The characteristics of interstitial lung disease patients attending Groote Schuur Hospital Respiratory clinic

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Date: 08/12/2022

Dedication

There are several people without whom this thesis might not have been written, and to whom I am greatly indebted to my family and especially my mother and late father; a unique feeling of gratitude to you for all your support and to those few special friends who are always cheering me on.

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Declaration

I, GURVEEN KAUR SOIN, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Rationale: Interstitial lung diseases (ILDs) encompass a myriad of clinical conditions posing diagnostic challenges in low-income settings. The incidence of Idiopathic pulmonary fibrosis (IPF) is unknown on the African continent. Groote Schuur Hospital (GSH) provides a tertiary referral and follow-up service for patients with suspected ILDs. We set out to determine the burden of IPF and progressive pulmonary fibrosis (PPF) in an African setting.

Methods: All patients attending the GSH respiratory clinic with known or suspected ILD were identified over six months. Demographics, spirometry, high-resolution CT findings, histology, and final diagnosis and treatments were captured. IPF incidence was estimated using published population and medical insurance numbers, hospital referral area/pattern, and new IPF diagnoses over a full year period. The presence of PPF was determined by worsening clinical features and lung function in accordance with ATS/ERS guidelines.

Results: A total of 103 patients (28 new and 75 follow-ups) were seen over six months. The follow-up patients were predominantly female (81%), diagnosed with systemic sarcoidosis (57%) & connective tissue disease-ILD (CT-ILD) 26%. Hypersensitivity pneumonitis accounted for 5% of follow-up patients, and only 2 IPF patients were in follow-up. CTD-ILD was the most common diagnosis in new patients: 43% and 29% had sarcoidosis. Five new patients were diagnosed with IPF during the 6-month study review and a total of 11 over 1 year.

31% of the CTD-ILD patients had systemic sclerosis SSC; 70% diffuse, and 30% limited. A further 25% had rheumatoid arthritis, and 13% had SLE. Six patients were confirmed to have hypersensitivity pneumonia. Thirteen patients met the criteria for PPF, and a further five patients had rates of decline over four months that, if projected to 12 months, would fulfil the PPF criteria. All 18 patients had an FVC decline of >100mls: mean(range) rate of decline 9.2% (5–22%).

Conclusions: Specialised resources and diagnostic modalities to identify and manage ILD patients are required in low resourced settings. The burden of IPF is low but requires confirmation and is likely an underestimate. The potential need for anti-fibrotic treatment is impacted upon by the definition of FVC decline over 12 months.

Acknowledgements

I would like to thank Professor Richard van Zyl-Smit, for his wisdom, patience and irreplaceable support and guidance throughout this research project. He has not only showed me the joy of research but has guided me in my everyday life and how to use this experience going forward and has demonstrated how far dedication and attention to detail can take you.

Thank you to the most amazing mentor and life coach, and I'll always remember "What is the question being asked (or what are you trying to answer)".

Format and Contributions

This thesis is presented in the Published/Publication-ready format. The thesis has been formatted and prepared for the *African Journal of Thoracic and Critical Care Medicine. An abstract of the* findings of this research has been submitted to the American Thoracic Society for the 2023 conference, pending review currently.

GK Soin assisted with conceptualisation of the study, collected, and analysed the data and wrote the manuscript. Prof van Zyl Smit assisted with conceptualisation of study, and analytic approach and revised and reviewed and editing of the manuscript.

List of Abbreviations

Abbreviation	Definition
AS	Ankylosis Spondylitis
ATS/ERS	American Thoracic Society/ European Respiratory Society
CT	Computed Tomography
CTD	Connective Tissue Disease
CT-ILD	Connective Tissue Disease-ILD
DAD	Diffuse Alveolar Damage
DLCO	Diffusing Capacity for Carbon Monoxide
DM	Dermatomyositis
FVC	Forced Vital Capacity
GSH	Groote Schuur Hospital
HIV	Human immunodeficiency virus
HP	Hypersensitivity Pneumonitis
HRCT	High-Resolution Computed Tomography
HREC	Human Research Ethics Committee
I-ILD	Idiopathic Interstitial Lung Disease
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
LIP	Lymphoid Interstitial Pneumonia
MCTD	Mixed Connective Tissue Disease
MMF	Mycophenolate Mofetil
NSIP	Nonspecific Interstitial Pneumonia
OP	Organising Pneumonia
PAH	Pulmonary Arterial Hypertension
PM	Polymyositis
PPF	Progressive Pulmonary Fibrosis
PSS	Progressive Systemic Sclerosis
RA	Rheumatoid Arthritis
SACE	Serum Angiotensin-Converting Enzyme

SLE	Systemic Lupus Erythematosus
SS	Sjogren's Syndrome
SSC	Systemic Sclerosis
TSCT	Thin Section Computed Tomography
UCT	University of Cape Town
UIP	Usual Interstitial Pneumonia

Introduction

Interstitial lung diseases (ILD) encompass a variety of clinical conditions that pose diagnostic challenges without specialist resources. Idiopathic pulmonary fibrosis (IPF), the prototypical relentlessly progressive ILD, remains rare and fatal with a median survival of 3 years [(1)]. However, new therapies have been shown to slow the rate of progression [(2)(3)]. The prevalence of IPF in the USA has been estimated as 14-27.9 per 100,000 population/year in Europe: 0.22-7.4 per 100,000 population/year [(4)] and 1.2- 4.16 per 100,000 population/year in Asia (South Korea, Taiwan, Japan) [(5)]. We did not come across data on the incidence of interstitial lung disease in Africa, however, there are two published case series with: 14 patients in Kampala, Uganda [(6)] and 31 cases of ILD among 318 Connective Tissue Disease (CTD) patients over a 7-year period from Nigeria [(7)].

With recent data from the INBUILD study [(8)] and the publication of the ATS/ERs update [(9)], the Progressive Pulmonary Fibrosis (PPF) phenotype has been highlighted. This new PPF classification incorporates all interstitial lung diseases that manifest progressive fibrosis as determined by dropping forced vital capacity (FVC), worsening symptoms, and or radiological progression occurring in the last year with no alternative explanation in a patient with an ILD other than IPF.

In low-income settings, access to high-resolution CT scanning, invasive tissue diagnostics, and multi-disciplinary teams is limited, making the diagnosis of a specific interstitial lung disease even more challenging. For example, the burden of tuberculosis often confounding the diagnosis of sarcoidosis and other lung diseases. Furthermore, access to immunosuppressive drugs besides corticosteroids is limited, as is access to the newer and often costly anti-fibrotic treatments.

The respiratory clinic at Groote Schuur Hospital (GSH) in Cape Town, South Africa, offers a tertiary referral centre for roughly 50% of the greater Cape Town population (4.6 million). Any patient in this drainage area with a suspected ILD is referred for evaluation to this clinic. Tygerberg Hospital serves the other half of the greater Cape Town and the Western Cape Region. Patients with known ILDs, including those with underlying multisystem sarcoidosis or connective tissue diseases, are seen in the dedicated clinic.

Confirmation of the ILD diagnosis is made at a multi-disciplinary meeting reviewing the requisite history, serology, radiology, and or histology for each patient. For those with an indeterminate or uncertain diagnosis, following the ATS/ERS recommendations, surgical lung biopsy is offered.

The opportunity thus exists to estimate the burden of new IPF on the African continent for the first time as well as evaluate the potential burden that interstitial lung diseases may place on a health system with the need for radiological, pulmonary physiology, serological and histological investigations and follow up for these patients. We thus set out to capture all referrals of patients with suspected ILD and those with a known ILD within our service over six months, post-COVID restrictions, to understand better the burden that interstitial lung diseases have in an African health care setting.

Methods

A respiratory clinic registry was established in 2021 when hospital services reopened post-national government COVID-19 restrictions. A specific ILD sub-registry was formalised to capture all prevalent and incident patients with ILD in our service.

Data from all confirmed patients with ILD seen over a 6-month period (January to June 2023) were extracted into an ILD-specific database for the purpose of this review. All patients are reviewed over a 3–6-month period, thus capturing all follow-up patients. Demographics, medical history, diagnosis, diagnostic criteria, and treatment were recorded. Lung function at visits, including those occurring in the past 12 months for patients known with an ILD, were documented. Lung functions were done according to the local South African guidelines of 2022. [10] To better estimate the incidence rate of IPF and it burden in this setting a full calendar year was used to identify new cases of IPF specifically. (the patients outside the 6-month study period were not included in any other analysis.)

To determine the prevalence of patients with a progressive pulmonary fibrosis phenotype of interstitial lung disease, symptoms, and rate of decline in FVC were determined, and CT scans, where available: For those that did not have 12 months of follow-up, the estimated/projected rate of decline over one year was extrapolated from serial lung function conducted at least four months apart.

Approval for this study was obtained by the Faculty of Health Sciences Human Health Research Ethics Committee (HREC R007/2021; HREC 418/2022), the Groote Schuur Hospital Institutional Research Committee. All participants were required to sign informed consent to have their personal and medical information stored in the registry.

Results

Twenty-eight new and 75 follow-up patients with an ILD were seen in a 6-month period. The follow-up patients were slightly older, median age of 53.7 years compared to the new patients at 51.9 years, with a female preponderance (57 - 81%) in the new & follow-up groups, respectively. Sarcoidosis and connective tissue disease-associated ILD (CTD-ILD) were the two most common diagnoses in the follow-up group, 57.3%, and 26.7%, respectively and of the new patients seen, 42.9% were CTD-ILD and 28.6% sarcoidosis. Two known patients with IPF and five incident IPF patients were seen in the 6-month period. (See Table 1) A total of 11 incident IPF patients were diagnosed over a 12 months period to estimate incidence.

Table 1: Characteristics of patients seen in the ILD clinic over a 6-month period.

	Total n=103	OLD n=75(72.8%)	NEW n=28 (27.2%)	
Age (median) IQR	54 (44-63)	55(45-62)	52 (41-62)	
male n (%)	26 (25.2%)	14 (18.7%)	12 (42.9%)	
Female n (%)	77 (74.8)	61 (81.3%) *	16 (57.1%) *	*P=0.012
Former/current smoking	44 (42.7%)	30 (42.9%)	14 (50%)	
HIV positive	6 (5.8%)	3 (4.3%)	3 (10.7%)	
DIAGNOSIS				
Sarcoidosis	51 (49.5%)	43 (57.3%)	8 (28.6%)	
CTD-ILD	32 (31.1%)	20 (26.7%)	12 (42.9%)	
IPF	7 (6.8%)	2 (2.7%)	5 (17.9%)	
I-ILD	6 (5.8%)	5 (6.7%)	1 (3.6%)	
HP	6 (5.8%)	4 (5.3%)	2 (7.1%)	
HIV- ILD	1 (1%)	1 (1.3%)	0	

IQR-interquartile range, n- number, HIV- Human immunodeficiency virus, CTD-ILD- connective tissue associated interstitial lung disease, IPF- idiopathic pulmonary fibrosis, I-ILD- idiopathic interstitial lung disease, HP- hypersensitivity pneumonitis, HIV-ILD- human immunodeficiency virus interstitial lung disease.

<u>Sarcoidosis</u>

Of the 103 patients seen at the ILD clinic, 51 had a diagnosis of sarcoidosis. The majority (78.4%) had the diagnosis made on a tissue biopsy, overwhelmingly by transbronchial biopsy (62.5%), skin (20%), and lymph node (10%). The remaining 22% (11) had a clinical-radiological diagnosis without histological confirmation. Of those 11, 10 had a positive serum ACE level, median (IQR), above the normal range of 74(49-124) (local reference range: 8-52 U/L). Only one was deemed to be likely sarcoid based on their clinico-radiological picture. Four (7.8%) sarcoid patients were confirmed to be living with HIV (CD4 cell count ranging from 37 - 449x109 cells/ml). Forty-one per cent of the sarcoid patients were current or former smokers.

Connective tissue disease associated ILD.

Thirty-two (31.1%) patients were diagnosed with connective tissue disease-associated ILD (CTD-ILD). The majority, 31.2%, had underlying systemic sclerosis, with 70% diffuse and 30% limited disease. Twenty-five per cent (8) had rheumatoid arthritis, and 13% (4) had SLE (See Table 2). All 32 CTD-ILD patients had serology testing; 25 (78.1%) had a positive autoantibody (Anti-nuclear antibody, Rheumatoid factor/ Anti-CCP or Anti-SCL 70). Of the ten patients with systemic sclerosis associated ILD, only 3 had positive Anti-SCL 70. All CTD-ILD patients were being followed up at the Groote Schuur Hospital rheumatology clinic, who made the final rheumatological diagnosis.

Table 2: Connective tissue disease, interstitial lung disease.

	No (%)
Systemic Sclerosis	10 (31.2%)
Diffuse	*7 (70%)*
Limited	*3 (30%)*
Rheumatoid Arthritis	8 (25%)
Systemic lupus erythematosus	4 (12.5%)
Other	4 (12.5%)
Mixed connective tissue disease	3 (9.4%)
Undifferentiated connective tissue disease	3 (9.4%)

Lung function was available in over 90% of the CTD-ILD patients; two patients could not perform adequate spirometry. Thirty-one percent (10) had mild impairment (>50% <80% predicted) in diffusing capacity for carbon monoxide (DLCO), 41% (13) had moderate impairment (50-30%), and 22% (7) severe (<30%).

Idiopathic interstitial lung disease (I-ILD)

Of the 103 patients seen over the six months, a total of 13 (12.6%) patients had I-ILD or IPF. A single new patient with an I-ILD was seen with 5 in follow-up compared to 5 new patients with IPF and only 2 in follow-up. Most of the I-ILD patients were diagnosed with NSIP, and a single patient with organising pneumonia (non-COVID related). None of the confirmed IPF patients were referred for surgical biopsy. A single case of NSIP was confirmed on surgical biopsy after consideration at the MDT and referral for biopsy.

Hypersensitivity pneumonitis

Six patients were confirmed to have hypersensitivity pneumonitis (HP): 2 of whom were new diagnoses in the six months period, and 66.7% had positive serology for avian exposure (pigeon and parrot).

Treatment

The majority (78%) of patients had received or were currently on treatment: corticosteroids (52,5%), methotrexate (27%), azathioprine (7.5%), and chloroquine (5%). All the 32 patients with CTD-ILD had received one or more forms of immunosuppressant therapy, and these included corticosteroids 53% (n=17), methotrexate 50% (n=16), mycophenolate mofetil (MMF) 31% (n=10),

cyclophosphamide 25% (n=8), chloroquine 13%, azathioprine 19%. Of the ten patients with systemic sclerosis, five (50%) were on corticosteroids, seven were on MMF, four were on methotrexate, and three had received cyclophosphamide previously.

IPF burden

The Groote Schuur Respiratory Clinic is the tertiary referral centre for all suspected cases of IPF for 49% of the population in the geographical region of Cape Town. The Cape Town Metropole has an estimated population of 4 602 248 [(11)], with 24,8% (376 648) of individuals in Cape Town covered by private medical funding [(12)]. A total of 11 new IPF patients were diagnosed from a population of roughly 2.25 million people.

Progressive pulmonary fibrosis

Thirteen (12.6%) patients met the current criteria for progressive pulmonary fibrosis (PPF), [(8)] (absolute decline of FCV ⩾5% within 12 months and worsening symptoms). HRCT criterion not used due to cost constraint. A further five patients had rates of decline that, if projected to 12 months, would meet the criteria at the 12-month period. All 18 patients had an FVC decline of ⩾100mls. Of the 13 identified with PPF, the range of absolute FVC decline was from 22%-5%, with a mean of 9.2%. (See Table 3).

Table 3: Progressive pulmonary fibrosis

Patient	Diagnosis	FVC (L)	FVC (L) % predicted	Follow-up FVC (L)	Follow-up FVC % predicted	Months between lung function	Change in FVC (%)	Estimated 12-month FVC (%) change	Absolute FVC drop (L)	Estimated 12-month absolute FVC drop (L)
1	CTD	2,77	78	1,97	56	7	-22	-37,7	-0,800	-1,371
2	CTD	2,52	75	1,99	59	4	-16	-48,0	-0,530	-1,590
3	SARCOID	2,01	66	1,61	53	6	-13	-26,0	-0,400	-0,800
4	SARCOID	2,92	94	2,50	83	9	-11	-14,7	-0,420	-0,560
5	CTD	2,93	118	2,70	110	9	-8	-10,7	-0,230	-0,307
6	CTD	2,05	86	1,87	78	8	-8	-12,0	-0,180	-0,270
7	SARCOID	2,59	51	2,24	44	5	-7	-16,8	-0,350	-0,840
8	CTD	2,59	101	2,39	94	13	-7	-6,5	-0,200	-0,185
9	I-ILD	3,01	105	2,84	99	7	-6	-10,3	-0,170	-0,291
10	SARCOID	1,12	51	1,00	45	9	-6	-8,0	-0,120	-0,160
11	CTD	3,04	96	2,91	90	11	-6	-6,5	-0,130	-0,142
12	SARCOID	2,76	92	2,58	87	5	-5	-12,0	-0,180	-0,432
13	SARCOID	2,06	72	1,89	67	9	-5	-6,7	-0,170	-0,227
14	SARCOID	1,19	60	1,08	56	7	-4	-6,9	-0,110	-0,189
15	CTD	0,87	36	0,77	32	7	-4	-6,9	-0,100	-0,171
16	SARCOID	1,57	48	1,46	44,5	4	-3,5	-10,5	-0,110	-0,330
17	IPF	1,40	48	1,30	45	5	-3	-7,2	-0,100	-0,240
18	SARCOID	1,88	67	1,76	64	7	-3	-5,1	-0,120	-0,206

FVC- forced vital capacity, L-litres, CTD-connective tissue disease, I-ILD- idiopathic interstitial lung disease, IPF- idiopathic pulmonary fibrosis. Presented are the absolute values of the lung functions with calculated change in FVC, FVC % predicted, to % decline per year. Selected are those with more than a 5% decline in one year

Discussion

Interstitial lung disease is not common and requires significant resources to diagnose and manage patients. Co-existing medical specialities will influence referral patterns of disease-specific ILDs, making accurate estimates of ILD prevalence challenging in resource-limited settings. In this context, however, due to the unique referral network for idiopathic interstitial lung diseases, an IPF incidence of 11 new cases per 2.25 million population is estimated. This is likely an underestimate but is the first attempt to quantify the burden in an African setting.

The burden of tuberculosis, HIV, and tobacco-related diseases [13] makes recognizing interstitial lung disease more challenging. Accurate estimates of connective tissue diseases and sarcoidosis in Africa are not available, making the estimates of CTD-ILD and pulmonary sarcoidosis complex as they rely on making the primary diagnosis first in addition to recognising the ILD. This notwithstanding, joint services between rheumatology and pulmonology are required in high- and low-income settings. The close working relationship between rheumatology and pulmonology in this centre, however, does offer the opportunity to co-manage and detect those with progressive respiratory disease early.

The burden of treatment is dependent on the underlying disease and its severity. Corticosteroids are inexpensive and generally freely available, but most conditions require the additional use of immunosuppressants such as methotrexate, azathioprine, and Mycophenolate Mofetil, particularly in patients with Sarcoidosis and Systemic Sclerosis. Seven patients with IPF would be eligible for an antifibrotic, and based on the estimates of progressive pulmonary fibrosis, an additional 13 to 18 could potentially be initiated on nintedanib. The very high cost of antifibrotics makes access only possible for IPF patients with private funding. Lack of easy access to follow-up CT scans also limits

the application of the current criteria for progressive pulmonary fibrosis, potentially missing progression in some patients.

The new criteria promoted by the ATS/ERS of progressive pulmonary fibrosis, with the indicated, to treat with the antifibrotic nintedanib, raises both diagnostic and therapeutic challenges in a resource-limited environment. Based on symptoms and lung function decline, we estimated that 18% (18) should be considered for antifibrotic (over and above the IPF) patients. The actual number depends on how the definition is interpreted, given that follow-up CT scanning of patients is logistically challenging. Interestingly, many patients fulfilling the progressive pulmonary fibrosis criteria were diagnosed with sarcoidosis. Sarcoidosis was the most common ILD in our centre, additionally placing a burden on bronchoscopy and histological services to make the diagnosis. It is estimated that only 30% of sarcoidosis is characterised by progressive fibrosis[(14)]; in our cohort, this was 44.4%. It is unclear why we are potentially seeing more with fibrosis, and further study is required to confirm this.

It furthermore raises the question of how to best identify those patients that need/are eligible for antifibrotics in routine follow-up. If they continued to progress at the same rate of decline) they would have exceeded the 5% FVC drop by 12 months but, at the time of review, had not. Would the delay in initiating when the predicted rate of decline would reach 5%/12 months affect patient outcomes is not known. The duration of review in patients with systemic sclerosis who had been initiated on MMF prior to initiating antifibrotic therapy also is not known, and early initiation based on the projected rate of decline may prevent lung function loss.

These data provide the first estimate of the IPF burden on the African continent. There are potentially many inaccuracies in the individual estimates at a population level, and they probably represent an underestimate given the requirement to suspect the diagnosis first. It is well known that specific work exposures, such as mining, woodwork, and cooking on wood, form a clear risk factor for developing ILDs. Socioeconomic disparities may not only be associated with a higher likelihood of work exposure and poor housing situations, but also with not having access to medical care. The prevalence of sarcoidosis and connective tissue disease is not evaluable from these data as there is significant referral bias for patients directly from the rheumatology clinics and the multisystemic nature of sarcoid and dedicated organs-specific clinics within the hospital.

These data are limited due to the single-centre nature of this review and the natural limitations of referral and follow-up in a resource-limited setting. The data, however, provide one of the largest cohorts of patients with ILD in Africa and provide some insights into the requirement for radiological and diagnostic (bronchoscopy/histology/serology) services to be able to diagnose ILD in Africa.

Conclusion

Interstitial lung diseases require resources for their diagnosis and management. The need for immunosuppressive and anti-fibrotic therapy depends on the nature of referrals and the ability to follow up and review these patients. The true prevalence and long-term outcomes remain to be defined.

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List of tables

Table 4: Characteristics of patients seen in the ILD clinic over a 6-month period

	Total n=103	OLD n=75(72.8%)	NEW n=28 (27.2%)	
Age (median) IQR	54 (44-63)	55(45-62)	52 (41-62)	
male n (%)	26 (25.2%)	14 (18.7%)	12 (42.9%)	
Female n (%)	77 (74.8)	61 (81.3%) *	16 (57.1%) *	*P=0.012
Former/current smoking	44 (42.7%)	30 (42.9%)	14 (50%)	
HIV positive	6 (5.8%)	3 (4.3%)	3 (10.7%)	
DIAGNOSIS				
Sarcoidosis	51 (49.5%)	43 (57.3%)	8 (28.6%)	
CTD-ILD	32 (31.1%)	20 (26.7%)	12 (42.9%)	
IPF	7 (6.8%)	2 (2.7%)	5 (17.9%)	
I-ILD	6 (5.8%)	5 (6.7%)	1 (3.6%)	
HP	6 (5.8%)	4 (5.3%)	2 (7.1%)	
HIV- ILD	1 (1%)	1 (1.3%)	0	

IQR-interquartile range, n- number, HIV- Human immunodeficiency virus, CTD-ILD- connective tissue associated interstitial lung disease, IPF- idiopathic pulmonary fibrosis, I-ILD- idiopathic interstitial lung disease, HP- hypersensitivity pneumonitis, HIV-ILD- human immunodeficiency virus interstitial lung disease.

Table2: Connective tissue disease, interstitial lung disease.

	No (%)
Systemic Sclerosis	10 (31.2%)
Diffuse	*7 (70%)*
Limited	*3 (30%)*
Rheumatoid Arthritis	8 (25%)
Systemic lupus erythematosus	4 (12.5%)
Other	4 (12.5%)
Mixed connective tissue disease	3 (9.4%)
Undifferentiated connective tissue disease	3 (9.4%)

Table 3: Progressive pulmonary fibrosis

Patient	Diagnosis	FVC (L)	FVC (L) % predicted	Follow-up FVC (L)	Follow-up FVC % predicted	Months between lung function	Change in FVC (%)	Estimated 12-month FVC (%) change	Absolute FVC drop (L)	Estimated 12-month absolute FVC drop (L)
1	CTD	2,77	78	1,97	56	7	-22	-37,7	-0,800	-1,371
2	CTD	2,52	75	1,99	59	4	-16	-48,0	-0,530	-1,590
3	SARCOID	2,01	66	1,61	53	6	-13	-26,0	-0,400	-0,800
4	SARCOID	2,92	94	2,50	83	9	-11	-14,7	-0,420	-0,560
5	CTD	2,93	118	2,70	110	9	-8	-10,7	-0,230	-0,307
6	CTD	2,05	86	1,87	78	8	-8	-12,0	-0,180	-0,270
7	SARCOID	2,59	51	2,24	44	5	-7	-16,8	-0,350	-0,840
8	CTD	2,59	101	2,39	94	13	-7	-6,5	-0,200	-0,185
9	I-ILD	3,01	105	2,84	99	7	-6	-10,3	-0,170	-0,291
10	SARCOID	1,12	51	1,00	45	9	-6	-8,0	-0,120	-0,160
11	CTD	3,04	96	2,91	90	11	-6	-6,5	-0,130	-0,142
12	SARCOID	2,76	92	2,58	87	5	-5	-12,0	-0,180	-0,432
13	SARCOID	2,06	72	1,89	67	9	-5	-6,7	-0,170	-0,227
14	SARCOID	1,19	60	1,08	56	7	-4	-6,9	-0,110	-0,189
15	CTD	0,87	36	0,77	32	7	-4	-6,9	-0,100	-0,171
16	SARCOID	1,57	48	1,46	44,5	4	-3,5	-10,5	-0,110	-0,330
17	IPF	1,40	48	1,30	45	5	-3	-7,2	-0,100	-0,240
18	SARCOID	1,88	67	1,76	64	7	-3	-5,1	-0,120	-0,206

FVC- forced vital capacity, L-litres, CTD-connective tissue disease, I-ILD- idiopathic interstitial lung disease, IPF- idiopathic pulmonary fibrosis

Appendices

Data Capture sheet

PATIENT DI-DENTIFIED CODE	1	2	3	4	5	6	7	8	9
NEW/fup									
SEX									
DOB									
AGE									
PRIMARY DIAGNOSIS									
Rheum Diagnosis									
DATE OF DIAGNOSIS									
CRITERIA HOW									
CT/ RAADIOLOGICAL DAIGNOSIS									
HAD A BIOPSY, DATE									
SYMPTOMS									
DURATION OF SYMPTOMS									
CO-MORBIDITIES									
HIV									
HTN									
DM									
SMOKING									
EXPOSURE									
TYPE OF EXPOSURE									
HSP TESTS									
SEROLOGY									
ANA POSITIVE									
RF< 14/ ANTI CCP									
Anti-SCL-70									
SACE									
OTHERS POSITIVE SEROLOGY									
WHATS BEEN DONE									
MEDICATIONS									
PREDNISONE									
MTX									
CYCLOPHOPHAMIDE									
AZA									
RITUX									
LEFLUNAMIDE									
MMF									
CQ									
SSZ									
comments									

Research Proposal

The characteristics of interstitial lung disease patients attending Groote Schuur HospitalRespiratory clinic

Gurveen Kaur Soin Student
number: SNXGUR001
Master of Medicine (Internal Medicine)

Supervisors:

Prof. Richard Van Zyl Smit

Prof Greg Calligaro

Table of contents

1. Introduction/Context

Idiopathic pulmonary fibrosis (IPF) is a progressive and ultimately fatal disease characterised by worsening dyspnoea and progressive loss of lung function. The estimated incidence of IPF among people aged 18–64 years in the northern hemisphere was 6.1 new cases per 100 000 person–years, primarily affecting older individuals, with amedian age at diagnosis of 66 years. The clinical course of IPF is variable but generally progressive. Some patients experience periods of stability followed by acute deteriorations in lung function known as acute exacerbations. IPF is ultimately fatal, withhistorical data suggesting a median survival time of 3–5 years from diagnosis; however, post-diagnosis survival time is likely to increase as patients are diagnosed earlier in the course of the disease. (1)

Our understanding of the pathogenesis of IPF has evolved from that of a predominantly inflammatory disease to one driven by a complex interplay of repeated epithelial cell damage and aberrant wound healing, involving fibroblast recruitment, proliferation anddifferentiation, and culminating in excess deposition of extracellular matrix. (1)

Connective tissue disease (CTD) is one of the common systemic diseases associated withILD. The connective tissue diseases (CTDs) demonstrating features of interstitial lung disease (ILD) include systemic lupus erythematous (SLE), rheumatoid arthritis (RA), progressive systemic sclerosis (PSS), dermatomyositis (DM) and polymyositis (PM), ankylosing spondylitis (AS), Sjogren's syndrome (SS), and mixed connective tissue disease(MCTD).Especially in patients with RA, interstitial lung abnormality(ILA) is reported to occur in 20-60% which is associated with a spectrum of functional and physiological decrement. (2)

Connective tissue disease-related interstitial lung diseases (CTD-ILDs) are diverse and include nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organising pneumonia (OP), apical fibrosis, diffuse alveolar damage (DAD), and lymphoidinterstitial pneumonia (LIP). (2)

The treatment options are dependent upon the underlying CTD. Hence, the guidelinesemphasise the classification of ILD based on aetiologies and uniformly recommended search for evidence of CTD in newly diagnosed ILDs. However, due to complexities in diagnosis and treatment of CTD

itself and lack of evidence, current guidelines do not clearly provide strategies for evaluation and management of CTD-ILD despite its significance. (2)

The identification of subclinical lung abnormalities can be appropriate in the managementof the disease and CT appears to be the gold standard for the evaluation of lung parenchyma. Thin-section CT (TSCT) help detect and characterise various kinds of lung abnormality related to interstitial lung diseases (ILDs) in patients with CTD. (2)

With the recent development of two effective treatments for patients with idiopathic pulmonary fibrosis, an accurate diagnosis is crucial. A major breakthrough in treatmentcame when, after decades of clinical trials which failed to identify an efficacious

treatment regimen, two therapies were successful in Phase-III trials. The advent of thesetherapies, Nintedanib and pirfenidone, meant that for the first time IPF patients had twotreatment options that could reduce disease progression.(2, 3)

Nintedanib is a tyrosine kinase inhibitor that has been shown to affect several crucial fibrotic mediators, including the platelet-derived growth factor receptor, fibroblast growth factor receptor, vascular endothelial growth factor receptor, and the kinase Src. In-vitro experiments have shown that Nintedanib inhibits human fibroblast proliferation,myofibroblast differentiation, and collagen release. Moreover, Nintedanib limits the severity of fibrosis in animal models of SSc and has the potential to prevent the development of PAH.(4)

Pirfenidone is also approved for the treatment of idiopathic pulmonary fibrosis. It has considerable anti-inflammatory and anti-fibrotic properties, and although its mechanism of action has not been fully elucidated, it is thought to involve the inhibition of transforming growth factor-β and inflammatory cytokines such as tumour necrosis factor-α. In the phase 2 LOTUSS trial, pirfenidone at a dose of up to 2403 mg/day for 16 weeks was found to be safe in patients with SSc-ILD. However, 32 (60%) of the 56 patients in thetreatment arm required a dose interruption or reduction, most commonly because of gastrointestinal side effects. (4)

According to a Taiwanese National Health Insurance Research database (between years 1993–2013) [4], the incidence of ILD related to CTD was greatest among patients with PSS(1364 per 105 years), followed by DM (1011 per 105 years), PM (831 per 105 years), SS (196 per 105 years), RA (109 per 105 years) and SLE (109 per 105 years). In this study, multivariable analyses showed that the risk of ILD is increased among patients with PSS(hazard ratio [HR], 172.63), DM (HR, 119.61), PM (HR, 84.89), SLE (HR, 32.18), SS (HR, 17.54), or RA (HR, 8.29).

The E16 Respiratory Clinic at Groote Schuur Hospital runs a dedicated interstitial lung disease clinic and is in the process of establishing an ILD registry. The clinic evaluates over15 new patients with suspected ILD and follows up over 50 ILD patients a month. The Clinic is an ideal location to evaluate the spectrum, burden and need for therapeutic interventions for ILD. Globally, advances in therapeutic options have progressed followinglarge-scale studies (almost exclusively conducted outside of Africa). Limited options exist for treatment in South Africa, in part due to cost and delayed registration of medications,but also due to poor documentation of the prevalence and distribution of patients with an ILD who are potentially eligible for therapy. The prevalence

of IPF, connective tissue disease associated ILD or sarcoid is completely unknown due to lack of disease specific registries and specialist centres looking after these patients.

This data will provide the most comprehensive and up to date perspective on the spectrum and burden of ILD within South Africa as well as inform on the burden ofvarious ILD's within the clinical service to aid in resource allocation
The data will furthermore provide a basis for prevalence calculation of IPF/ connective tissue-ILD/ rapidly progressive ILD that require intensive follow up, and intervention priorto potential lung transplantation.

2. Study Objectives

2.1 Primary Objectives

- To retrospectively evaluate all patients with ILD attending the Specialist ILD clinicat Groote Schuur Hospital, thereby identifying, the burden and severity of ILD within the Hospital referral area.

2.2 Secondary Objectives

- To determine the potential need for additional therapy (cyclophosphamide, MMF, Pirfenidone, nintedanib) and future need for lung transplantation in patients with progressive disease.

3. Methods

3.1. Study design

Data will be collected from the current E16 respiratory clinic registry. Patients will be identified based on their diagnosis. (The ILD specific registry is currently in development and comprehensive data is not entered onto the E16 Registry). The diagnostic data will thus be extracted into an ILD specific database. Demographics, medical history, diagnosis,and diagnostic criteria along with treatment will be captured from the E16 Respiratory and medical records. Lung function trajectory will be calculated to identify those who have serial spirometry measures fulfilling criteria for progressive disease.

3.2. Sample

The study population includes all new and follow up patients attending the ILD clinic overa 6-month period. Approximately 15 new patients per month, and 50 old patients seen every 4-6 months. Targeting 200 patients, sample size.

3.2.1. Inclusion criteria

All individuals identified as having an ILD in the E16 clinic will be eligible for inclusion.

3.2.2. Exclusion criteria

No patients will be excluded if identified with an interstitial lung disease.
However, those that have not yet had serial spirometry over a 6-month period will not beincluded in the evaluation of progressive disease, in the lung function cohort.

3.3. Materials and Methods

ILD patients will be identified from the E16 Database, and their DATA entered into an ILDspecific spread sheet. Additional information on Laboratory testing, medical history, radiological findings, and histology will be extracted from the medical records. No study specific testing will be conducted as all data will have been established as part of routineclinical care.

3.4. Data collection

The following data will be identified and recorded, into an ILD specific database:

- Patient demographics, height age and weight (for lung function reference values)
- Patient medical history including exposures to tobacco smoke, occupational and environmental toxins.
- Primary interstitial lung disease diagnosis and diagnostic criteria and preceding or subsequent therapies.
- Serological markers for rheumatological or exposure hypersensitivity associateddisease.
- Lung function at presentation and progression over time if available.
- Severity of Lung function and duration of symptoms to diagnosis will be captured.

3.6. Bias

This study will only include patients referred to Groote Schuur Hospital with a suspectedInterstitial lung disease and will thus underestimate the incidence and prevalence of ILDin the community.

4. Data analysis and statistics

Summary statistics will be reported using frequencies and percentages for categorical responses and means with standard deviations for continuous measurement. If the needarises for inferential statistics, this will typically involve cross tabulations, ANOVA or correlation analyses depending on the types of variables compared.

5. Ethics

All patients currently within in E16 are being retrospectively entered into the HREC approved E16 Registry (HREC R007/2021) following informed consent. HREC approval willbe obtained for this study to capture additional data contained in the medical records noton the registry approval specific to ILD as outlined above, and to analyse the data collected. All patient data will be kept confidential and de-identified for analytic purposes.The data used for this study will be retrospective, and additional consent will not be obtained from the patients as only patient file review will be undertaken after their initialregistry consent. Institutional approval will be sought.

The research project will be held accountable at all times before, during and subsequentlyafter completion of the study by the following departments/committees of the University of the Cape Town respectively:

1. Department of Internal Medicine
2. Division of Clinical Pulmonology, Department of Medicine, Groote Schuur Hospital
3. Faculty of Health Sciences Human Research Ethics committee

Patient confidentiality will be maintained throughout with patient records allocated a unique identifier that is only known to the primary investigator. The records of the patients will be reviewed at their storage place at Groote Schuur Hospital and will not beremoved.

5.1. Data safety

Data will be anonymised by allocating a random number to each patient. The key to this code will only be available to me and my supervisors. Anonymised data will be entered into an Excel document which is suitably password-protected and stored on a laptop andnot on any public domain. The data will be backed up from time to time. Suitably password-protected backup data will be stored on my co-supervisors UCT computers.

Access to all confidential study-related data will remain strictly limited to my co-supervisors and me.

6. Timings

Month of the Year	Feb 2022	March	April	May	June-Aug	Sep	Oct	Nov	Dec 2022
Literature search									
Reading literature									
Summarising literature									
Preparing Protocol (divisional presentation)									
Protocol Assessment									
Ethics application									
Collecting data									
Data analysis									
Writing up thesis									
Submit: marking									
Writing up paper									

7. Budget

No funding has been granted for this study.

Data capture and entering (±200 hundred patients ~ 15 hours)	R 0.00
Stationery, filing, printer cartridges, paper etc.	R 2 500,00
Computing database support, analytical/statistical support & statistical software etc.	R 7 500,00
Publication costs (e.g.ERJ, SAMJ)	R 10 000,00
TOTAL	**R 20,000**

All expenses will be borne by the researchers.
There are no anticipated problems to my research study, including during the process of collecting and summating data and records.

8. Implications of Research

This data will provide the most comprehensive and up to date perspective on theincidence of newly diagnosed ILD in addition to the spectrum and burden of ILD within South Africa.

The data will inform on the burden of various ILDs within the clinical service to aid in resource allocation.

These data will provide insights into referral delays and possible areas forintervention to ensure earlier diagnosis.

This group of patients receive a variety of medications like methotrexate, rituximaband

corticosteroids which result in high cost and considerable morbidity. The evaluation of the burden and need for intensive therapy and potential lung transplantation will enable better resource allocation and interventions.

9. References

1. Raghu G. Idiopathic pulmonary fibrosis: lessons from clinical trials over thepast 25 years. Eur Respir J. 2017;50(4).
2. Yoo H, Hino T, Han J, Franks TJ, Im Y, Hatabu H, et al. Connective tissue disease-related interstitial lung disease (CTD-ILD) and interstitial lung abnormality(ILA): Evolving concept of CT findings, pathology and management. Eur J Radiol Open. 2021; 8:100311.
3. Martinez FJ, Chisholm A, Collard HR, Flaherty KR, Myers J, Raghu G, et al. Thediagnosis of idiopathic pulmonary fibrosis: current and future approaches. The Lancet Respiratory Medicine. 2017;5(1):61-71.
4. Perelas A, Silver RM, Arrossi AV, Highland KB. Systemic sclerosis-associatedinterstitial lung disease. The Lancet Respiratory Medicine. 2020;8(3):304-20.

Ethics Approval Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

13 June 2022

HREC REF: 337/2022

Prof R van Zyl-Smit
Division of Pulmonology
E-16 Respiratory Clinic NGSH
Email: richard.vanzylsmit@uct.ac.za
Student: soin.gurveen@gmail.com

Dear Prof van Zyl-Smit

PROJECT TITLE: THE CHARACTERISTICS OF INTERSTITIAL LUNG DISEASE PATIENTS ATTENDING GROOTE SCHUUR HOSPITAL RESPIRATORY CLINIC-SUB-STUDY LINKED TO R007/2021-
(MMED CANDIDATE-DR GURVEEN SOIN)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19. Please refer to guidance letter dated 02 February 2022 on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Approval is granted for one year until the 30 June 2023.

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Gurveen Soin will also be involved in this study.

Please quote the HREC REF 337/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Hospital Approval Letters

Western Cape Government

GROOTE SCHUUR HOSPITAL

Enquiries: Dr Bernadette Eick
e-mail: GSHReserach.Request@westerncape.gov.za

Professor Richard van Zyl-Smit
UNIVERSITY OF CAPE TOWN

E-mail: richard.vanzylsmit@uct.ac.za

Dear Professor R van Zyl-Smit

RESEARCH PROJECT: The Characteristics of Interstitial Lung Disease Patients Attending Groote Schuur Hospital Respiratory Clinic-Sub-Study Linked to R007/2021

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 June 2023**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) Confidentiality must always be maintained.
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) If the researcher is not GSH staff member, a supernumerary contract is required before commencement of the research.
m) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
n) Kindly submit a copy of the publication or report to this office on completion of the research.
o) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.
p) Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.

I would like to wish you every success with the project.

Yours sincerely

pp
DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 05 August 2022
C.C. Mr. L. Naidoo, Mr. A. Mohamed, Professor N. Ntusi, Dr. N. Khumalo

The African Journal of Thoracic and Critical Care Medicine

General formatting guidelines

General article format/layout

Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

General:

- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

Each paper should have a clear rationale, logical study aims, sufficiently detailed methods, and well supported conclusions. It is advisable to clearly state the hypothesis or aim of the work in the introduction section. The discussion and abstract conclusions should be clearly stated and should be backed up by the data presented in the manuscript. The study outcomes or metrics used to inform the conclusions should be clearly stated and outlined.

Study synopsis: All studies submitted with an abstract should, in addition, have a study synopsis sub-section, with a maximum word count including sub-headings of 120 words.

The purpose is to crystalise the findings of the study and thus improve understanding and retention. The study synopsis should have 2 sub-headings: ‘What the study adds’ and ‘Implications of the findings'.

The first sub-heading should tersely outline what new knowledge or additional information the study brings to the field. The second sub-heading should provide the implication of the findings to researchers, clinicians, policy makers, and other stakeholders and could allude to the broader implications of the work.

The study synopsis should not repeat verbatim what is already in the abstract but provides an additional opportunity to emphasise key findings of the study and the implications of the work.

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this requirement are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make ‘new rows’:

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

Figures/illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All graphs, diagrams, charts, etc. must be in PDF form. Scans should be in jpeg.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

IMAGES/PHOTOGRAPHS

Acceptable file types

The image file should be submitted as a high resolution jpeg or tiff Important: Images embedded in a Word document are not acceptable.

Resolution

Images must have a minimum resolution of 300 dpi (dots per inch).

Screenshots and images from the internet

Screenshots and images from the internet are usually only 72 dpi – this is the average resolution that computer screens use – therefore images downloaded from the internet are almost always too small to use for print even though they might look fine on screen.

Author Quick check

If the actual size of the file is:

• less than 500 kb - not great for print

• 500kb - 1000 kb (1 mb) - better

• greater than 1000 kb (i mb) - ideal

The image sent has to be the original i.e. the very first image created.

If it was taken on a camera/cell phone, then that image has to be sent directly from the device's image gallery.

Not a screenshot of the image or via a secondary app (Word, Whatsapp) or uploaded to a website.

Cameras (cell phones) should be set to the highest possible image size.

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting..*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
    - Alongside 'url =' copy the URL between { }.
    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

Genetic nomenclature

AJTCCM is a medical journal covering all aspects of respiratory health, therefore for articles involving genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.