12) South Africa was the fifth largest supplier of chrysotile in the world.(12) Owing to previous extensive use,

there are many possible sources for asbestos exposure. (12) Despite negligible asbestos mining exposure, people may still be exposed to asbestos through removal of asbestos-containing products such as ceiling boards.(12) Pulmonary fibrosis with asbestos exposure makes the diagnosis of asbestosis likely.(12) High resolution computerized tomography (HRCT) scan frequently demonstrates parenchymal fibrosis with pleural plaques.(12) In silicosis, the dust burden exposure is the main determinant of disease.(14) Silicosis increases the risk of tuberculosis (TB).(14) Prevalence of silicosis, HIV and TB is known to be extremely high in South African gold miners.(14)

1.5 Drug induced DPLD

Drug-induced lung injury may involve all the compartments, including small and large airways, lung parenchyma, mediastinal structures, pleura, and pulmonary vessels.(10) The commonest type of drug-related lung toxicity is drug-induced interstitial lung disease (DILD).(10) The clinical, radiological and histopathological findings of DILD are non-specific and therefore, diagnosis of DILD is not straight forward.(15) Diagnosis of DILD is largely dependent on a definite temporal relationship between exposure to the drug and the onset of respiratory symptoms and signs.(15) Nearly all the histopathological subtypes of DPLD may be seen including, acute interstitial pneumonia (AIP) or diffuse alveolar damage (DAD), usual interstitial pneumonia (UIP), lymphoid interstitial pneumonia (LIP), non-specific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), organizing pneumonia (OP), eosinophilic pneumonia (EP), hypersensitivity pneumonitis (HP) and granulomatous lung disease.(10) DILD may be caused by cytotoxic drugs (bleomycin), cardiovascular drugs (amiodarone, beta-blockers, hydrochlorothiazide), anti-inflammatory agents (non-steroidal anti-inflammatories, methotrexate, sulphasalazine), antimicrobials (isoniazid, amphotericin B)

and biological agents (rituximab, bevacizumab).(15) Some drugs, however, may produce stereotypical histopathological reaction in the lungs. For example, methotrexate induces acute granulomatous lung disease; minocycline induces EP and nitrofurantoin induces cellular type of NSIP.(10) DILD may present with signs ranging from minimal infiltrates to acute respiratory distress syndrome (ARDS) that could be life threatening.(10) The likelihood of developing drug-induced lung injury remain mostly random and idiosyncratic.(7,10) Patients with chronic inflammatory diseases such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) and those on cancer chemotherapy are at increased risk of developing DILD.(15) This may also be related to other factors such as smoking.(9)

1.6 Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (HP) is a complex immunological response syndrome caused by exposure to various organic particles.(16) Fungi, bacteria, protozoal, animal and insect proteins and other chemical compounds are some of the causative agents.(16) The prevalence of HP varies around the world depending on the definition of HP, host genetic risk factors, method used for diagnosis, nature of exposure, geographical conditions, agricultural and industrial practices.(16) The clinical presentation is similar despite various antigens being responsible for the development of HP and has been conventionally classified into acute, subacute, and chronic forms.(16,17) This classification, however, is now being challenged and a set of clinical predictors has been proposed.(17)

1.7 Connective tissue disease associated DPLD

Connective tissue diseases (CTD) or autoimmune diseases are a diverse group of immune mediated systemic inflammatory diseases that frequently target the lungs.(16) DPLD is common in many of these disorders including scleroderma or systemic sclerosis (SS), RA, systemic lupus erythematosus (SLE) and inflammatory myopathies.(16) DPLD may be the first sign of a connective tissue disorder.(11) A study reported that 3.5% of patients were diagnosed with DPLD before they were diagnosed with RA.(11) DPLD may occur in all connective tissue disorders, with an estimated incidence of 15%.(11) This justifies excluding autoimmune conditions in patients with suspected idiopathic DPLD.(11) In RA, DPLD is the commonest and potentially most devastating extra-articular manifestation.(11) The long term prognosis of patients with connective tissue disorder complicated by DPLD has recently been shown to be less severe than that of IPF.(8,9) DPLD as a complication of RA affects twice as many men as women.(11) Besides cardiac disease, DPLD is the next most common cause of mortality in RA and is estimated to be between ten and twenty percent.(8,9) The most frequent histological patterns seen in CTD-DPLD include NSIP and UIP.(11) Organizing pneumonia may occur in polymyositis (PM) and RA.(11) LIP is mostly found in Sjögren's syndrome and RA and usually responds to corticosteroids.(11) DAD or AIP is seen in RA, PM, SLE and undifferentiated CTD.(11) Psoriasis, an auto-immune skin condition, is a rare cause of DPLD.

1.8 Smoking related DPLD

Smoking-related DPLD comprises a heterogeneous group of conditions which have traditionally been viewed as individual entities.(18) These disorders frequently co-exist with the main common sequelae of cigarette smoking-induced injury such as chronic obstructive pulmonary disease (COPD) and bronchogenic carcinoma.(18) Traditionally there are DPLD related to smoking namely, respiratory bronchiolitis–associated interstitial lung disease (RB-

ILD), DIP, and pulmonary Langerhans cell histiocytosis (PLCH).(18) These types of DPLD are seen in current and former smokers. There may also be deterioration of lung function in spite of smoking cessation.(18) Smoking has also been associated with poor outcome in other DPLD that are not usually associated with smoking, like RA.(18) Cigarette smoking is a known risk factor for the development of IPF or UIP.(18)

1.9 Human immunodeficiency virus associated DPLD

Patients infected with human immunodeficiency virus (HIV) are at an increased risk for opportunistic infections and non-infectious lung complications such as DPLD.(19,20) The various HIV-related DPLD have no clear unifying aetiology. It is thought that DPLD may occur as a result of immune dysregulation and/or reconstitution as well as some associated co-infections.(20) LIP is characterized by an influx of lymphocytes into the alveolar space. HIV-infected patients in several studies have normal airways at baseline but the DLCO was seen to be diminishing over time.(19,20) NSIP and LIP are manifestations of immune dysregulation and their frequency has declined significantly due to availability of antiretroviral treatment (ART).(20)

1.10 Sarcoidosis

Sarcoidosis is a systemic condition characterized by the development of non-caseating granulomas.(17) Sarcoidosis affects different organs such as the eyes, skin, nervous system, lymph nodes, bone marrow, liver and blood. The clinical presentation depends mostly on the organ involved.(18) Sarcoidosis typically affects younger adults and has predilection for lungs.(19) In countries with high TB prevalence such as South Africa, sarcoidosis is often

misdiagnosed as TB as the two diseases have similar clinical, radiological and pathological features.(20)

1.11 Other DPLD

Other rare causes of DPLD are lymphangioleiomyomatosis (LAM), PLCH, EP, vasculitis, and neurofibromatosis.(7,8) LAM and PLCH are rare conditions characterised by the presence of pulmonary parenchymal cysts.(21) Diffuse alveolar haemorrhage (DAH) may be a manifestation of pulmonary vasculitis.(22) DAH is usually seen in small-vessel vasculitides, namely microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA).(22) It may also be associated with Goodpasture's syndrome, Henoch Schönlein purpura and SLE.(22) EP include a spectrum of lung diseases that may present with peripheral blood eosinophilia ($>0.5\times10^9$/L) and/or alveolar eosinophilia (>25%).(23) Drugs and parasitic infections are some of the causes of eosinophilic pneumonia.(23) However, chronic EP remains largely idiopathic.(23) Pulmonary alveolar proteinosis (PAP) is a rare diffuse lung disease characterised by alveoli filling with proteinaceous material.(11)

2.0 Idiopathic interstitial pneumonitis

The idiopathic interstitial pneumonitis (IIP) are a subset of DPLD without a known cause.(24) As illustrated in figure 1, they are classified into the IPF and non-IPF groups. The non-IPF group can be further subdivided histologically into NSIP, DIP, cryptogenic organizing pneumonia (COP), RB-ILD, AIP and LIP.(18,19) It is vital to exclude known causes of DPLD. The diagnosis of IIP requires exclusion of known causes of DPLD such as drugs, inhalational exposure or HP and CTD.(25) While the term 'idiopathic' specifies the lack of a known

causative factor, there is much postulation as to the pathogenesis of these disorders.(26) Cigarette smoking is a risk factor in the pathogenesis of IIP.(26) Furthermore, smoking is believed to have a significant role in the development and progression of IPF.(26)

2.1 Idiopathic pulmonary fibrosis

The most common and deadly subtype of IIP is IPF.(27) The term IPF is now applied exclusively to the syndrome associated with the morphological pattern of UIP.(2) Patients with IPF are usually in their sixth decade at presentation and men are affected slightly more often than women.(2) The median survival from diagnosis varies between 2 to 5 years.(2)

2.1.1 Epidemiology

This subtype of IIP is considered rare, however, it seems to be increasingly reported with greater frequency worldwide.(28) Incidence of IPF varies across the world. Lower incidence has been reported in Asia and Southern America where it ranges from 0.5 to 4.2 per 100 000 people per year.(28) Europe and North America have higher incidence between 2.8 and 18 cases per 100 000 people per year.(29) No studies have reported the incidence of IPF in Africa or South Africa.

2.1.2 Aetiology

The aetiology of IPF is not known. It is thought that many factors are involved in its pathogenesis.(28) Interaction between genetics and environmental factors with recurrent local damage to ageing alveolar epithelium play a significant role.(28) Aberrant epithelial-fibroblast

interaction, induction of matrix-producing myofibroblasts with marked extracellular matrix accumulation and remodeling of lung interstitium is the result of these micro-injuries.(28) There is also maladaptive repair process involving dysregulation of type 2 pneumocytes which is believed to be crucial to fibrogenesis in IPF.(28)

2.1.3 Clinical presentation

The presentation of IPF is usually insidious over a period of at least 3 months.(30) Symptoms are usually non-specific. These include dyspnoea on exertion which may be accompanied by dry cough.(28) These may initially be attributed to other conditions such as obesity, ageing, emphysema and cardiovascular diseases.(28) On clinical examination, patients usually have digital clubbing with bibasilar late inspiratory “Velcro” crackles.(28) Other known causes of DPLD such as CTD-DPLD, exposure related DPLD, sarcoidosis and other IIP should be excluded with detailed history, clinical examination and investigations.(28,30) Lung function tests show restrictive impairment of varying extent depending on disease stage.(30) DLCO is typically remarkably impaired.(30) The above typical lung function tests may be different in combined pulmonary fibrosis and emphysema (CPFE) where lung volumes are preserved but with significant diminished DLCO and the ratio of FEV1/FVC may either be normal or demonstrate an obstructive ventilatory pattern.(30)

2.1.4 Diagnosis

Clinical suspicion is important in patients over the age of 50 that present with insidious onset of exertional dyspnoea with or without cough.(28) An experienced multidisciplinary team should be responsible for making the diagnosis of IPF on clinical and radiological findings with

or without histological confirmation.(30) Chest radiograph is an important initial investigation to direct further investigations into the underlying diagnosis.(19) However, this investigation is neither specific nor sensitive.(19) The standard investigation in patients suspected to have IPF or any DPLD is HRCT.(19,30) HRCT is often the only special investigation necessary to make a definitive diagnosis of IPF which shows typical radiological UIP pattern.(30) However, other causes of UIP should be excluded.(30) This may have significant therapeutic and prognostic implication.(27) If the HRCT scan is not conclusive or if the patient presents with atypical clinical and radiological features, lung biopsy should be performed.(30) Patients that are regarded as unsuitable for surgical lung biopsy can be assessed as IPF based on the opinion of the experienced multidisciplinary team.(30)

The typical features of UIP on HRCT are interlobular septal thickening, reticular opacities and traction bronchiectasis, predominantly bilateral, peripheral, and basal in distribution. In addition there are clusters of subpleural, cystic airspaces with honeycombing and absent or minimal ground glass opacities. These typical radiographic features confirm the diagnosis of IPF and if present it is usually not necessary to perform a surgical lung biopsy.(2,27)

The histological feature of IPF is a UIP pattern. This includes temporal and spatial heterogeneity within the same biopsy i.e., areas of normal looking lung alternating with interstitial fibrosis, fibroblastic foci, architectural distortion and honeycombing with minimal or no inflammation.(25,28)

2.1.5 Treatment

2.1.5.1 Immunomodulatory drugs

A Cochrane review exploring the efficacy of corticosteroid in the treatment of adults with IPF did not find any eligible studies.(31) Azathioprine is an immunosuppressant that blocks the function of proliferating cells such as T-cells and B-cells.(32) The use of azathioprine and prednisone demonstrated an improvement in lung volumes and gaseous exchange in a small retrospective study performed in 1978.(32) This was also analysed in a prospective randomised double blind controlled study by Raghu *et al* in 1991, where azathioprine and prednisone vs. prednisone alone were compared and found that there was a trend towards survival benefit.(33) However, it did not reach statistical significance. Cyclophosphamide, a cytotoxic chemotherapy agent, in combination with prednisone has been evaluated in 2 retrospective studies.(34,35) One showed survival benefit in patients with early disease while the other showed no difference.

2.1.5.2 N-acetyl cysteine

The PANTHER-IPF and another randomized double-blind placebo controlled study showed that a triple combination of azathioprine, prednisone and N-Acetyl cysteine (NAC) was associated with greater mortality (11% vs 1%), more hospitalization (29% vs 8%) and more serious side effects (31% vs 9%).(36,37) These side effects were not observed with either the dual therapy or with NAC alone. The triple regimen also, did not show any difference in lung function. There was no significant benefit observed with NAC alone compared with placebo.(37) However, in the IFIGENIA study, it was found that the triple regimen had favourable outcome compared to the standard treatment of azathioprine plus prednisone as evidenced by slower decline in FVC and DLCO.(38) The investigators, however, did not conclude on the side effects associated with the triple regimen. In addition, they also did not

have a group of patients on NAC alone and therefore it was unknown whether NAC alone would be associated with better outcome compared to placebo or other drug regimen.

2.1.5.3 Antacid therapy

Many studies have documented the co-existence of gastro-oesophageal reflux disease (GORD) and IPF.(33,34,35) Raghu *et al*. have shown that 87% of their study patients had GORD and 53% of these patients were asymptomatic.(34) In the recent post-hoc analysis of antacid therapy in three trials of pirfenidone (CAPACITY 004, CAPACITY 006 AND ASCEND), antacid therapy was not associated with better rates for mortality or decrease in FVC.(40) Hospital admissions were not lower. In fact, hospital admissions were non-significantly higher. Side effects were similar between treatment and placebo groups. Overall infections and pulmonary infections were found to be higher with the antacid group in patients with advanced disease.

2.1.5.4 Anti-fibrotic agents

Recently, two new oral anti-fibrotic agents have approval for the treatment of IPF. Pirfenidone is an anti-fibrotic drug with anti-oxidant and anti-inflammatory properties.(40,41) The efficacy of pirfenidone in IPF has been mixed.(30) In the ASCEND study, pirfenidone, was found to reduce the decline in 6-minute walk distance and also progression free survival. The decline in FVC was also significantly reduced as compared with placebo.(42) CAPACITY trials also found reduction in decline in FVC and an increase in progression free survival and there was increase in oxygen saturation on the treatment group.(40,41). Nintedanib is a drug that inhibits receptor tyrosine kinases.(19) This drug was shown by 2 studies INPULSIS-1 and INPULSIS-2 with identical designs to significantly lower the annual rate of change in FVC compared to

placebo.(43) A difference of 125ml and 94ml annually was demonstrated in the INPULSIS-1 and INPULSIS-2 clinical trials respectively. In INPULSIS-1, however, no difference between the nintedanib and placebo groups in the time to the first acute exacerbation of IPF was found. The Food and Drug Administration (FDA) approved nintedanib for the treatment of IPF on October 2014. Both pirfenidone and nintedanib are not registered in South Africa. They can, however, be obtained through section 21 order.(30) The South African Thoracic Society recommends that these drugs be offered to patients with IPF with FVC 50-80%.(30) However, treatment should be stopped if FVC declines by at least 10%. This is an indication of disease progression.(30)

2.1.5.5 Lung transplantation

At the current moment, lung transplantation is the only intervention that improves survival in select patients with IPF.(44) One year post transplant, survival was increased by 79% in a study of 46 patients awaiting transplant.(45) Data from the international society for heart and lung transplantation has demonstrated that between January 2000 and June 2005, one and five year survival rates for single lung transplant (SLT) in IPF were 76% and 45% and for bilateral lung transplant (BLT) were 77% and 52% respectively.(46) This form of treatment is difficult to access as there are limited resources in the public sector and long-term post-transplant care is also a challenge in South Africa.(30)

3.0 Study aims and objectives

3.1 Aims

The aim of this study is to document the clinical profile of patients with IPF seen at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Respiratory Clinic. In addition we aim to record the spectrum of DPLD encountered.

3.2 Objectives

1. To document and study the clinical profile of patients with IPF attending the CMJAH Respiratory Clinic.
2. To determine the causes and spectrum of diffuse parenchymal lung disease encountered.

3.3 Methods

3.3.1 Study design

Retrospective record review

3.3.2 Study population

Patients with diffuse parenchymal lung disease attending the respiratory outpatient department at the CMJAH in the last 5 years will be identified. The clinical profile of patients with a diagnosis of IPF will be studied.

3.3.2.1 Site and size of study

The study will take place at CMJAH Respiratory Clinic. CMJAH is a tertiary hospital situated in Parktown, Johannesburg, South Africa. It has 1088 usable bed and is one of the 3 main

teaching hospitals in Johannesburg affiliated to the University of the Witwatersrand. It also serves as a referral centre for a number of hospitals in its drainage area in and around the Gauteng province. There are approximately 70 to 100 patients that attend the CMJAH respiratory clinic on a weekly basis. These include both new and old patients. Patients diagnosed with DPLD in the last 5 years, January 2011 to December 2015, will be documented and the records of those patients with IPF will be evaluated.

3.3.2.2 Measurements and observations

Medical records of patients who attended CMJAH pulmonology OPD will be reviewed for the diagnosis of diffuse parenchymal lung disease. Those with a diagnosis of IPF will be studied. Data will be collected for these patients attending the clinic in the last 5 years (January 2011 to December 2015). Files will be reviewed and a data collection sheet will be utilised to record data obtained from the files. Patient names will be replaced by numbers to protect patient confidentiality. Clinical, radiographic and laboratory data will be recorded and analysed

3.3.2.3 Inclusion criteria

Those patients with diffuse parenchymal lung disease with a diagnosis of IPF attending Respiratory Clinic at CMJAH

3.3.2.4 Exclusion criteria

Patients whose diagnoses are unclear

3.3.2.5 Limitations or potential problems

Data collection from files may not always be present or complete.

3.4 Data analysis

The data will be collected using a data collection sheet, and will be analysed using STATA version13. For data management a spreadsheet will be used. Categorical variables will be expressed using frequency distribution. Continuous data will be expressed using descriptive statistics such as mean, standard deviation, median and range. The assistance of a statistician will be used to interpret the data collected.

3.5 Ethics

Ethics approval shall be obtained from the Human Research Ethics Committee of the University of the Witwatersrand as well as the University's Postgraduate Committee before commencement of the study. Permission will also be obtained from the hospital management of CMJAH.

3.6 Timing

	Jul 2015	Aug 2015	Sep 2015	Oct 2015	Nov 2015	Dec 2015	Jan 2016	Feb 2016	Mar 2016	Apr 2016	May 2016	Jun 2016
Literature review												
Preparing protocol												
Protocol assessment												
Ethics application												
Collecting data												
Data analysis												
Writing up												

3.7 Funding

No costs are anticipated other than that necessary for stationery, photocopying, printing, and binding which will be covered by myself.

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CHAPTER TWO: SUBMISSIBLE ARTICLE

Spectrum of Diffuse Parenchymal Lung Disease with Special Reference to Idiopathic Pulmonary Fibrosis: Experience at Charlotte Maxeke Johannesburg Academic Hospital

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ABSTRACT

Background

Diffuse parenchymal lung diseases (DPLD) encompass a group of diseases with a wide range of causes with varied presentations and prognosis. The known causes include occupational or environmental exposure, drug induced lung diseases, hypersensitivity pneumonitis and connective tissue disease (CTD). Among the DPLD with unknown cause, idiopathic pulmonary fibrosis (IPF) is the commonest and has the worst outcome. The earlier publications from this country described cryptogenic fibrosing alveolitis. With subsequent characterisation of idiopathic interstitial pneumonia (IIP), and an increase in the burden of IPF reported worldwide, we evaluated the clinical features of patients with IPF in the South African context.

Objectives

To evaluate the clinical spectrum of DPLD encountered in Johannesburg, South Africa, and to describe the clinical profile of patients with IPF.

Methods

A retrospective record review of patient files was conducted who attended the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Respiratory Clinic in the past 5 years from January 2011 to December 2015. Patients with DPLD were identified and the diagnoses were noted. The records of patients with IPF were further analysed.

Results

We identified 132 patients with DPLD. Sarcoidosis (37.8%), IPF (21.2%), connective tissue associated diffuse parenchymal lung disease (CTD-DPLD) (14.3%), and hypersensitivity pneumonitis (HP) (9.8%) were the four most common subtypes. IPF was seen in all racial groups. Of the 28 patients with IPF in our cohort, there was a slight female predominance (1.3:1). The mean age of the patients in our study was 63.8 years and the majority were Whites. Cough (96.4%), dyspnoea (92.8%) and bilateral crackles (96.4%) were the commonest clinical features. The majority of patients (78.5%) were diagnosed by high resolution computerised tomography (HRCT) scan.

Conclusion

IPF is the second most common DPLD disease encountered after sarcoidosis at the CMJAH. IPF is seen in all racial groups in Johannesburg, South Africa, and the characteristics of patients with IPF are similar to those seen in other parts of the world.

Introduction

Diffuse parenchymal lung diseases (DPLD) encompass a wide spectrum of disorders, with varied presentations and prognosis.(1–3) DPLD can be broadly classified into exposure related, connective tissue disease associated interstitial lung disease (CTD-ILD), idiopathic interstitial pneumonia (IIP), granulomatous lung disease and other miscellaneous group of lung diseases.(1,4) The known causes include occupational or environmental exposure, drug induced lung diseases, hypersensitivity pneumonitis and connective tissue disease (CTD).(7,8) Among the DPLD with unknown cause, idiopathic pulmonary fibrosis (IPF) is the commonest and has the worst outcome.(5,6) The earlier publications from this country described cryptogenic fibrosing alveolitis.(7,8) With subsequent characterisation of idiopathic interstitial pneumonia (IIP), and an increase in the burden of IPF reported worldwide(2,6,9,10) we evaluated the clinical features of patients with IPF in the South African setting There is a lack of published data in South Africa regarding, prevalence, presentation, management and outcomes of IPF.

Aim

The aim of this study was to evaluate the clinical profile of patients with IPF at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Respiratory Clinic. In addition, we aimed to record the spectrum of DPLD encountered at the Clinic.

Materials and Methods

We retrospectively reviewed records at CMJAH Respiratory Clinic over a 5 year period, from January 2011 to December 2015. All patient records were perused and patients with DPLD

were identified. Patients with DPLD were further divided into different diagnoses and patients with IPF were included in the study if they were 18 years and older. In addition, they had to have adequate records which at a minimum, had to have IPF as their diagnosis and a high resolution CT scan and/or lung biopsy results. Approval for the study was obtained from the Hospital administration and the Human Research Ethics Committee of the University of the Witwatersrand.

Results

One hundred and thirty two patients with diffuse parenchymal lung disease (DPLD) were identified. Sarcoidosis, IPF, CTD-ILD, and HP were the four most common DPLD subtypes in our population. As shown in Table 1, fifty (37.8%) patients were diagnosed with sarcoidosis, the commonest DPLD encountered, and twenty-eight (21.2%) patients were diagnosed with idiopathic pulmonary fibrosis (IPF), the second most common DPLD seen in the study. CTD-ILD was seen in 19 (14.3%) patients and HP in 13 (9.8%) patients. The records of the patients with IPF were further analysed.

Of the 28 patients that were diagnosed with IPF, 12 were males (42.8%) and 16 females (57.1%), ratio of males to females was 1:1.3. The mean age of the cohort of patients was 63.8 years. Whites comprised 42.8% of the patients, 29.5% were Black, 25% Indian and 1 patient was a Coloured female. The sex ratio was equal among the Whites and 1.7 times more common in the Black males than the female patients. There were 6 females and 1 male among the Indian patients. The majority, 27 (96.4%) patients, were over of the age of 50. Ten (35.7%) patients were older than 70 years old. The youngest patient was 47 years old (Table 2 and Figure 2).

Seventeen (60.7%) patients were either current or ex-smokers. In seven patients there was information regarding the amount and duration of cigarettes smoked and the average pack-years was 20. One patient was an underground gold-miner.

Cough was the most common presenting symptom in 27 (96.4%) patients followed by dyspnoea in 26 (92.8%) patients while chest pain was present in only 1 (3.5%) patient. Bibasilar crackles were found in almost all patients (96.4%), central cyanosis in 13 (46.4%) patients and clubbing in 12 (42.8%) patients, respectively (Table 4).

Coexistent diseases that were seen in these patients are listed in Table 5. Pulmonary hypertension was present in 12 (42.8%) patients, systemic hypertension in 8 (28.5%) patients, followed by chronic obstructive pulmonary disease (COPD) (14.2%), gastro-oesophageal reflux disease (GORD) (7.1%) and hypothyroidism (7.1%). Two (7.1%) patients were HIV-positive and the CD4+ was 580 and 98/µL respectively. Other diseases that were present included aortic stenosis, diabetes mellitus, breast cancer and osteoporosis (in 4 different patients).

Six (21.4%) patients had surgical lung biopsies. Of the 6 patients, 5 patients had a confirmed usual interstitial pneumonia (UIP)-pattern on histology and one patient had a suspected chronic HP. After comprehensive review of the HRCT scan, histopathology and clinical parameters the patient was deemed to have IPF and treated as such. The anti-nuclear antibody (ANA) was positive in low titre (≤1:128) in 5 (17.8%) patients with IPF. (Table 6)

Twenty two (78.5%) patients were diagnosed as having IPF by HRCT scan with the typical features of UIP. Interlobular septal thickening, reticular opacities associated with traction bronchiectasis, predominantly bilateral, peripheral, and basal distribution, clusters of subpleural, cystic airspaces of similar diameters with honeycombing and absent or minimal ground glass opacities are the typical radiographic features of UIP. Four (14.2%) patients had combined pulmonary fibrosis and emphysema (CPFE).

The lung functions (Table 7) demonstrates that the forced expiratory volume in 1 second (FEV1) was decreased in 17 patients; between 60-80% predicted in 11 patients and between 40-59% predicted in 6 patients. The FVC was normal in 10 patient and decreased in 18 patients; between 60-80% predicted in 12 patients and between 40-59% predicted in 6 patients. The mean FVC percent predicted ± SD was 74 ± 17. None of the patients had an obstructive defect i.e. FEV1/FVC ratio below 70%. The total lung capacity (TLC) was decreased in 16 patients (13 between 60-80% predicted and 3 between 40-59% predicted). The mean TLC percent predicted ± SD was 76 ± 12. Ten patients had a RV/TLC ratio > 50% predicted of whom 4 had RV/TLC >100% predicted. The diffusion capacity for carbon monoxide (DLCO) was decreased in all 25 patients in whom it was measured; between 60-80% predicted in 3, between 40-59% in 8 and <40% predicted in 14 patients. The mean DLCO percent predicted ± SD was 37 ± 18.

Ten (35.7%) patients were treated with corticosteroids (CS) alone. Six of these patients were on CS for an average of 30 months. Eight (28.5%) patients were on azathioprine (AZA) alone,

half of whom were on it for approximately twenty-six months. Five (17.8%) patients received N-Acetylcysteine (NAC) alone. Three (10.7%) patients were treated with a triple drug regimen consisting of CS, AZA and NAC. These patients were younger age 50, 54 and 58 years respectively. The durations of follow up for these patients were 36, 48 and 36 months respectively. One patient was treated with a combination of CS and NAC. (Table 8)

Only 1 patient, who had medical insurance, was referred for assessment for lung transplantation at a private facility, during the study period. This patient was a 66 year old female with a 5 pack-year smoking history. She was seen at the clinic for 2 months and was referred for lung transplantation. The outcome of this patient is not known.

Nine (32.1%) patients received domiciliary oxygen therapy. The average duration of follow-up of these patients was 27.4 months. Four patients were on diuretics for right heart failure secondary to cor pulmonale. Three patients received therapy for GORD (2 patients received omeprazole and 1 patient ranitidine).

Eleven (39.2%) patients were known to be still alive and attending the clinic while the other 17 (60.7%) patients did not return for follow-up clinic visits.

Discussion

Spectrum of DPLD seen at CMJAH

IPF is the second most common DPLD encountered at the CMJAH Respiratory Clinic after

sarcoidosis, which is the commonest.

Gender

In the United States of America, males had a higher incidence of IPF than females. Higher incidences were also observed among males in Europe.(11) In Norway, however, females had higher incidence of IPF compared to males 4.6 vs 4.0 per 10,000 person years.(12) IPF may also progress faster in men and result in worse survival.(13) Our study showed a slight female predominance (1.3:1), though small study number.

Age and Race

IPF was prevalent in all racial groups. IPF is more commonly seen in patients between the ages of 40 and 70.(14) Raghu *et al* reported higher IPF prevalence among older males of 65 years or older. (15) A similar trend was observed in a European study.(12) In general, IPF prevalence increases with age, with highest prevalence in patients over the age of 75 years with no clear sex predominance.(16) In a study done in Hillbrow Hospital, Johannesburg, South Africa, by Smith *et al*. in 1990, Blacks had a similar clinical spectrum to other groups in other parts of the world.(7) The mean age of the patients in our study was 63.8 and Whites predominated compared to other races. The mean ages in the different population groups in Whites, Blacks Indians and Coloureds were 64, 60, 67, and 78 years, respectively.

Smoking

Smoking is thought to play a significant role in the pathogenesis, development and progression

of IPF.(9) Smith *et al* showed that cigarette smoking was associated with a worse outcome.(7) In the current study more than half of the patients were either current or ex-smokers. There were no differences in the lung functions (TLC and DLCO) between smokers and non-smokers. Four patients in our study had CPFE on HRCT scan.

Symptom and signs

Cough, dyspnoea and bilateral crackles were present in 96.4%, 92.8% and 96.4% of patients respectively. Cyanosis was noted in 46.4% and clubbing in 42.8% of patients. This correlates with many other studies (10-13). Of note, there were no skin lesions present in patients with IPF in the current study.

Comorbid diseases

As IPF is a disease of older adults, a number of other coexisting conditions may be present in these patients, as was seen in this cohort. Pulmonary hypertension was documented in 42.8% of the study patients, which may be a marker of severity of disease, as was suggested by others.(6,7) GORD may be a comorbid disease in these patients and has also been implicated in IPF exacerbations. It is important to diagnose and treat these comorbid conditions as this may impact on the patient's quality of life.

Diagnosis

In a Swedish study by Giovanni *et al*, the diagnosis of IPF was mostly based on clinical and radiological features and only 10% of the patients underwent invasive procedures such as lung

biopsy.(11) In the current study most (78.5%) of the patients were diagnosed by HRCT scan that had typical features of UIP. Six patients (21.4%) had surgical lung biopsies to confirm the diagnosis. This was consistent with the data reported in the literature.(17).

Lung function tests

The FVC was decreased in 18 patients and TLC was decreased in 16 patients, which are typical of a restrictive defect. None of the patients had an obstructive defect. The DLCO was decreased in all 25 patients in whom it was measured. Ideally the DLCO should be measured in all patients (if facilities are available) suspected of having IPF, as it may have diagnostic and prognostic implications.(18)

Treatment

Due to the small number of the study population, retrospective nature of the study, and unavailability of some data, analysis of the treatment options and outcome could not be ascertained and accurately analysed.

Limitations

This study had numerous limitations. Firstly, missing information plagues the retrospective design. Some findings are difficult to interpret and to compare with other centres due to the small study population size and variations in patient characteristics. Patients with autoimmune or connective tissue disease attend the Rheumatology Clinic at our institution and not necessarily the Respiratory Clinic. Therefore, our study may underestimate the number of cases

of CTD-DPLD. In addition, a substantial proportion of patients did not return for their follow-up clinic visits. Whether these patients were deceased or not, could not be ascertained from the records.

Conclusions

IPF is the second most common DPLD disease encountered after sarcoidosis at the CMJAH. It is prevalent in all racial groups in Johannesburg, South Africa. This study showed similar trends to those reported in other parts of the world with regard to age of onset, White race predominance and the survival rates of patients with IPF. We did not, however, observe the higher incidence reported in males. We had a slight female preponderance, as was observed in the Norwegian study.

Future direction

Despite the limitations of this study, our findings add valuable clinical and epidemiological information to the paucity of data that exists for IPF in Africa and South Africa. In the future, we plan to conduct a prospective study identifying and evaluating the prevalence, clinical profile and outcome of patients with this devastating disease.

Acknowledgements

Nil

Disclosure statement

The authors have no conflict of interest to declare

Table 1. Aetiology of diffuse parenchymal lung disease

Spectrum of DPLD (n=132)	Number of cases (%)
Sarcoidosis	50 (37.8)
Idiopathic pulmonary fibrosis (IPF)	28 (21.2)
Connective tissue disease associated ILD (CTD-ILD)	19 (14.3)
Hypersensitivity pneumonitis (HP)	13 (9.8)
Silicosis and progressive massive fibrosis (PMF)	3 (2.2)
Cryptogenic organising pneumonia (COP)	2 (1.5)
Desquamative interstitial pneumonitis (DIP)	2 (1.5)
Lymphoid interstitial pneumonia (LIP)	2 (1.5)
Pulmonary alveolar proteinosis (PAP)	2 (1.5)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	1 (0.7)
Psoriasis	1 (0.7)

Table 2. Demographic data of IPF patients (n=28)

Demographic Data	
Mean Age ± SD (range)	63.86 ± 11.02 (47-78)
Male: Female	12 (42.8):16 (57.1)
Age > 50 years No. (%)	27 (96.4)
Racial breakdown (W:B:I:C)	12:8:7:1

W-Whites, B-Blacks, I-Indians, C-Coloureds

Table 3. Clinical parameters of patients with IPF

Clinical Features	Number of cases (%)
Smoking history	
Smoker or ex-smoker *	17 (60.7)
Occupation	
Gold miner	1 (3.5)
Symptoms	
Cough	27 (96.4)
Dyspnoea	26 (92.8)
Chest pain	1 (3.5)
Signs	
Bilateral crackles	27 (96.4)
Cyanosis	13 (46.4)
Clubbing	12 (42.8)
Skin lesions	0 (0)

*mean pack years ± SD, (range); 20 ± 19.1, (4-55)

Table 4. Comorbid diseases in IPF patients

Comorbid Diseases	Number of cases (%)
Pulmonary hypertension	12 (42.8)
Hypertension	8 (28.5)
Chronic obstructive pulmonary disease (COPD)	4 (14.2)
Gastroesophageal reflux disease (GORD)	2 (7.1)
Hypothyroidism	2 (7.1)
Human immunodeficiency virus infection	2 (7.1) (CD4+ = 580 and 98/µL)
Aortic stenosis	1 (3.5)
Diabetes mellitus	1 (3.5)
Breast cancer	1 (3.5)
Osteoporosis	1 (3.5)

Table 5. HRCT, surgical and serum markers

HRCT, surgical and serum markers	Number of cases (%)
HRCT	
HRCT typical features of UIP	22 (78.5)
CPFE (IPF and emphysema)	4 (14.2)
Surgical lung biopsy	6 (21.4)*
Serum markers	
ANA positive	5 (17.8)

HRCT High resolution computerised tomography scan

*One patient was suspicious for possible hypersensitivity pneumonitis, but eventually diagnosed as idiopathic pulmonary fibrosis

Table 6. Pulmonary function tests of IPF patients

Pulmonary functions	
FEV1	n=28
>80% predicted	11
60-80% predicted	12
40-59% predicted	5
Forced Vital Capacity	n=28
>80% predicted	10
60-80% predicted	12
40-59% predicted	6
Ratio of FEV_1/FVC	n=28
>90%	9
70-90% predicted	19
<70% predicted	0
TLC	n=26
>80% predicted	10
60-80% predicted	13
40-59% predicted	3
RV/TLC	n=25
>100% predicted	4
>50%-100% predicted	6
30-50% predicted	15
DLCO	n=25
60-80% predicted	3
40-59% predicted	8
<40% predicted	14

FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
TLC	Total lung capacity
RV	Residual volume
DLCO	Diffusion capacity for carbon monoxide

Table 7. Therapy and outcome of IPF patients

Therapy	Number of cases (%)
CS (mean duration 30 months)	10 (35.7)
AZA (mean duration 26 months)	8 (28.5)
NAC	5 (17.8)
CS + AZA + NAC (mean duration 40 months)	3 (10.7)
CS + NAC	1 (3.5)
Long term oxygen therapy (mean duration 27 months)	9 (32.1)
Furosemide (cor pulmonale and right heart failure)	4 (14.2)
Antacid therapy [omeprazole (2) and ranitidine(1)]	3 (10.7)
Lung transplantation referral	1 (3.5)
Outcome	
Returned for follow up	11 (39.2)
Did not return for follow up (presumed deceased)	17 (60.7)

CS Corticosteroids
AZA Azathioprine
NAC N-acetylcysteine

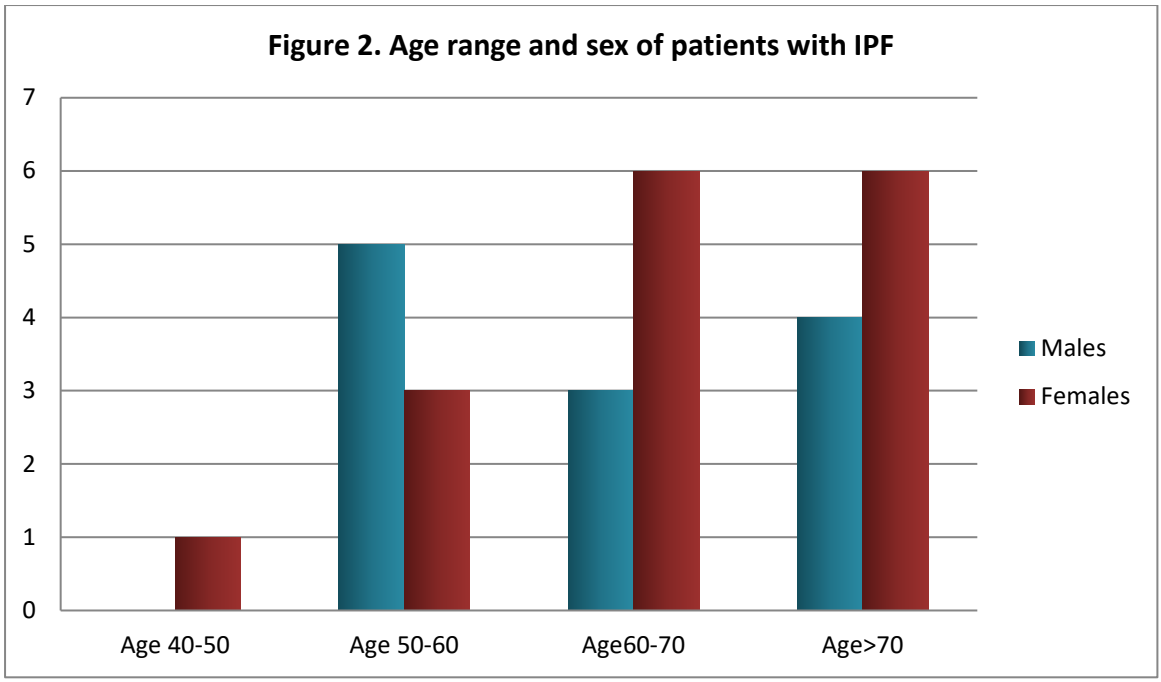
Figure 2. Age range and sex of patients with IPF
7
6
5
4
3
2
1
0
Age 40-50
Age 50-60
Age60-70
Age>70
Males
Females

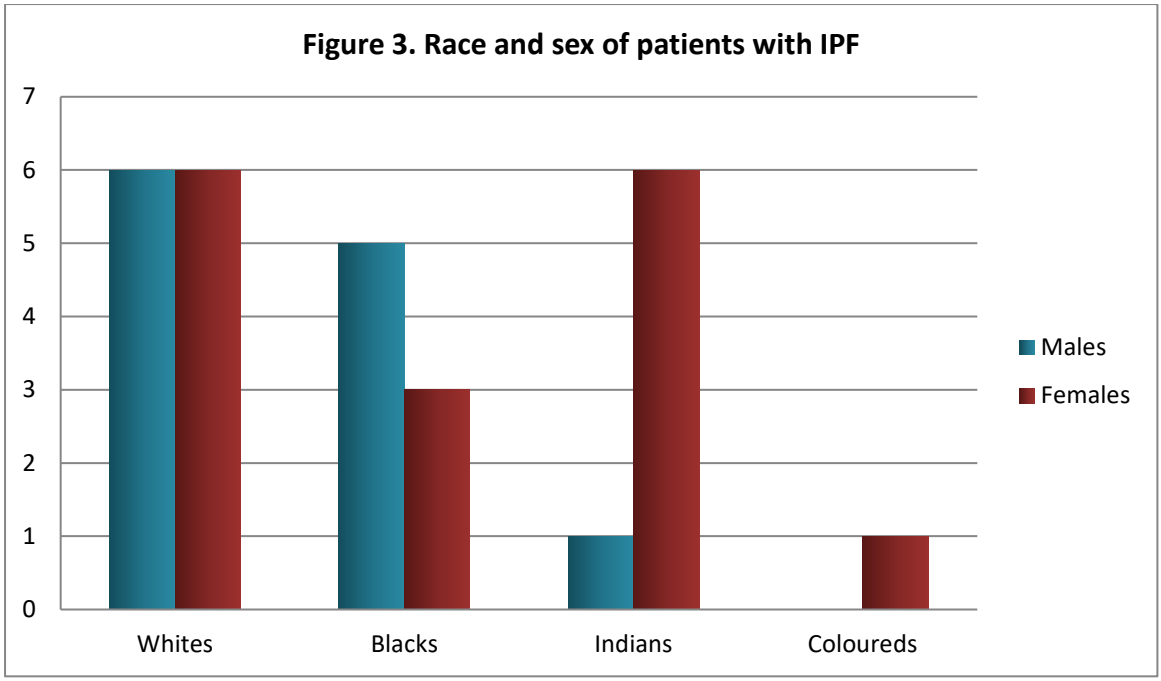
Figure 3. Race and sex of patients with IPF
7
6
5
4
3
2
1
0
Whites
Blacks
Indians
Coloureds
Males
Females

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CHAPTER 3: APPENDICES

3.1 Data collection sheet (study number)

A. DEMOGRAPHICS AND HISTORY		
1. Gender	Male	
	Female	
2. Age		
3. Race		
4. Smoker	Yes	
	No	
5. Occupational history		
6. HIV status	Negative	
	Positive	
6.1. If on ARVs	Durations	
6.2. Name of ARVs		
	CD4	
	VL	
7. Other medical conditions		
8. Drug history		
9. CTD	Yes	
	No	
9.1. If yes, specify		
9.2. Treatment of CTD		
B. SYMPTOMS		
1.Cough		
2.Dyspnoea		
3.Chest pain		
C. SIGNS		
1.Clubbling		
2.Cyanosis		
3.Crackles		
4.Pulmonary Hypertension		
5.Skin lesions		
Other organ involvement		
D. INVESTIGATIONS		
1. Chest X-ray		
2. Lung Function Test		
FEV1		
FVC		
FEV1/FVC		
TLC		
DLCO		
RV/TLC		

3. HRCT scan results		
4. Lung biopsy results 4.1. Transbronchial lung biopsy 4.2. Open lung biopsy		
5. FBC	WCC	
	Hb	
	HCT	
	PLT	
Differential count	Neutrophils	
	Lymphocytes	
	Eosinophils	
	Basophils	
	Other	
6. U&E		
7. Calcium		
8. CRP		
9. ESR		
10. RF		
11. ANA		
12. SCL 70 (DNA topoisomerase)		
13. ANCA		
14. ACE		
15. Other bloods		
E. TREATMENT		
1. Corticosteroids and duration		
2. Other immunosuppressive drugs and duration		
3. Other treatment Rx e.g. PPI		
4. Home oxygen		
5. Lung transplant referral Lung transplant done/not		
6. Months or Years of follow up		
7. Dead or Alive		
8. Cause of death		

3.2 Ethics approval certificate

R14/49 Dr Ndikundisani Ananius Tshiovhe

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M151038

NAME: (Principal Investigator)	Dr Ndikundisani Ananius Tshiovhe
DEPARTMENT:	Internal Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Spetrum of Diffuse Parenchymal Lung Diseases with Special Reference to Idiopathic Pulmonary Fibrosis at Chartlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	30/10/2015
DECISION:	Approved unconditionally
CONDITIONS:	Title change (12/05/2016)
SUPERVISOR:	Prof Rajen Morar
APPROVED BY:	Professor P. Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	12/05/2016

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 in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the 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 review in October and will therefore be due in the month of October each year.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES