The Diagnosis and Management Landscape of Idiopathic Pulmonary Fibrosis: An Australian experience

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Statement of Authorship and Originality

The work of this thesis was carried out in the Department of Respiratory and Sleep Medicine at Royal Prince Alfred Hospital, under the primary supervision of Professor Tamera Corte and co-supervision of Professor Ian Glaspole (Department of Respiratory and Sleep Medicine, Alfred Hospital, Melbourne) and Professor Brian Oliver (Respiratory Cellular and Molecular Biology Research Group, Woolcock Institute of Medical Research, Sydney). This statement is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for consideration for any other degree. I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and all relevant sources have been acknowledged.

Chapter Two: "*Essential Features of an Interstitial Lung Disease Multidisciplinary Meeting: An International Delphi Survey*" has been published in Annals of American Thoracic Society. I co-designed and conducted the study, analysed data and was the primary author of all manuscript drafts.

Chapter Three: Part B "*Blood Monocyte Counts as a Potential Prognostic Marker for IPF: Analysis from the Australian IPF registry*" has been published in European Respiratory Journal. I conducted the study, analysed data and was the primary author for manuscript drafts.

Chapter Five: "*Diagnosis and Antifibrotic Choice for Idiopathic Pulmonary Fibrosis: Analysis from the Australian Idiopathic Pulmonary Fibrosis Registry*" has been submitted for review in Respirology. I co-designed and conducted the study, analysed data and was the primary author for the manuscript drafts.

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Abbreviations

AIP	Acute interstitial pneumonia
ANA	Antinuclear antibody
ANCA	Antineutrophil cytoplasmic antibody
BAL	Brochoalveolar lavage
BMI	Body mass index
CCP	Cyclic citrinullated peptide
CFA	Chronic fibrosing alveolitis
CHP	Chronic hypersensitivity pneumonitis
CI	Confidence interval
COP	Cryptogenic organising pneumonia
CPI	Composite physiological index
CRP	Clinical, radiological and physiological (score)
CTD	Connective tissue disease
DAD	Diffuse alveolar damage
DLCO	Diffusing capacity of the lung for carbon monoxide
DM	Dermatomyositis
DMARD	Disease modifying
dsDNA	Double strandeded deoxyribonucleic acid
ECM	Extracellular matrix
ENA	Extractable nuclear antigen
ER	Endoplasmic reticulum
FEV1	Forced expiratory volume in one second
FPF	Familial pulmonary fibrosis

FVC	Forced vital capacity
GORD	Gastroesophageal reflux disease
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
HAD	Hospital Anxiety Depression (score)
HP	Hypersensitivity pneumonitis
HR	Hazard ratio
HRQOL	Health-related quality of life
HRCT	High resolution computed tomography
LIP	Lymphoid interstitial pneumonia
MCTD	Mixed connective tissue disease
MD	Mean difference
MDM	Multidisciplinary meeting
MMP	Matrix metalloproteinase
mMRC	Modified Medical Reseach Council
NAC	N-acetylcysteine
NSIP	Non-specific interstitial pneumonia
OP	Organising pneumonia
OSA	Obstructive sleep apnoea
PF-ILD	Progressing fibrotic interstitial lung disease
PFT	Pulmonary function test
PH	Pulmonary hypertension
PJP	Pneumocystic jiroveci pneumonia
PM	Polymyositis

PPF	Progressive pulmonary fibrosis
PROM	Patient reported outcome measure
RA	Rheumatoid arthritis
RB-ILD	Respiratory bronchiolitis interstitial lung disease
RR	Risk ratio
SD	Standard deviation
SDB	Sleep disordered breathing
SFTP	Surfactant protein
SGRQ	St George's Respiratory Questionnaire
SLB	Surgical lung biopsy
SLE	Systemic lupus erythromatous
SSc	Systemic sclerosis
TERT	Telomerase reverse transcriptase
TERC	Telomerase RNA component
TGF-b	Transforming growth factor beta
TBLC	Transbronchial lung cryobiopsy
TLC	Total lung capacity
TNF-a	Tumour necrosis factor alpha
UCSD SOBQ	University of California San Diego Shortness of Breath Questionnaire
VATS	Video assisted thoracic society
6MWT	Six-minute walk test

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Abstract

Idiopathic pulmonary fibrosis (IPF) is the most common form of the fibrosing idiopathic interstitial pneumonias, in which its aetiology remains unknown. The condition is characterised by incessant and progressive lung function decline, often leading to worsening symptoms of dyspnoea, impaired physical exercise capacity and poorer quality of life. The overall prognosis of IPF is poor with historical data suggesting a median survival of merely 3-5 years. While the disease remains incurable, the advent of novel antifibrotic therapies of pirfenidone and nintedanib that both reduce disease progression, herald a new dawn in the management of IPF. However, akin to its unknown aetiology, many questions regarding the diagnostic process and the true impact of antifibrotics on the management of IPF, remains unanswered

The main objective of this thesis is to further investigate components in the diagnostic process of IPF and to explore the effect of antifibrotics on IPF management, with a focus on the Australian experience. In Chapter Two, we sought consensus through a Delphi methodology, on the essential features of an interstitial lung disease multidisciplinary meeting (ILD MDM) which is currently considered the 'gold standard' for the diagnosis of ILD. Our study identified essential and desirable features that may be first steps towards the standardisation of the ILD MDM.

Chapter Three is divided into two parts exploring the use of potential diagnostic and prognostic biomarkers in IPF. In Part A, we investigated the effect of nintedanib and pirfenidone on extracellular matrix components in IPF. We showed that tenascin-C and periostin to be affected by nintedanib, shedding some light on a possible pathogenic pathway and therapeutic target, while negative findings on pirfenidone reinforces the need for further studies. Our study in Part B investigated the role of monocyte count as a prognostic marker for IPF. Using data from the

Australian IPF Registry, we showed that monocyte count remained on multivariate analysis to be associated with poorer survival. Our findings added further validity to similar findings from other international studies and suggests that more studies are needed to understand the true role of monocytosis as a prognostic biomarker for IPF.

In Chapter Four, we conducted a meta-analysis and systematic review of antifibrotics for the treatment of both IPF and other ILD with a progressive pulmonary fibrosis (PPF) phenotype. The study's aim was to review and summarise the efficacy and safety profiles of antifibrotic therapies. We showed that nintedanib and pirfenidone reduced lung function decline and were safe to use for the treatment of IPF and PPF. However, effects of antifibrotics on patient reported outcome and progression-free survival remained uncertain due to the lack of standardisation of study outcomes.

Chapter Five and Six describe the Australian experience on the use of antifibrotics for the treatment of IPF. Using data from the Australian IPF Registry, we studied the diagnostic process of IPF, the prescription practices of antifibrotics and the management strategies used for the treatment of IPF in Australia. We also described the experiences and sentiments of both patients and physicians using antifibrotic therapies. While satisfaction levels with antifibrotics and overall care received remained high in the first year, areas such as improvement in diagnostic delays, patient education and non-pharmacological and allied health service referrals, needed improvement.

Overall, the thesis highlighted the need for further standardisation of the ILD MDM and the need for further studies to identify both new diagnostic and prognostic biomarkers in the diagnosis process of IPF. We studied the efficacy and safety of nintedanib and pirfenidone as

novel antifibrotic therapies for the treatment of IPF and additionally, PPF. We drew on the Australian patients and physicians' experiences to describe the use of antifibrotic therapies in IPF while exploring how these new therapeutic options fit in the current management landscape of IPF.

Chapter One: Introduction

1.1 Interstitial Lung Disease

1.1.1 Classification

Interstitial lung diseases (ILD) are a group of diffuse parenchymal lung disease (DPLD), resulting in varying degrees of damage to the lung parenchyma. They represent a heterogenous group of chronic lung disease with a wide array of aetiological factors, variable clinical presentation and prognosis. Despite differences among various disease entities, they share common radiological, pathological and physiological features, allowing them to be easily distinguishable from other forms of diffuse lung disease. However, terminologies historically lacked standardisation amongst different countries with the diagnosis often needing further revision as more potential environmental associations were described [1, 2, 3]. Furthermore, being mostly rare conditions, the collective global experience in the diagnosis and management of such conditions, were limited.

Technological advances such as the use of high resolution computerised tomography (HRCT) and the availability of video-assisted thoracoscopic lung biopsy not only improved knowledge and understanding of aetiologies and behaviours of ILD, but also enabled the development of a new classification system, one utilising the trinity of clinical, radiological and pathological findings [4, 5, 6, 7]. Hence, a major revision of the classification of ILD was proposed through an international multidisciplinary consensus guideline in 2002 [8]. Such concerted effort to establish a global uniform set of criteria for the definition of ILDs, would lay the groundwork for future research in the field, with a further update published in 2013 [9]. The major subtypes of ILD include: (1) ILD of known association, (2) Idiopathic interstitial pneumonias (IIP), (3) granulomatous ILD and (4) other/miscellaneous ILD (Figure 1.1)

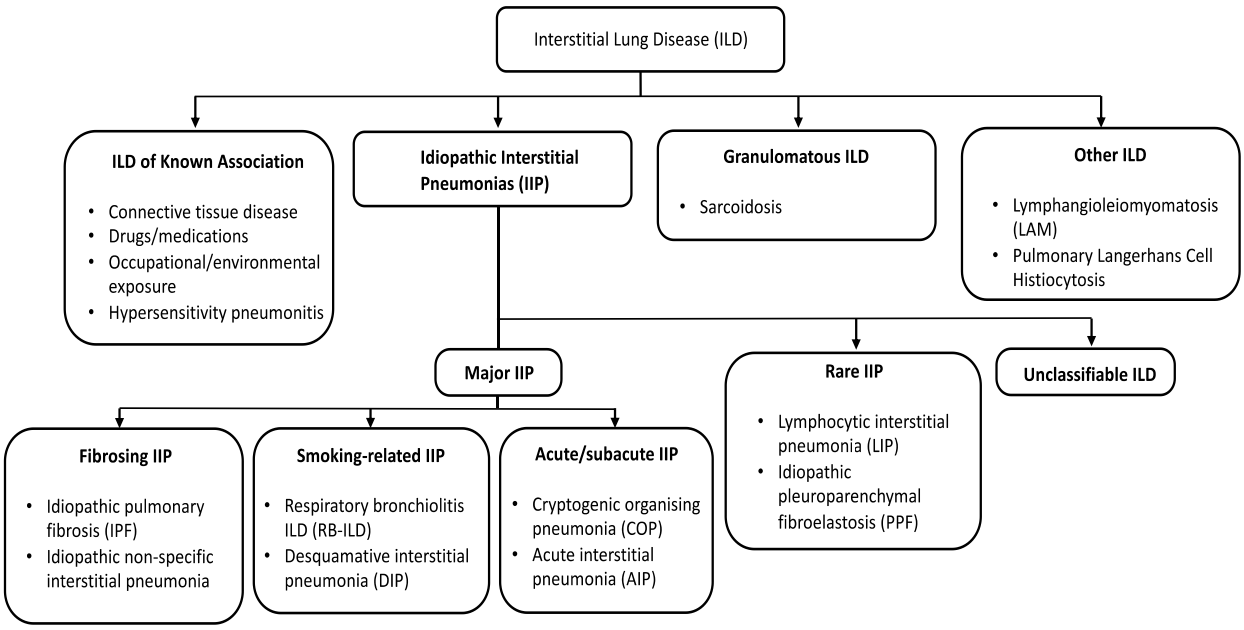

Figure 1.1 Classification of Interstitial Lung Diseases. Adapted from [8].

1.1.2 Interstitial Lung Disease of Known Association

Previously known as 'collagen vascular disease', connective tissue diseases (CTD) encompass a broad range of systemic auto-immune conditions which are often associated with organ damage. ILDs are commonly seen in CTD, often increasing morbidity and remains the leading cause of mortality in such patients [10]. While all patients with CTDs are at risk of developing an ILD, be it the first or a forme fruste of the disease, some such as rheumatoid arthritis (RA), Sjogren's syndrome, systemic sclerosis (Ssc), mixed connective tissue disease (MCTD) and poly-/dermatomyositis (PM/DM) are more commonly associated with ILD as compared to the likes of systemic lupus erythematous (SLE) [11].

Apart from CTD, other aetiologies known to cause ILD include drugs or medications. As the field of medicine continues to advance with ever increasing numbers of newer therapeutic

agents, so does the list of culprit drugs associated with lung toxicity (Table 1.1). The most common drugs known to cause ILD are disease-modifying antirheumatic drugs (DMARDs), antiarrhythmics, antimicrobial and more recently, the exponential increased use of antineoplastic and biological agents including monoclonal antibodies and tyrosine kinase inhibitors [12].

Environmental exposure in the form of both organic and inorganic dusts or antigens, have been showed to directly cause ILDs. Hypersensitivity pneumonitis (HP) is driven by a dysregulated inflammatory response to inhaled antigens. The most common recognised antigens include bird dander/droppings, mould, farming and contaminated metal working fluids (Table 1.2) [13, 14]. Though similarly caused by inhalation, occupational pneumoconiosis such as coal dust and more recently, silica exposure from the manufacture of artificial stone, continue to remain a global issue [15].

Table 1.1: Main drugs associated with radiological patterns of ILD.

Radiological pattern of ILD	Medications
Acute or subacute ILD	Antiarrythmic (amiodarone) Chemotherapeutics ICIs TKIs (crizotinib, EGFR inhibitors, erlotinib, gefitinib) Rituximab Methotrexate TNF – alpha antagonists
Fibrotic non-specific interstitial pneumonia	Chemotherapeutics (cyclophosphamide, carmustine, bleomycin, gemcitabine)

	Antiarrythmic (amiodarone) Antibiotics (nitrofurantoin)
Eosinophilic pneumonia	Antibiotics Anticonvulsants Antidepressants NSAIDs Mesalazine
Organising pneumonia	Antiarrythmic (amiodarone) ICIs Rituximab Sirolimus Radiation therapy
Granulomatosis	ICIs Daclizumab
Pleuroparenchymal fibroelastosis	Cyclophosphamide Alkylating agents

Adapted from [16]. ICI: immune checkpoint inhibitors, TKI: tyrosine kinase inhibitors, EGFR: Epithelial growth factor receptor, TNF: tumour necrosis factor, NSAID: nonsteroidal anti-inflammatory drug

Table 1.2. Occupational and environmental exposure related ILD

Microbial particulate matter
Water damage/flooding Mouldy hay/silage Standing water Visible or smelly mould Humidifiers/ air conditioners Hot tubs/pools/spas Mouldy wood Organic matter (compost/manure) Musical instruments (trombone, saxophone, bagpipes)
Plant/animal proteins
Bird feathers/dropping/dander Down/feather products Farming Vegetable production (incl. mushrooms, onions, potatoes) Food production - Salami washers - Cheese washers - Wheat - Sugarcane - Malt Wood dust
Chemical agents
Isocyanates (spray paint, adhesives, polyurethane foam)

Metalworking fluids Vapours, gases, fumes Food flavouring
Inorganic dust
Silica Asbestos Coal workers Hard metals Beryllium Aluminium Talc powder Siderosis (arc welder's lung) Nylon-flock Indium

Adapted from [15, 17, 18].

1.1.3 Granulomatous Interstitial Lung Disease

Granulomas are compact, centrally organised collection of macrophages and epithelioid cells, which are surrounded by lymphocytes. In chronic cytokine-stimulated inflammation, such macrophages undergo further differentiation leading to phagocytic functional loss, formation of multinucleated giant cells, increased fibroblastic activity and eventual organ architectural distortion and dysfunction [19].

The primary condition within this ILD category is sarcoidosis. The pathogenesis of sarcoidosis is proposed to be due to a dysregulated response to unknown environmental antigens in genetically-susceptible individuals, leading to a granulomatous inflammatory process as described above. The clinical presentation of sarcoidosis is highly variable with the potential of multiorgan involvement, including the lungs, heart, skin, eyes, kidneys and the nervous system [20].

1.1.4 Idiopathic Interstitial Pneumonias

Idiopathic interstitial pneumonias (IIP) define a group of parenchymal lung disease affecting the interstitium of the lung and are not known to have any clear, identifiable cause to date. This group of ILD underwent a major reclassification based on international consensus. Using historical sets of histological patterns, the new classification recategorized IIP into clinic-radiologic-pathologic diagnoses [8] and was further updated and refined in 2013 [9]. The revised classification is divided into major, rare and unclassifiable IIPs. Some of the conditions include idiopathic pulmonary fibrosis (IPF), idiopathic non-specific interstitial pneumonia (NSIP), cryptogenic organising pneumonia (COP), idiopathic lymphoid interstitial pneumonia (LIP). Figure 1.1 depicts the most updated classification, and a summary of radiological features and differential diagnoses is shown in Table 1.3.

Table 1.3. Common radiological features and differential diagnoses of IIP and their corresponding histological pattern.

Clinical diagnosis	Histological pattern	Radiological features	Differential diagnoses
IPF	UIP	Basal and subpleural distribution. Reticulation, honeycombing, traction bronchiectasis, architectural distortion, focal/limited ground glass opacities	Asbestosis, CTD-ILD, chronic HP, sarcoidosis
NSIP	NSIP	Peripheral distribution. Ground glass opacities and irregular lines	HP
COP	OP	Subpleural/peribronchial distribution. Patchy consolidation and/or nodules	Infection, vasculitis, sarcoidosis, alveolar carcinoma, lymphoma, eosinophil pneumonia
AIP	DAD	Diffuse distribution. Ground glass opacities often with lobular sparing, consolidation and traction bronchiectasis (later)	Pulmonary oedema, pneumonia
DIP	DIP	Peripheral and lower zone distribution. Ground glass attenuation and reticular lines.	RB-ILD, HP, sarcoidosis, PJP infection
RB-ILD	RB	Diffuse distribution.	DIP, NSIP, HP

		Bronchial wall thickening, centrilobular nodules and ground glass opacities.	
LIP	LIP	Diffuse distribution. Centrilobular nodules, ground glass opacities, septal and bronchovascular thickening, thin-walled cysts	Sarcoidosis, lymphangitic carcinoma, Langerhans' cell histiocytosis

Adapted from [9]. IPF: idiopathic pulmonary fibrosis, UIP: usual interstitial pneumonia, CTD-ILD: connective tissue disease-associated interstitial lung disease, HP: hypersensitivity pnuemonitis, NSIP: nonspecific interstitial pneumonia, COP: cryptogenic organising pneumonia, AIP: acute interstitial pneumonia, DAD: diffuse alveolar damage, DIP: desquamative interstitial pneumonia, RB-ILD: respiratory bronchiolitis-ILD, PJP: pneumocystis jiroveci pneumonia, LIP: lymphoid interstitial pneumonia.

There is an overlap of radiological patterns seen in IIP with that of ILD related to connective tissue disease, the most common being NSIP. Although the idiopathic form of NSIP is recognised as a separate IIP entity, patients in a study were often found to have positive serologies for a possible underlying connective tissue disease [21]. Within this cohort, there are patients that do not fulfil criteria for a defined rheumatological disorder despite the presence of clinical and serological manifestations. An attempted standardised terminology of idiopathic pneumonia with autoimmune features (IPAF) was introduced to collectively describe this cohort [22]. The proposed classification uses a list of features that are organized into three central domains; (1) a clinical domain consisting of specific extra-thoracic features suggestive of an underlying CTD, (2) a serological domain with specific autoantibodies and (3) a morphologic domain comprising of specific radiological, histological and pulmonary physiological features

(Table 1.4), with patients needing to have at least one feature from at least two domains. The use of this IPAF classification has yet to be validated in large prospective cohorts and currently remains a research tool, not incorporated into current ILD guidelines [23].

Table 1.4 Proposed classification criteria for interstitial pneumonia with autoimmune features (IPAF). Adapted from Fischer *et al*. [22]

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) and, 2. Exclusion of alternative aetiologies 3. Does not meet criteria of a defined connective tissue disease and, 4. At least one feature from at least two of these domains: A. Clinical domain B. Serologic domain C. Morphologic domain
A. Clinical domain 1. Distal digital fissuring (i.e. "mechanic hands") 2. Distal digital tip ulceration 3. Inflammatory arthritis or polyarticular morning joint stiffness ⩾60 min 4. Palmar telangiectasia 5. Raynaud's phenomenon 6. Unexplained digital oedema 7. Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)
B. Serologic domain

1. ANA ⩾1:320 titre, diffuse, speckled, homogeneous patterns or ANA nucleolar/centromere pattern (any titre)

2. Rheumatoid factor ⩾2x upper limit of normal

3. Anti-CCP

4. Anti-dsDNA

5. Anti-Ro (SS-A)

6. Anti-La (SS-B)

7. Anti-ribonucleoprotein

8. Anti-Smith

9. Anti-topoisomerase (Scl-70)

10. Anti-tRNA synthetase (myositis antibodies)

11. Anti-PM-Scl

12. Anti-MDA-5

C. Morphologic domain

1. Suggestive radiology patterns by HRCT (see text for descriptions):
   - NSIP, OP, NSIP with OP overlap, LIP

2. Histopathology patterns or features by surgical lung biopsy:
   - NSIP, OP, NSIP with OP overlap, LIP, Interstitial lymphoid aggregates with germinal centres, diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)

3. Multi-compartment involvement (in addition to interstitial pneumonia):
   a. Unexplained pleural effusion or thickening
   b. Unexplained pericardial effusion or thickening
   c. Unexplained intrinsic airways disease# (by PFT, imaging or pathology)

d. Unexplained pulmonary vasculopathy

HRCT: high resolution computerised tomography, ANA: antinuclear antibody, CCP: cylic citrullinated peptide, dsDNA: double stranded deoxyribonucleic acid antibodies, OP: organising pneumonia, LIP: lymphoid interstitial pneumonia, NSIP: nonspecific interstitial pneumonia, PFT: pulmonary function test.

1.1.5 Other Interstitial Lung Disease

Lymphangioleiomyomatosis (LAM) is a sporadic rare cystic lung disease seen predominantly in women, with similar findings also seen in up to 10% of those with tuberous sclerosis complex (TSC), a multisystem genetic condition caused by mutation in TSC genes [24]. Sporadic LAM is generally slowly progressive and is also associated with abdominal tumours and chylous fluid accumulation. Radiologically, LAM is characterised by bilateral thin-walled cysts which are round, diffusely distributed and devoid of internal structure, often resulting in a spontaneous pneumothorax as a first presentation in women in their fourth or fifth decade of life. Advances in the understanding of the genetics of LAM have led to the development of clinical guidelines and treatment with mechanistic target of rapamycin (mTOR) inhibitors, showing efficacy in stabilising lung function [25].

Langerhan's cell histiocytosis (LCH), previously known as histiocytosis X is the most common histiocytic disorder of unknown cause, characterised by aberrant function and differentiation of histiocytes, a historical term describing phagocytes with mononuclear morphologic features [26]. The disease is characterised by granulomatous lesions containing langerin-positive (CD207+)

histiocytes arising in single- or multiorgan systems but most commonly affecting bones, skin, lungs and the pituitary gland. While the exact pathogenesis of pulmonary LCH remains unknown, tobacco is considered a major factor leading to cystic lung parenchymal destruction [27].

1.2 Idiopathic Pulmonary Fibrosis

1.2.1 Definition

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic and progressive fibrosing interstitial lung disease (ILD) with an unknown cause. It is the most common of the idiopathic interstitial pneumonias (IIP).

The first cases were described as an 'acute interstitial fibrosis of the lungs' in young adults and followed a relatively acute process over a span of months [28]. Subsequent case series described a chronic type of diffuse interstitial fibrosis were in older people and followed a slower, chronic trajectory associated with gradual increase in clinical symptoms [29]. Histological studies described alveolar wall thickening and reactive cells within the alveoli termed 'alveolar pattern reaction' and predominant alveolar wall thickening 'mural pattern reaction'. These findings hypothesised an initial alveolar response to an unknown trigger, capable of leading to advanced diffuse interstitial pulmonary fibrosis and was called cryptogenic fibrosing alveolitis (CFA) [30]. Early retrospective studies showed a male preponderance and worsening symptoms of dyspnoea closely associated with reduction in vital capacity [1]. The use of the term IPF became widespread in North America during the 1970s but is synonymously describing the same

condition as CFA without any serological or clinical features of a concomitant connective tissue disease [31].

In an attempt to standardise the definition of IPF, the American Thoracic Society (ATS) and European Respiratory Society (ERS) developed a list of consensus criteria for the diagnosis of IPF, one that hinges on histopathological presence of a usual interstitial pneumonia (UIP) pattern [32]. However, not every suspected IPF case would have available lung biopsy samples to confirm this. A set of major and minor criteria was developed to improve the likelihood of a correct diagnosis of IPF in such cases. It requires the presence of all major criteria and at least three out of four minor criteria (Table 1.5).

Table 1.5. Joint American Thoracic Society (ATS) and European Respiratory Society (ERS) 1999 consensus guidelines criteria for the diagnosis of IPF. Adapted from [26].

Available histopathological evidence of Usual interstitial pneumonia (UIP)	
Criteria	(i) Exclusion of other known causes of ILD such as drug toxicities, environmental exposures and connective tissue disease (ii) Abnormal pulmonary function tests including evidence of restriction (reduced VC often with increased FEV1/FVC ratio) and/or impaired gas exchange (iii) Bibasal reticular abnormalities with minimal ground glass opacities on HRCT scans

No available lung biopsy tissue	
Major criteria	(i) Exclusion of other known causes of ILD such as drug toxicities, environmental exposures and connective tissue disease (ii) Abnormal pulmonary function tests including evidence of restriction (reduced VC often with increased FEV1/FVC ratio) and/or impaired gas exchange (iii) Bibasal reticular abnormalities with minimal ground glass opacities on HRCT scans (iv) Transbronchial lung biopsy or bronchoalveolar lavage (BAL) without features supporting an alternative diagnosis
Minor criteria	(i) Age >50 years (ii) Insidious onset of otherwise unexplained exertional dyspnoea (iii) Duration of illness ≥ 3 months (iv) Bibasilar, inspiratory crackles (dry/ 'Velcro' quality)

ILD: interstitial lung disease, VC: vital capacity, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, HRCT: high resolution computerised tomography.

A further rigorous review of available evidence since the release of the guidelines above, led to an updated joint statement and guideline by the ATS, ERS, Japanese Respiratory Society (JRS) and Latin American Thoracic Society (ALAT), published in 2011 [33]. While the diagnosis of IPF still requires the exclusion of other known causes of an ILD, other diagnostic criteria were simplified to either having a UIP pattern on HRCT in patients without a surgical lung biopsy, or a specific combination of HRCT and surgical lung biopsy patterns (Table 1.6). One important caveat to this is that the diagnostic accuracy increases with a multidisciplinary discussion

among pulmonologists, radiologists and pathologists experienced in the diagnosis of ILD, a critical concept in ILD that will be discussed later in this chapter. Since then, the IPF guidelines have undergone several updates, the first in 2018 with an important update on the categorisation of a UIP pattern on HRCT and lung biopsies [34]. The guideline advocated the use of four distinct radiological and histopathological categories namely 'UIP pattern', 'probable UIP', 'indeterminate UIP' and 'alternative diagnosis' as a basis of the IPF diagnostic algorithm (Table 1.7). The most recent update to the diagnostic algorithm is that the presence of a probable UIP histopathological pattern on an adequate lung biopsy sample despite an 'alternative diagnosis' pattern on HRCT, allows for an 'indeterminate' diagnosis of IPF that can be further deliberated in a multidisciplinary setting [35]. Another important impact from the current updated algorithm is that a probable UIP pattern on HRCT negates the need for a lung biopsy to achieve a diagnosis of IPF.

Table 1.6. 2011 Consensus criteria requiring combination of HRCT and SLB findings for the diagnosis of IPF*. Adapted from Raghu *et al.* [33].

	Surgical lung biopsy pattern				
HRCT pattern	UIP	Probable UIP	Possible UIP	Nonclassifiable fibrosis†	Not UIP
UIP	IPF	IPF	IPF	IPF	Inconsistent with IPF
Possible UIP	IPF	IPF	Probable IPF‡	Probable IPF‡	Inconsistent with IPF
Inconsistent with UIP	Possible IPF‡	Inconsistent with IPF	Inconsistent with IPF	Inconsistent with IPF	Inconsistent with IPF

*requires multidisciplinary discussion

[†]pattern of fibrosis that do not meet above criteria for UIP

[‡]Possibility of diagnosis of IPF still exists and further multidisciplinary discussion is required.

HRCT: high resolution computed tomography, UIP: usual interstitial pneumonia, IPF: idiopathic pulmonary fibrosis

Table 1.7. 2018 IPF guidelines combination of radiological and histopathological patterns for the diagnosis of IPF. Adapted from Raghu et al [34].

	Histopathological pattern (if biopsy performed)			
HRCT pattern	UIP	Probable UIP	Indeterminate UIP	Alternative diagnosis
UIP	IPF	IPF	IPF	Non-IPF
Probable UIP	IPF	IPF	IPF (likely)	Non-IPF
Indeterminate UIP	IPF	IPF (likely)	Indeterminate[*]	Non-IPF
Alternative diagnosis	IPF (likely)	Non-IPF	Non-IPF	Non-IPF

[*]without an adequate biopsy is unlikely to be IPF, but can be reclassified if adequate biopsy and further multidisciplinary discussion

1.3 Epidemiology

Despite Idiopathic pulmonary fibrosis (IPF) being the most common form of idiopathic interstitial pneumonias (IIP), it still remains a relatively rare disease. The true incidence and prevalence is challenging to determine due to continued evolution of its diagnostic criteria, ongoing changes in diagnostic codes used to identify IPF on administrative databases and

heterogenous epidemiological study designs [33, 34, 35, 36]. Previous attempts of standardisation had been proposed using a 'broad' versus 'narrow' diagnostic code definition of IPF, with the latter requiring a lung biopsy or chest CT confirming the diagnosis [37].

Table 1.8 summarises findings from individual epidemiological studies showing highly variable incidence and prevalence rates, which are appear generally higher in American studies compared to European and Asian. A recent targeted literature review with statistical modelling showed worldwide variability with an overall incidence and prevalence to be estimated to be in the range of 0.09-1.30 and 0.33-4.51 per 10,000 persons, respectively [38].

Table 1.8. Incidence and prevalence of IPF.

First Author	Study period	Region/Country	Data Source	Incidence per 10, 000	Prevalence per 10, 000
Navaratnam [39]	1968-2009	UK	Primary care	7.44	2.54
Mannino [40]	1979-1991	USA	Death certificate	3.2 (1979)** 3.65 (1991)**	n/a
Kolek [41]	1981-1990	Czech Republic	Retrospective study	0.74	6.5
von Plessen [42]	1984-1998	Norway	Hospital record	4.3	23.4
Coultas [43]	1988-1990	USA	Population-based registry	10.7 (male) 7.4 (female)	20.2 (male) 13.2 (female)
Gribbin [44]	1991-2003	UK	Primary care	4.6	n/a
Thomeer [45]	1992-1996	Belgium	Population-based registry	0.22	1.25
Olson [46]	1992-2003	USA	Death certificate	5.08	n/a
Raghu [47]	1996-2000	USA	Healthcare claim database	16.3 (broad) 6.8 (narrow)	42.7 (broad) 14 (narrow)

Fernandez Perez [48]	1997-2005	USA	Clinical and administrative database		17.4 (broad) 8.8 (narrow)	63 (broad) 27.9 (narrow)
Hodgson [49]	1997-1998	Finland	Pulmonary clinic database			16-18
Lai [50]	1997-2007	Taiwan	Administrative database	1998	0.6 (broad) 0.5 (narrow)	0.7 (broad) 0.5 (narrow)
				2007	1.4 (broad) 1.2 (narrow)	6.4 (broad) 4.9 (narrow)
Hutchinson [51]	1999-2012	Worldwide	Death certificate		USA 6.16 England & Wales 8.28 Australia 5.08 Spain 4.64 Canada 6.38	n/a
Xaubet [52]	2000-2001	Spain	Population-based registry		7.6	n/a
Raghu [37]	2000-2011	USA	Medicare claims*	2001	31.1 (broad) 15.9 (narrow)	82.6 (broad) 30.5 (narrow)
				2011	43 (broad) 31.1 (narrow)	233.3 (broad) 145.7 (narrow)
Hyldgaard [53]	2003-2009	Denmark	Clinical and administrative database		1.3	n/a
Natsuizaka [54]	2003-2007	Japan	Clinical database and medical benefit data		2.23	10
Karakatsani [55]	2004	Greece	Questionnaire		0.93	3.38
Ohno [56]	2005	Japan	Clinical database and medical benefit data		1.2	1.7
Agabiti [57]	2005-2009	Italy	Hospital and mortality database		7.5	25.6
Musellim [58]	2007-2009	Turkey	Questionnaire		5.13	n/a

Behr [59]	2012-2014	Germany	Population-based registry	‡Incident cases: 171	‡Prevalent cases: 331

*5% random sample, ** Study assumed age-adjusted annual mortality rate reflects disease incidence rate, ‡number of IPF cases:502

1.4 Pathogenesis

The exact pathogenesis of IPF remains unknown. However, there has been substantial progress made into the understanding of the pathophysiology of this condition. One favoured conceptual model proposes that recurrent lung epithelial injury from exposure to environmental triggers, and accelerated epithelial aging leading to dysregulated cell repair, proliferation of lung myofibroblasts, aberrant collagen deposition and progressive, permanent lung function decline [60]. Environmental triggers may be external such as air pollutants, cigarette smoke and organic antigens or could be host-orginating like microaspiration and gastroesophageal reflux. While such correlations have been documented, it is difficult to demonstrate a causal link between such exposures to the development of IPF [61]. Furthermore, such complex and defective mesenchymal cross-talk are likely part of a more complex mechanism of disease, one where genetic susceptibility also plays a role.

1.4.1 Genetics

IPF can occur sporadically and are also known to affect families. Familial pulmonary fibrosis (FPF) where having two or more family members with an idiopathic interstitial pneumonia, represent approximately 5-20% of IPF cases, supporting the notion that genetic susceptibility plays a role in its pathogenesis [33]. While specific genetic mutations identified have contributed

to the understanding of IPF pathogenesis, most variations on their own, are unnecessary or insufficient to cause pulmonary fibrosis.

The most common genetic variant in IPF is the MUC5B r35705950 allele. Its pathological mechanism is poorly understood but is thought to be related to mucin production and impaired clearance. It has been documented to present in 30% of sporadic IPF patients and is associated with a 20-fold increase in risk for the disease in homozygotes [62]. Furthermore, exploratory evidence shows a favourable therapeutic response to N-acetylcysteine (NAC), once thought to be harmful when combined with other immunosuppressants. While further research is much needed, such findings may suggest a future in which therapeutic options may be influenced by genomic factors.

Mutations in the telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC) causes telomerase dysfunction. Telomeres are found at the end of chromosomes and function to protect against the loss of genetic material during mitosis. Dysfunction of telomerase, the enzyme that catalyses DNA synthesis to maintain telomere length, causes telomere shortening ultimately leading to cell-cycle arrest, limits the replicative capacity of organ tissues and is associated with poorer survival in IPF [63, 64]. Other gene variants conferring increased risk of developing IPF include the desmoplakin gene (DSP) involved in cell adhesions, and the surfactant protein C and A (SFTPC and SFTPA) [65, 66, 67].

1.4.2 Epithelial cells

In healthy lungs, type 1 alveolar cells (AT1) are the primary facilitators of gas exchange while type 2 cells (AT2) produce surfactant and serve as primary progenitors for injured AT1 cells.

In IPF, AT2 cells are subject to higher levels of apoptosis, senescence and impaired renewal and differentiation. Studies have shown a unique population of epithelial cells in IPF lungs that had features of AT1, AT2, basal and proximal airway cells. These cells expressed highly dysregulated program markers such as matrix metalloproteinase 7 (MMP7), up-titration of epithelial-mesenchymal transition (EMT) gene expression pathways and having features of senescence [68]. Being a significant risk factor of IPF, aging makes the lung more susceptible to mitochondrial dysfunction by means of enlarged mitochondria and increased mitochondrial reactive oxygen species. This dysfunction is linked to senescence in AT2 cells IPF [69]. While the development of senescence is caused by multiple pathways, it is characterised by the secretion of inflammatory mediators of fibrosis, such as transforming growth factor-beta (TGF-β) and tumour necrosis factor-alpha (TNF-A).

1.4.3 Endoplasmic Reticulum Stress

Endoplasmic reticulum (ER) is an organelle of eukaryotic cells forming a network of membrane structures responsible for protein synthesis and lipid and carbohydrate metabolism. ER stress is characterised by imbalances in protein homeostasis, leading to accumulation of unfolded proteins and activation of unfolded protein response (UPR). In the case where UPR is unable to diffuse ER stress, cell apoptosis pathways are triggered. In IPF, markers for ER stress and UPR are increased in AT2 cells. In animal studies, such findings are implicated to be associated with cell depletion, recruitment of pro-inflammatory and pro-fibrotic cytokines and epithelial-to-mesenchymal transition but have fallen short of showing a direct effect of ER stress causing fibrosis. [70, 71].

1.4.4 Fibroblasts

While fibrocytes are bone marrow derived mesenchymal cells capable of differentiation into fibroblasts, fibroblasts are critical in wound healing by deposition of extracellular matrix (ECM) proteins and can further differentiate into myofibroblasts which secrete collagen and generate contractile force for wound closure [72]. In normal healthy states, resolution of wound repair is needed to deactivate myofibroblastic activity, derecruit fibroblasts and ensure resorption of ECM and cellular debris. Fibrotic conditions are characterised by upregulation of TGF-β, a well-known pro-fibrotic mediator, secreted by various cell types and once bound to target cell receptors, initiates a fibrotic signalling cascade [73].

It is not currently clear whether the fibrotic process in IPF is caused by recurrent, injury-driven wound repair or dysregulation of the wound repair itself and its ability to disengage in the process. Furthermore, the precise origin or fibroblasts in IPF is also not known. One such source are circulating fibrocytes which have been found in IPF lung parenchyma and blood circulation, with one study showing that higher levels seen in IPF were independently associated with poorer prognosis [74, 75]. However, the use of single-cell RNA sequencing techniques paint a different story and points to a spectrum of overlapping and specialised mesenchymal cell population that cannot be differentiated by unique markers and that there may not be a specific lineage of fibroblast responsible in IPF [72].

1.4.5 Epithelial-To-Mesenchymal Transition

Epithelial-to-mesenchymal transition (EMT) is a process where epithelial cells acquire mesenchymal cell properties following activation of TGF- β or ER stress. This process is part

of development and wound repair but is dysregulated in diseases such as cancer. While the presence of EMT markers has been demonstrated in IPF lungs, mesenchymal cells cannot be clearly traced back to an epithelial origin and the precise effect of EMT in IPF has yet to be discovered [68, 76, 77].

1.4.6 Extracellular Matrix

The pulmonary extracellular matrix (ECM) is a three-dimensional structural meshwork made up of proteins (such as collagen), glycoproteins and proteoglycans, and also contain numerous signalling molecules such as TGF- β, osteopontin, periostin and fibronectin. ECM in IPF lungs has been shown to be remodelled pathologically with abnormal cross-linking of collagen. This results in aberrant ECM stiffness and increased signals by mechanosensing fibroblasts to mesenchymal cells to further release more ECM proteins, thus perpetuating a forward-feedback loop of matrix deposition and remodelling, ultimately contributing to the propagation of lung fibrosis [78, 79].

1.4.7 Immune Cells

While IPF was initially described as a disease driven by inflammation, the use of immunosuppressive agents in clinical trials showing potential harm raised doubts on this notion [80]. However, both innate and adaptive immune systems are very much involved in all forms of wound healing and fibrosis. Their roles include an early inflammatory response from T-helper 2 cells for the formation of ECM and in later stages, phagocytosis of excessive ECM, inhibiting proliferation and removal of apoptotic cells. In IPF, there is a profibrotic inflammatory process involving altered inflammasome regulation and alveolar macrophage population [72]. Monocytes

have been suggested to play an important role in IPF pathogenesis [81]. The ease of obtaining monocyte counts through minimally invasive means have garnered interest in its use as a prognostic biomarker, one that would be explored later in this thesis.

1.5 Morphology

1.5.1 High Resolution Computed Tomography

An accurate diagnosis of IPF is centrally reliant on a high-resolution computed tomography (HRCT). Newer CT scanners with improved technology allows for volumetric scanning of the chest replaced sequential CT scans, where it provides thin sections (<2mm), improves detection of abnormalities and allows precise analysis of lesions using multiplanar and cross-sectional reformations. The most recent technical requirements of HRCT for the purpose of ILD diagnosis were summarised in the ATS/ERS/JRS/ALAT clinical practice guideline in 2018 [34]. HRCT scans are normally performed with a several acquisitions. The first being in the supine position at sustained end-inspiration allowing for accurate volumetric acquisition. This is usually followed by acquisition at sustained end-expiration which allows for identifying features of gas trapping and mosaic heterogeneity, and lastly, a third acquisition in the prone position allowing for delineation of position-dependent changes from true parenchymal abnormalities [82, 83].

The usual interstitial pneumonia (UIP) pattern seen on HRCT are characterised by the presence of honeycombing, traction bronchiectasis or bronchiolectasis, increased reticulation in the subpleural and basal regions of the lung and may be associated with minor areas of ground glass attenuation [34]. Honeycombing is defined as clustered, thick-walled cystic spaces, generally

measuring three to five millimetres. They are usually made up of several layers of cysts stacked onto each other but can present itself as a single layer [84]. The definition has been subject of multiple revisions with studies still showing a degree of interobserver disagreement among expert radiologists and other subspecialties and appears to be also dependent on geographical locations of practice [85, 86]. Traction bronchiectasis and bronchiolectasis represent irregular bronchial and bronchiolar dilatation resulting from increased retractile forces related to surrounding parenchymal fibrosis [87]. The presence of traction bronchiectasis not only indicates the presence of lung fibrosis on CT imaging but also carries prognostic implications in fibrotic idiopathic interstitial pneumonias [88]. Increased reticular markings seen in UIP patterns of fibrosis refer to the network of fine lines seen on CT imaging which are often irregularly spaced with a mixture of both fine and thicker lines. These normally contrast to nonspecific interstitial pneumonia patterns where lines are generally homogeneous in thickness and spacing [89]. While increased hazy attenuation of the lung parenchyma are often labelled as ground glass opacities, this remains to be an uncommon finding in the UIP pattern. It has previously been postulated that such ground glass opacities may actually be alveolar wall thickening and are indicative of early 'fine' fibrosis [90]. The presence of other UIP features such as traction bronchiectasis can be helpful and likewise, extensive areas of ground glass changes may point toward an alternate diagnosis.

The ongoing evolution of the clinical guidelines of IPF has also changed the way HRCT imaging are incorporated into the diagnostic process. In 2018, four categories of radiological UIP feature were proposed (Table 1.9). A definite UIP pattern requires the presence of honeycombing (Figure 1.2). Previous studies have shown a high positive predictive value for the presence of UIP on histopathological samples, resulting in the move away from a strict histopathological requirement to diagnose IPF in such cases [7, 91, 92]. A 'probable UIP' pattern

defined by the presence of subpleural, basal-predominant reticulation and traction bronchiectasis or bronchiolectasis (Figure 1.3), is the next iteration of a 'possible UIP' with several studies reporting patients fitting a 'possible UIP' pattern with traction bronchiectasis in the correct clinical setting were more likely to have histopathological UIP [93, 94]. An 'indeterminate pattern' is assigned when HRCT shows fibrotic features not fitting a definite or probable UIP pattern. The last category labelled 'alternative diagnosis' is reserved for cases in which HRCT imaging show other predominant features such as mosaic attenuation, bronchocentric fibrosis, upper lobe distribution or extensive ground glass opacities [34]. These categories were retained in the most recent updated clinical guidelines [35].

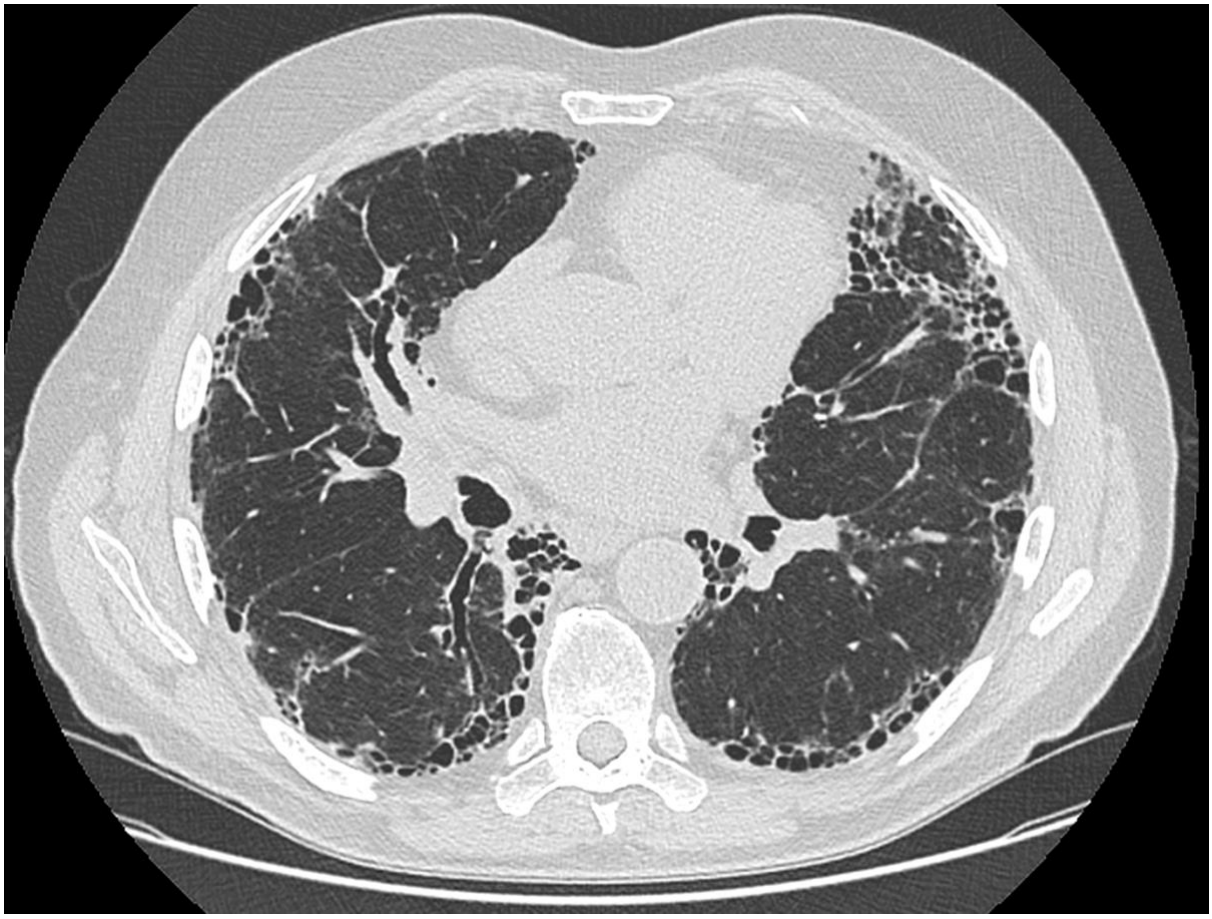

Figure 1.2 Definite UIP pattern on HRCT showing subpleural fibrosis, honeycombing and traction bronchiectasis. UIP: usual interstitial pneumonia, HRCT: high resolution computed tomography

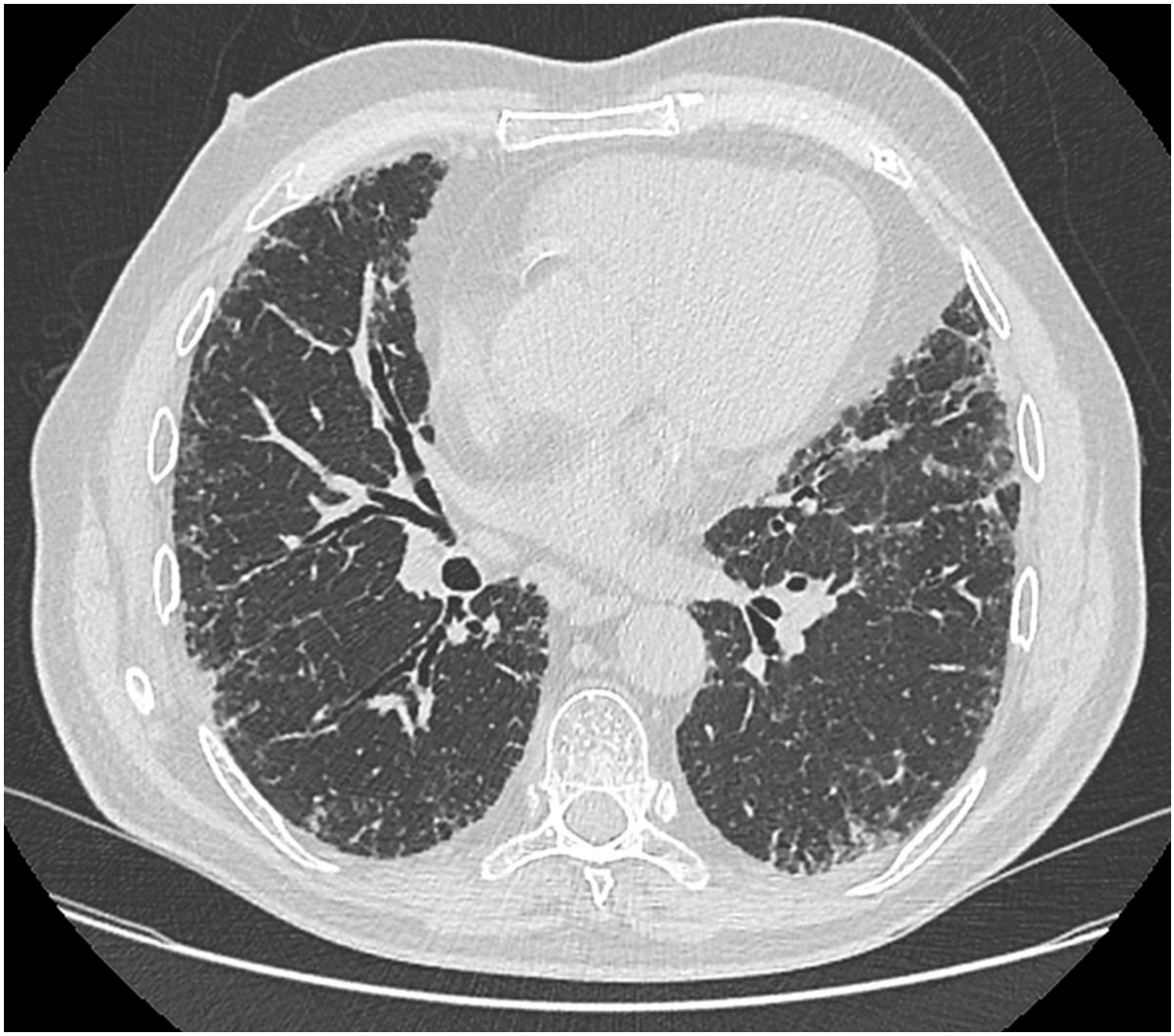

Figure 1.3. Probable UIP pattern on HRCT showing subpleural reticulation and traction bronchiectasis without honeycombing. UIP: usual interstitial pneumonia

Table 1.9. High-Resolution Computed Tomography Patterns in Idiopathic Pulmonary Fibrosis. Adapted from [33, 34].

Definite UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
1) Subpleural, basal-predominant distribution 2) Honeycombing with or without bronchiectasis or bronchiolectasis 3) Increased reticular markings 4) May have mild GGO and pulmonary opacities	1) Subpleural, basal-predominant distribution 2) Increased reticulation with traction bronchiectasis/bronchiolectasis 3) May have GGO 4) Absence of subpleural sparing	1) Diffuse distribution without subpleural predominance 2) Features of fibrosis without specific evidence to support other specific aetiologies	Findings suggestive of other diagnosis: 1. CT features: cysts, marked mosaic attenuation, predominant GGO, centrilobular and profuse micronodules, consolidation. 2. Peribronchovascular and perilymphatic, upper/mid-lung distribution and subpleural sparing. 3. Other: pleural plaques and effusions, dilated oesophagus, distal clavicular erosions, extensive LN enlargement

UIP: usual interstitial pneumonia, GGO: ground glass opacities, LN: lymph node

1.5.2 Histopathological Pattern

The hallmark histological features of a UIP pattern are architectural distortion and destruction with honeycomb formation, fibroblastic foci, patchy heterogeneous distribution and involvement of lung lobule peripheries [95] (Figure 1.4). Mild inflammation can be present with patchy interstitial lymphocytic and plasma cell infiltrates. Histopathological assessment can also be helpful in excluding features of alternative diagnoses such as bronchiolocentric distribution of lymphocytic infiltrates, granulomas, pneumoconiosis or organising pneumonia [34]. Similar to HRCT categories, histopathological UIP patterns are divided into 'definite UIP', 'probable UIP', 'indeterminate for UIP' and 'alternative diagnosis', summarised in Table 1.10. Of note, a definite UIP histopathological pattern can still be made when all typical features are present even in the absence of honeycombing. Historically, a definite diagnosis of IPF was heavily dependent on the histopathological evidence of a UIP pattern, the lack of which would only render a likely diagnosis.

Table 1.10. Histopathological categories of Usual Interstitial Pneumonia pattern in 2018. Adapted from [33].

Definite UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
1. Dense fibrosis, architectural distortion. 2. Predominant subpleural distribution. 3. Patchy lung involvement. 4. Fibroblastic foci	Histological features similar but not to extent of definite UIP pattern. AND Absence of alternative diagnosis features	1. Fibrosis +/- architectural distortion with features favouring non-UIP pattern.	1. Features of other histological patterns.

5.Absence of features to suggest alternative diagnosis.	OR Honeycombing only	2. Some features of UIP pattern but with alternative diagnosis features.	2. Histological findings of other diseases.

UIP: usual interstitial pneumonia

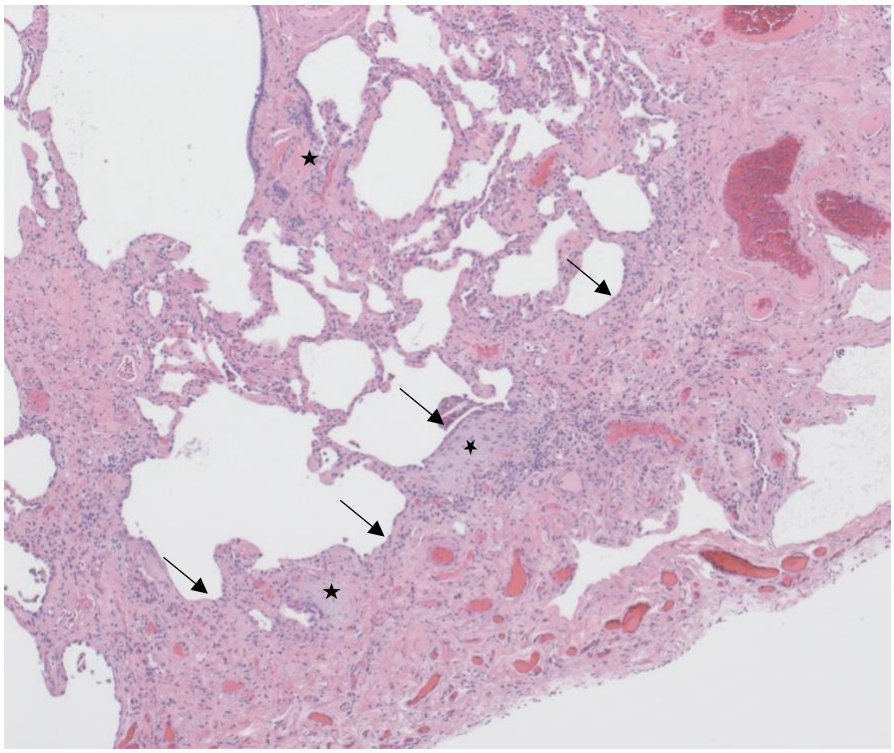

Figure 1.4. Usual interstitial pneumonia (UIP) on histopathology. Evidence of spatial and temporal heterogeneity with subpleural predominant fibrosis (arrowed) with fibroblastic foci (starred).

1.5.1.1 Surgical Lung Biopsy

Video-assisted thorascopic (VATS) surgical lung biopsies (SLB) have been shown to provide equivalent specimen volume and diagnostic accuracy to historical open lung biopsies with the added benefit of shorter recovery time and hospital length of stay and equivocal complication rates [4, 96, 97]. Such procedures are not without risks and may cause an acute exacerbation of the underlying lung disease, persistent air-leak, haemothorax, pleural infections and the need for mechanical ventilation [98]. Furthermore, a SLB in the setting of an acute exacerbation of IPF results in significantly higher 30-day mortality rates [51, 99]. Hence, the final decision on performing a SLB hinges on individual patient factors, the clinical situation and surgical expertise. However, there is an increasing reliance of radiological imaging in the diagnostic algorithm for IPF. As a result, fewer patients, particularly those with a UIP pattern on HRCT, would not need to have a SLB for the purpose of diagnosing IPF. Upon reviewing evidence to date, the international consensus guidelines in 2018 concluded that patients with a HRCT UIP pattern would not require a SLB for the diagnosis of IPF and those with other HRCT patterns, a SLB should be considered in conjunction with a multidisciplinary discussion [34].

1.5.1.2 Transbronchial Lung Cryobiopsy

Transbronchial lung cryobiopsy (TBLC) is a new technique of obtaining lung histopathological samples using a cryoprobe. Cryoprobes have been proven to retain excellent tissue integrity and quality for the purposes of immunohistochemistry and histopathological review [100]. Studies have shown TBLC to be a viable option in providing accurate diagnosis of ILD while showing a low mortality risk and good safety data. However, there was variable approach to the procedure and adverse event rates, with no studies prior to the 2018 clinical guidelines,

comparing TLBC directly to standard SLB within the same population [101, 102, 103, 104, 105, 106]. The landmark prospective study by Troy et al. compared the diagnostic accuracy of TBLC to SLB for the diagnosis of ILD. The study showed both high levels of histopathological agreement between TBLC and SLB, and diagnostic agreement when used in a multidisciplinary discussion [107]. The recent updated IPF clinical guidelines made a conditional recommendation that TBLC can be considered as an alternative to SLB for the purpose of histopathological diagnosis of ILD on the basis of low quality evidence to date, with an important caveat that the procedure should be performed in centres with standardized protocols, appropriate facilities along with procedural and interpretative experience [35].

1.6 Clinical Presentation

IPF is generally a disease of the elderly where it tends to occur after the sixth decade of life. The condition also is more prevalent in men, though women can also be affected by it. People with IPF usually present with chronic and unexplained dyspnoea, a dry cough and less frequently, fatigue or unexplained weight loss. Importantly, the appearance of such symptoms are insidious in nature and may have a highly variable time period before attention is brought to them [33, 108, 109]. Clinical signs include velcro-like crepitations heard on lung auscultation, finger clubbing and acrocyanosis [110]. The combination of a later age of presentation and non-specific nature of symptoms which could sometimes be attributed to other comorbid conditions, often result in diagnostic delays and negatively impacts on patient survival [111]. Familial forms of IPF tend to present earlier with a cohort study showing a more aggressive disease course and a faster lung function decline than sporadic cases [112].

1.7 Other Investigations

While the diagnosis of IPF is heavily guided by the presence of a radiological or histopathological UIP pattern in the absence of other known causes of an ILD, there are other clinical investigation tools that are useful adjuncts to the diagnostic process. One of the most important of such investigations is a pulmonary function test (PFT). PFTs are usually performed in a respiratory function laboratory and are comprised of three parts, spirometry and lung volumes providing both dynamic and static lung volumes and capacity, and a measurement of the gas transfer capacity of the lungs. In IPF, PFT measurements often reveal varying degrees of lung restriction with a reduced forced vital capacity (FVC) and total lung capacity (TLC) as well as gas transfer capacity impairment by means of measuring the diffusing capacity for carbon monoxide of the lung (DLCO) [33]. PFT measurements may be normal in cases of early disease or may be pseudonormalised due to existing diseases such as emphysema [113].

The diagnosis of IPF mandates the exclusion of other known causes of an ILD such as a connective tissue disease-associated ILD (CTD-ILD). In 2018, international IPF consensus guidelines provided a motherhood statement recommending that serological testing be performed in an undifferentiated ILD who are suspected to have IPF for the primary purpose of excluding a connective tissue disease (CTD) as a potential cause. This attest to the notion that the mere presence of a UIP pattern is not always indicative of an IPF diagnosis as a UIP pattern can also be seen in CTD-ILD [114, 115]. Furthermore, the presence of serological autoantibodies even in the setting of a radiological UIP pattern may indicate a *forme fruste* version of a CTD, one that may evolve to a multisystem condition in due time [116]. However, there is little agreement and no recommendation thus far on what precise autoantibodies should be tested as part of said serological testing. As a minimum, there was agreement that routine

testing should include C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP). The utility of more specific serological tests such as an extended myositis and extractable nuclear antigen (ENA) panel is less clear, and a case-based decision be made according to accurate clinical history and signs.

Bronchoalveolar lavage (BAL) involves the instilment of room temperature normal saline through a flexible bronchoscope that is wedged within the desired target bronchopulmonary segment of the lung. The standard procedure requires a total volume of 100-300ml instilled and then retrieved by applying negative suction pressure, with the minimum retrieved volume of 5% or ideally more than 30% [117]. In ILD, the cellular differential analysis of a BAL sample is recommended to assist the diagnosis of the underlying ILD and further microbiological testing can also be performed to exclude coexisting infections. BAL still remains as a diagnostic adjunct rather than a true stand-alone test. In 2018, the IPF guidelines suggested that a BAL can be considered in cases of suspected IPF but with a probable, indeterminate UIP pattern or cases with a pattern suggesting an alternative diagnosis. In suspected IPF cases with a clear UIP pattern, a BAL is not suggested [34].

The search for an ideal diagnostic and prognostic biomarker continues, with one yet to be found or utilised routinely in clinical practice. Serum-based biomarkers such as matrix metalloproteinases (MMPs) and Krebs von den Lungen-6 (KL-6) have been shown to predict prognosis, transplant-free survival and correlate with acute exacerbations of ILD [118, 119]. However, their use in clinical practice is hampered by non-specificity to IPF, which could lead to misdiagnosis and a lack of global standardisation across laboratories. Other form of biomarkers come in the form of volatile organic compounds (VOC) that can be detected in

exhaled breath. Compounds such as nitric oxide (NO) that have been studied more heavily in airways disease, have garnered interest as a potential biomarker in IPF [120, 121]. This is once again offset by a lack of standardisation and consistency, which could often lead it being less reliable in a clinical setting. Within this thesis, we sought to explore a few diagnostic and prognostic biomarkers in IPF and the effect of current available therapies on their expression.

A genomic classifier tool developed using machine learning and whole transcriptome RNA sequencing in surgical lung biopsies was shown to be able to differentiate UIP from other patterns of ILD. A more recent study further validated its use on smaller transbronchial lung biopsy specimens with both studies highlighting the potential utility of genomic classification as another diagnostic tool to be incorporated into the multidisciplinary diagnostic algorithm of IPF without the need for invasive surgeries [122, 123]. Pooled data shows a high specificity of 92% of predicting a histopathological UIP pattern but only a sensitivity of 68% [124]. However, genomic classification has yet to be incorporated into the most recent IPF clinical guidelines due to current low sensitivity, insufficient evidence of additional diagnostic value compared to standard practice, the widespread use of new antifibrotic therapy for other fibrotic lung disease, the reliance on a transbronchial lung biopsy which carries risks and that the test is yet to be widely available [35].

Several other clinical investigations commonly performed are six-minute walk tests (6MWT), transthoracic echocardiogram and in selected cases, a sleep polysomnogram or an arterial blood gas. Whilst these are not used to diagnose IPF, they remain important for the diagnosis of comorbid conditions that may impact on the overall prognosis of the individual patient.

1.8 Interstitial Lung Disease Multidisciplinary Meeting (ILD MDM)

In 2002, the ATS/ERS consensus classification of IIPs highlighted the importance of standardised terminologies defined by a set of histological patterns in combination with clinical and radiological data. The final diagnosis should only be rendered once all pathological, radiological and clinical data have been reviewed by their respective specialist physician, leading to the concept of a clinical-radiologic-pathologic (CRP) diagnosis [8]. This perhaps was the first iteration of the current concept of an interstitial lung disease multidisciplinary meeting (ILD MDM). While previous guidelines had placed more importance on a histologically confirmed diagnosis of IPF, the ILD MDM is now considered the current 'gold standard' component in achieving an accurate ILD diagnosis.

In the landmark study by Flaherty *et al*., clinical, radiological and histopathological data of 58 patients were presented sequentially in a stepwise manner to a panel of clinicians, radiologists and pathologists with the goal of reaching a consensus diagnosis and an attached confidence level [125]. The study showed a modest interobserver agreement with a K of 0.41 among clinicians when only HRCT images were provided without relevant clinical data or opportunities for discussion. However, with increasing layers of available information and opportunities to discuss diagnostic impressions with radiologists and pathologists, the agreement k score increased to 0.86, indicating a good interobserver agreement. One important finding was that a diagnosis of IPF by clinicians with only clinical and radiological data coincided with the pathological diagnosis in most cases, suggesting that patients suspected to have IPF may not necessarily be subjected to a lung biopsy provided that the clinical and radiological information is consistent with a confident diagnosis of IPF.

A further multicentre study showed that clinicians at expert centres that were provided with radiological and histopathological data, had an 87.2% overall accuracy in diagnosing IPF. However, interobserver agreement between radiologists and pathologists remain moderate to fair (k = 0.40 and k = 0.30 respectively) for the presence of UIP [126]. It is important to note that early studies investigating the concept of multidisciplinary discussion in the diagnostic ILD algorithm were limited to expert centres with ILD expertise. This was evident in a subsequent study showing a higher final diagnostic agreement among academic clinicians when compared to community-based clinicians [127]. More recently, another international study comparing the diagnosis of IPF made by non-academic clinicians, university-affiliated clinicians and an international panel of IPF experts, also showed that the number of IPF diagnosis and high confidence cases were significantly higher among experts and university-affiliated clinicians compared to other, non-academic clinicians. While attendance at MDM meetings was not necessarily associated with more frequent IPF diagnosis, the diagnostic agreement for a first-choice diagnosis of IPF was lowest in clinicians without access to an MDM. Furthermore, the study showed that non-university hospital clinicians with over 20 years of experience and those who attended weekly MDMs, showed near expert level prognostic accuracy in diagnosing IPF [128].

In the 2013 international clinical guideline update on IIP, ILD MDM remained an essential diagnostic component for IIPs. While the benefits of an MDM discussion for the diagnosis of ILD have previously been shown, there are several aspects revolving the concept of MDM as a diagnostic tool for ILD that remain unanswered and require further studies. These include but are not limited to a lack of consensus on a clear outline for the purpose and role of an MDM in the diagnosis of ILD, the prerequisite composition of its member participants and the governance structure of the MDM. A multinational study by Walsh et al. showed only a

moderate overall inter-MDM agreement for the first choice ILD diagnoses (k = 0.50) among seven different MDMs made to evaluate the same cohort of cases independently [128]. Additionally, despite a good agreement for the diagnostic likelihood of IPF (weighted k = 0.73), this was only moderate and fair for non-specific interstitial pneumonia (NSIP) (weighted k = 0.42) and hypersensitivity pneumonitis (weighted k = 0.29). Another study by Jo et al. surveyed 10 international ILD MDMs and showed significant heterogeneity with regards to their membership, logistical organisation, governance and clinical data outcomes [129].

Taken together, there appears to be a need for further standardisation on the ILD MDMs. Despite this, the ILD MDM has solidified its role for the diagnosis of ILD in both real-world care and clinical research (Figure 1.5). Further research is very much needed to further evaluate the role and best practices of ILD MDMs to ensure consistent and accurate ILD diagnoses are made. Chapter three of this thesis describes a Delphi analysis among international ILD experts on essential features for the optimal running of an ILD MDM.

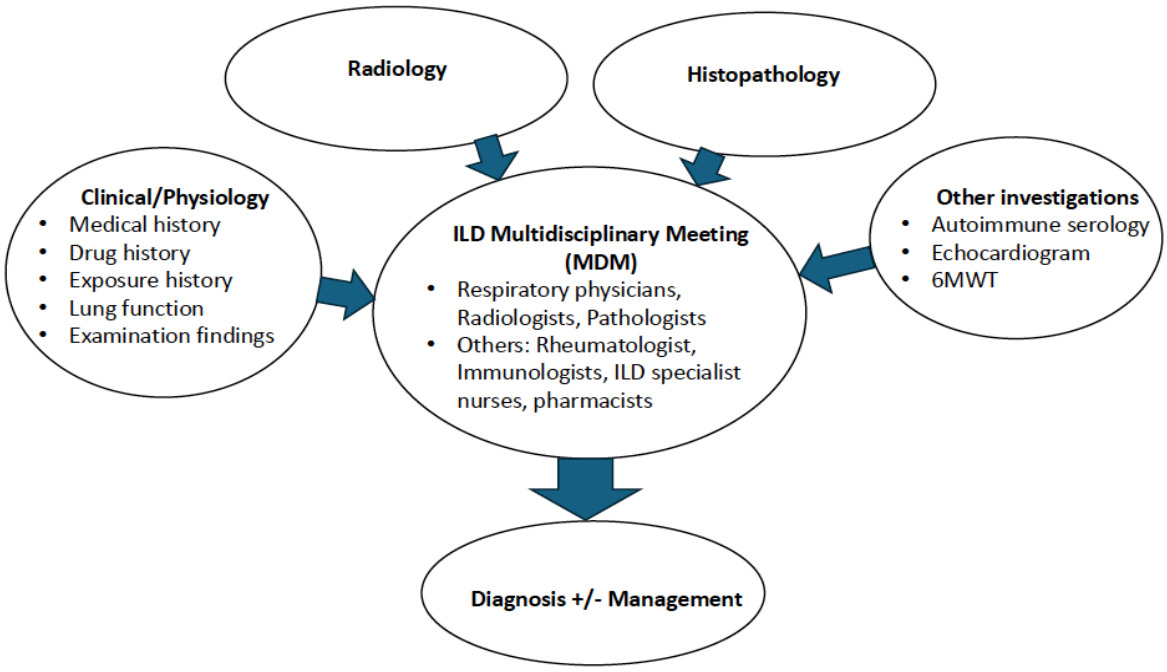

Figure 1.5. General concept of the interstitial lung disease multidisciplinary meeting (MDM). 6MWT: six-minute walk test.

1.9 Management of Idiopathic Pulmonary Fibrosis

1.9.1 Pharmacological Agents

Treatment options for IPF have historically been limited with studies on numerous agents disappointingly returning with negative results. These included classes of medication such as pulmonary vasodilators, antioxidants and immunomodulatory agents [32, 130, 131, 132, 133]. The IFIGENIA trial introduced the concept of combination regimes and showed that high dose N-acetylcysteine (NAC) when added to prednisone and azathioprine significantly slowed the decline in both vital capacity (VC) and DLCO when compared to the placebo arm of just prednisone and azathioprine [134]. However, such combination therapy approaches when evaluated in the PANTHER trial investigating the use of prednisone, azathioprine and NAC showed both a lack of clinical benefit and a harmful signal with increased risk of death and hospitalisation [80]. The study was stopped early due to findings of an increased mortality rate in the triple therapy arm of 10%, compared to just 1% in the placebo arm. A further study of NAC versus placebo also showed disappointing results [135].

1.9.1.1 Antifibrotic Therapy

The development of antifibrotic therapies as treatment options for IPF were years in the making and came to the forefront following landmark studies in 2014. The two agents, pirfenidone and nintedanib, carried such impact in the management of IPF, they have both been included as recommended treatment in the recent IPF clinical practice guidelines.

1.9.1.1.1 Pirfenidone

Pirfenidone, or 5-methyl-1-phenyl-2-(1H)-pyridone is an orally available and active small molecule comprised of a modified phenyl pyridone. While the exact mechanism of action is not entirely known, it has demonstrated antifibrotic activity in animal and bleomycin model of fibrosis studies through the inhibition of proteins and cells responsible for the accumulation and deposition of ECM [136, 137]. It's antifibrotic properties are show in some studies to be at least in part, through the modulation of cytokines and growth factors such as transforming growth factor – beta (TGF-B), basic fibroblast growth factor (bFGF) and tumour necrosis factor-alpha (TNF-a) [138, 139]. These effects have also been demonstrated across multiple organ system in vivo animal models and cell-based assays [140].

Pirfenidone first made its way into clinical use in an open-label, prospective phase II study in patients with severe IPF. Consecutive patients with ongoing deterioration despite conventional therapy or those who could not tolerate them, were treated with oral pirfenidone. Study results were encouraging and showed stabilisation in patients whose lung functions were progressively declining before treatment initiation. Additionally, adverse effects from pirfenidone were described as being relatively minor [141]. Following this pilot study, two Japanese phase III studies further investigated the effect of pirfenidone in IPF. The first study showed a significant reduction in vital capacity (VC) decline in patients receiving pirfenidone, despite the study being stopped prematurely due to increased incidences of acute exacerbations in the placebo arm [142]. The other randomised, double blind, placebo-controlled study showed similar findings, with patients receiving 1800mg/day of pirfenidone had a significantly lower decline in VC ($p=0.0416$) at 52 weeks and a better progression-free survival ($p=0.028$) [143].

The CAPACITY (Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes) programme further evaluated the effect of pirfenidone in IPF. Two large, multinational, randomised, double-blind, placebo-controlled phase III trials, CAPACITY 1/study 004 (NCT00287729) and CAPACITY 2/study 006 (NCT00287716), were simultaneously run [144]. Patients with mild to moderate IPF (FVC ≥ 50% and DLCO ≥ 35%) were eligible for the study and the primary efficacy endpoints of interest was the change in percentage of predicted FVC from baseline up to week 72. A host of secondary outcomes were listed including categorical FVC, progression-free survival, worsening idiopathic pulmonary fibrosis, dyspnoea and functional status and percentage of predicted DLCO changes. While both trials were performed separately with their respective cohorts and CAPACITY 1 studying two treatment arms with different doses, they were of similar design. Interestingly, despite similarities between both studies, the results were different. In CAPACITY 1, the primary endpoint was met with FVC -8.0% in patients receiving pirfenidone 2403mg/day versus -12.4% in patients on placebo groups (35% relative reduction, p=0.001). Progression-free survival defined as the time to confirmed ≥10% decline in percent predicted FVC, ≥15% decline in percent predicted DLCO or death, also improved with a hazard ratio (HR) of 0.64, 95% CI 0.44 to 0.95, p=0.023). However, in CAPACITY 2, the study failed to meet the primary endpoint (FVC -9.0% versus -9.6% in pirfenidone treatment and placebo arms respectively, p=0.501), but a significant treatment effect was evident at every timepoint between week 12 until week 48 of the study. No significant effect on progression-free survival was seen. Nonetheless, pooled analysis of the primary endpoint still showed a significant difference in treatment effect with a mean change in FVC of -8.5% in the pirfenidone 2403mg/day arm versus -11.0% in the placebo arm (p=0.005). Pooled data showed that progression-free survival was prolonged by 26% compared to placebo (HR 0.74, 95% CI 0.57 to 0.96, p=0.025). Furthermore, there was an absolute difference in pooled 6-minute walk

distance of 24m (-52.8m versus -76.8m in pirfenidone and placebo groups respectively, p=0.0009) which was clinically meaningful.

While the study was well-received and an independent Cochrane Collaboration meta-analysis which included the CAPACITY trials and the two Japanese phase III studies, showing a significantly better progression-free survival time, a further study was requested by the Food and Drug Administration (FDA) in light of the mixed results seen in the CAPACITY trials [145]. To confirm the effect and support the approval of pirfenidone for the treatment of IPF, the ASCEND (Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis) trial was performed [146]. The study was another large, multinational, placebo-controlled, randomised phase III clinical trial which included patients with FVC 50-90% predicted and DLCO 30-90% predicted, an FEV1/FVC ratio ≥ 0.80 and a 6-minute walk distance of ≥ 150m. These minor modifications of eligibility criteria were chosen to allow enrolment of patients with an increased risk of disease progression. Procedures for diagnosis, spirometry and adjudication of deaths were also centralised and the study duration was reduced to the 'standard' 52-week period. The proportion of patients with a ≥10% decline in FVC% predicted or who died, was reduced by 47.9% in the pirfenidone arm compared to placebo while the proportion of patients without an FVC% predicted decline was increased by 132.5% when compared to placebo. Treatment effect was once again seen from week 13 and increased for the duration of the study with a mean FVC decline of 235ml in the pirfenidone group compared to 428ml in the placebo group (relative difference 45.1%, P=0.001). A reduction in the decline in 6-minute walk distance and an improvement in progression-free survival was also seen with patients receiving pirfenidone. While all-cause mortality rates were not significantly different in this study, pre-specified pooled analysis of ASCEND and CAPACITY studies showed that

pirfenidone reduced the risk of death from all causes at 1 year by 48% (HR 0.52, 95%CI 0.31 to 0.87, p=0.01) and IPF-related mortality by 68% (HR 0.32, 95% CI 0.14 to 0.76, p=0.006)

Early meta-analysis of pirfenidone clinical trials showed significantly higher rates of nausea, dyspepsia, diarrhoea, fatigue, rash and photosensitivity with significantly more frequent treatment withdrawals when compared to placebo [147]. However, a comprehensive study comprising patients across the phase III CAPACITY studies and two open-label studies evaluated 789 patients with a median duration of 2.6 years and cumulative exposure of 2059 person exposure sure. Gastrointestinal and skin-related adverse events were found to be the most common such as nausea (39.9%), diarrhoea (29.3%), dyspepsia (20.8%) and rash (26.4%). While such events were reportedly frequent, majority of them are mild in nature and less than 3% result in treatment discontinuation. Hepatic transaminitis (3x ULN) was only noted in 2.7% of patients [148]. A further study which also included patients recruited onto the ASCEND trial showed similar rates of adverse events, with incidences reducing after the initial 6-month period and most being reversible [149]. Overall, pirfenidone appears to be safe and well-tolerated for the treatment of IPF.

1.9.1.1.2 Nintedanib

Previously known as molecule BIBF 1120, nintedanib is a small molecule tyrosine kinase inhibitor, also known as a triple angiokinase inhibitor by inhibiting three major signalling pathways involved in angiogenesis. Platelet-derived growth factor (PDGF), vascular-endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are mitogenic factors heavily involved in tumour angiogenesis, ECM proliferation and fibrogenesis [150]. BIBF 1120 targets multiple receptors including PDGFR – a and b, VEGFR 1-3 and FGFR 1-3. While

initially studied for its antiangiogenic properties for the treatment of solid organ malignancies such as non-small cell lung cancer, it demonstrated antifibrotic properties by attenuation of PDGF or FGF-stimulated migration of lung fibroblasts and inhibited TGF-B-induced myofibroblastic transformation in primary human lung fibroblasts derived from IPF patients. Total lung collagen was also reduced in mouse models treated with BIBF 1120 [151, 152, 153].

The TOMORROW trial was a phase II randomised, placebo-controlled, dose-finding trial of nintedanib for the treatment of IPF [154]. The study included 432 patients with IPF who were randomly assigned to four treatment arms with varying doses (50mg daily, 50mg twice daily, 100mg twice daily and 150mg twice daily) or a placebo group. The primary study endpoint of the annual rate of decline in FVC was 0.06L (95% CI -0.14 to 0.02) in the 150mg twice daily arm compared to 0.19L (95% CI -0.26 to -0.12) in the placebo arm. Using a pre-specified hierarchical test without correction for multiplicity, 150mg twice daily arm was significantly superior compared to placebo with a 68.4% reduction in the annual rate of decline. Additionally, the 150mg twice daily dose also resulted in significantly fewer patients with an FVC decrease of >10% or >200ml (24%), when compared to patients in the placebo group (44%). Patients receiving nintedanib 150mg twice daily also showed a small reduction in the total St George's Respiratory Questionnaire (SGRQ) scores from baseline indicating a better quality of life compared to the placebo group (-0.66 versus 5.46 points, p=0.007). Lastly, the incidence of acute exacerbations was lower in those receiving nintedanib 150mg twice daily than the placebo group (2.4 versus 15.7 per 100 patient-years, p=0.02).

The landmark INPULSIS 1 and 2 trials were two replicate phase III randomised, placebo-controlled studies that concurrently assessed the efficacy and safety of nintedanib 150mg twice daily in a total of 1066 patients with IPF [155]. The primary endpoint was the annual rate of FVC

decline and key secondary endpoints were the time to the first acute exacerbation of IPF and the change in total SGRQ score from baseline. Both INPULSIS 1 and 2 showed significantly lower annual rates of FVC decline in those treated with nintedanib compared to placebo (difference of 125.3ml/year and 93.7ml/year respectively). Additional pre-specified pooled analysis showed significantly more patients in the nintedanib group than in the placebo group had an 'FVC response', which was defined as an FVC decline < 5% and < 10% points. However, there were no significant differences seen in the adjusted mean change in total SGRQ scores or the time to the first acute exacerbation.

In both clinical trials, the most common adverse events from nintedanib were reported to be gastrointestinal in nature, including diarrhoea, nausea and vomiting [154, 155]. While these were the most common reasons for treatment discontinuation, nintedanib remained well tolerated with majority of events reported to be only mild in severity. In both INPULSIS trials, elevations in hepatic transaminases >3x ULN were infrequent (4.9% and 5.2% respectively). The open-label extension period of the trials (INPULSIS-ON) showed no new safety signals [156]. Diarrhoea remained the most experienced adverse event, which led to treatment discontinuation in only 5% of patients continuing on nintedanib and 10% in those commencing treatment in the open-label period. Post-marketing surveillance data in the USA showed the incidence of diarrhoea was 1053 per 1000 patient-years, lower than the reported rate in the INPULSIS trials [157]. Bleeding adverse events stemming from its mechanism of action on vascular endothelial growth factors appear to be lower in post-marketing data, with most events described to be mild and occur more frequently with concomitant anticoagulation therapy. A further study using four years of global pharmacovigilance data show that the overall safety profile of nintedanib to be similar to clinical trial data with no new concerns identified [158].

1.9.2 Non-Pharmacological Approaches

1.9.2.1 Pulmonary Rehabilitation

While the impact of antifibrotic therapies on the management of IPF cannot be disputed, IPF remains a progressive disease that continue to cause symptomatic exertional dyspnoea and markedly reduced exercise tolerance, eventually leading to poor health-related quality of life. This is evident in both recent landmark trials with both nintedanib and pirfenidone failing to show a significant improvement in St George's Respiratory Questionnaire and University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) scores respectively [146, 155]. Pulmonary rehabilitation is defined as a comprehensive intervention which includes exercise training, education and behavioural changes. It usually involves a thorough patient assessment enabling an individualised approach to improve both physical and psychological status of patients living with chronic respiratory diseases [159]. Exercise training forms the core component of pulmonary rehabilitation and encompasses endurance, resistance, interval and upper limb training. While the benefit of pulmonary rehabilitation studied in mostly chronic obstructive pulmonary disease (COPD) patients, early randomised trials demonstrated short-term improvements in functional exercise tolerance, dyspnoea and quality of life in ILD [160, 161]. While such benefits may seem smaller in magnitude compared to COPD patients, such improvements may remain clinically significant in progressive diseases with limited treatment options, such as IPF [162]. A real-world study found similar completion rates and magnitude of response when comparing IPF patients with COPD patients receiving pulmonary rehabilitation.

In a IPF subgroup analysis from an updated Cochrane review of randomised controlled trials of pulmonary rehabilitation in ILD, there was moderate certainty evidence that pulmonary

rehabilitation yielded a mean difference of 37.25 meters in 6-minute walking distance (95% CI 26.16 to 48.33; 278 participants) and -7.91 points in total SGRQ scores (95% CI -10.55 to -5.26; 194 participants) [163]. Pulmonary rehabilitation may also reduce dyspnoea with a standardised mean difference of -0.41 (95% CI -0.74 to -0.09; 155 participants), although evidence is of low certainty. The ATS/ERS/JRS/ALAT international IPF guidelines previously made a weak recommendation for pulmonary rehabilitation to be offered as treatment to patients with IPF but recognised that it may not be reasonable for some people and that the long-term benefit of pulmonary rehabilitation remains unclear. Further research is needed to explore long term outcomes of pulmonary rehabilitation in the management of IPF.

1.9.2.2 Supplemental Oxygen Therapy

In animal models, chronic intermittent hypoxaemia during sleep have been linked to increased oxidative stress, chronic inflammation. Further disruption of oxygen homeostasis is associated with maladaptive cardiovascular and respiratory sequalae such as the development of secondary pulmonary hypertension and worsening pulmonary fibrosis [164, 165]. Studies have also shown that nocturnal hypoxaemia is associated with poorer survival in ILD [166, 167, 168]. There are relatively few studies investigating the effect of supplemental oxygen therapy in IPF and it is unknown if the prevention of hypoxaemia truly reduces mortality risk.

Despite international IPF management guidelines making a strong recommendation that patients with clinically significant resting hypoxaemia should be treated with supplemental oxygen, it was acknowledged that evidence was of low quality and extrapolated from two large COPD trials showing a survival benefit [33, 169, 170].

A previous systematic review identified only 12 studies evaluating the impact of oxygen therapy in people with ILD [171]. The quality of evidence was limited by mostly retrospective studies, while many were likely plagued by selection bias and lack of blinding. While few randomised controlled trials show a positive impact of short-term oxygen therapy on exercise performance, participant numbers were low. Furthermore, short term studies showed no consistent effect of oxygen therapy on dyspnoea. Similarly, a Cochrane meta-analysis found insufficient evidence to support the use of ambulatory oxygen in ILD due to the limited number of available studies [172]. A multicentre prospective, open-label, mixed-method, crossover randomised controlled trial (AmbOx, NCT02286063) recruited fibrotic ILD patients across three sites in the United Kingdom who were not hypoxic at rest but demonstrated exertional oxygen desaturation below 88% on a 6MWT, randomising them to receive either portable oxygen or placebo air for two-week periods [173]. The aim of the trial was to evaluate the effect of ambulatory oxygen treatment on health-related quality of life in patients with fibrotic ILD, following evidence demonstrating that hyperoxia improved exercise tolerance and endurance while also reducing dyspnoea in ILD patients [174, 175]. The study showed improvements in King's Brief Interstitial Lung Disease questionnaire (K-BILD) scores in patients receiving ambulatory oxygenwith a mean difference (MD) in breathlessness scores of 3.7 points (95% CI 1.8 to 5.6, p<0.0001), activity scores (MD 8.6, 95% CI 4.7 to 12.5, p<0.0001) and chest symptoms (MD 7.6, 95% CI 1.9 to 13.2, p=0.009) but failed to show a significant improvement in psychological subdomain scores (MD 2.4, 95% CI -0.6 to 5.5, p=0.12). Further studies such as the PFOX study (NCT03737409) are currently underway aiming to compare the clinical efficacy and cost-effectiveness of ambulatory oxygen versus ambulatory air in patients with fibrotic ILD [176]. In addition to the small body of evidence to date to guide oxygen treatment for IPF, it is noteworthy that other factors can influence the patients' experience on such therapies. Treatment expectation of symptomatic relief and physical benefits, psychosocial stigma and

fear of dependence along with the cost, size and manoeuvrability of portable oxygen delivery devices are among such factors [177]. Hence, careful balancing of these variables are needed in individualised management of patients living with IPF.

1.9.2.3 Lung Transplantation

Notwithstanding the therapeutic advances for IPF in the last decade, a cure remains elusive for this progressive disease. Currently, lung transplantation remains the only definitive and curative option. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation (ISHLT) previously noted that lung transplantation for idiopathic interstitial pneumonias accounted for 26.1% of the total number of transplantation globally, of which have been increasing since the 1990s. Median post-transplant survival for IIP was reported to be 5.2 years while other ILDs transplanted between 1992-2017 was 6.7 years, with these generally improving in recent years [178, 179]. Analysis from the United Network for Organ Sharing database in the US showed improved survival rates in IPF lung transplant recipients in the era of 2010-2014 when compared to the 5-year period before (HR 0.83, 95% CI 0.76 to 0.91) despite an aging population with more severe disease and more comorbidities [180]. The ATS/ERS/JRS/ALAT clinical guidelines for management of IPF made a strong recommendation for appropriate individuals to undergo lung transplantation but recognised huge variations among lung transplant programs eligibility [33].

The international IPF guidelines also acknowledged the lack of data to help guide clinicians on the best timing for a referral to be made to a lung transplant centre. Previously, evidence of disease progression by means of serial lung function decline were proposed as simple criteria triggering a referral to a lung transplant unit [181]. Potential weaknesses of this approach include

the need for time to monitor for progression, the risk of missing the closing window of opportunity of intervening early and the heterogeneity of disease behaviour among IPF patients. An ISHLT consensus document for the selection of lung transplant candidates recommended that ILD cases should be referred at the time of diagnosis, regardless of disease severity [182]. The presence of hypoxia, dyspnoea and functional limitation should also trigger an early assessment referral for the suitability of lung transplantation. Unfortunately, the eligibility for lung transplantation is not uniform and as such, not every patient with IPF will be amenable to one. Absolute contraindications include a recent history of malignancies, presence of other untreatable end-organ disease, uncorrected atherosclerotic disease with suspected organ ischaemia, acute medical instability, uncorrectable bleeding diathesis, chronic infections with highly virulent or resistant microbes, active mycobacterium tuberculosis infection, significant chest wall or spinal deformity, obesity (BMI>35kg/m^2), history of non-adherence to therapies, psychiatric conditions rendering the inability to adhere to medical or allied health therapies, inadequate social support structures and lastly, poor functional status with poor rehabilitation potential.

1.9.2.4 Palliative Care and Psychological Support

For IPF patients who are ineligible for lung transplantation, current therapeutic options with antifibrotic therapies do not curb the progressive and often debilitating symptoms of dyspnoea, cough and fatigue. Palliative care defines a field focusing on the management of such symptoms with the aim of improving quality of life while developing support structures which integrates psychosocial and spiritual aspects of patient care [183]. An important aspect of palliative care is that such concepts should be introduced relatively early during the management process, rather than near the end of life. However, individualised discussion in a shared decision-making

process is needed given the highly sensitive nature and potential social stigma commonly attached to terminal disease and death [184].

1.9.3 Management of Comorbidities

1.9.3.1 Coronary Artery Disease

Studies have shown an increased prevalence of coronary artery disease (CAD) in patients with IPF, ranging up to 68% [185]. Risk factors for both conditions are strikingly similar, including male gender, older age and a smoking history. More importantly, the presence of CAD in patients with IPF is associated with poorer survival (HR 3.30, 95% CI 1.11 to 9.83) with a median survival of merely 572 days following left heart catheterisation [185]. Despite the significant association, patients with lung disease in general have been found to be less likely to receive coronary artery revascularisation. Taken together, early recognition of the coexistence of CAD is important in the management of IPF. Studies have highlighted the value of coronary artery calcification grading using routine CT scans used in the diagnosis of IPF. The presence of moderate to severe coronary artery calcification had a high sensitivity and specificity in detecting CAD [186]. Implementation of strategies to tackle known reversible risk factors for CAD such as hypercholesterolemia and tobacco smoking, are also important.

1.9.3.2 Pulmonary Hypertension

Pulmonary hypertension (PH) is a known complication in IPF with a prevalence range of 3 to 86%, and a greater prevalence with advanced and end stage disease. Its true prevalence is unknown as right heart catheterisation, the current gold standard method of diagnosis is not

routinely performed. Furthermore, the more readily available transthoracic echocardiogram is often plagued by limited accuracy in the setting of IPF [187]. Its presence is often associated with increased mortality risk (HR 4.03, 95% CI 1.17 to 27.9, p=0.03) when combined in the presence of coexisting emphysema [188]. However, a smaller study showed no significant association with poorer survival in IPF patients [189]. Nonetheless, patients with coexisting PH are known to have significantly worse physiological impairment in diffusing capacity and poorer ventilatory efficiency, ultimately leading to significantly reduced exercise capacity and poorer quality of life [190].

There are unfortunately, no current approved therapeutic options for PH related to IPF in Australia. Clinical trials of agents commonly used in Group 1 pulmonary arterial hypertension such as sildenafil, bosentan, macitentan, ambisentan and riociguat have all failed to demonstrate efficacy in this condition [133, 191, 192, 193, 194]. However, a recent multicentre randomised control study on inhaled treprostinil for the treatment of PH related ILD showed improved 6MWD, a reduction in NT-proBNP levels and reduced rate of clinical worsening, when compared to placebo [195]. Post-hoc analysis showed a more significant improvement in lung function in IPF patients, suggesting it as a promising therapy for PH related to IPF [196]. As such, a trial is currently underway to further investigate the effect of inhaled treprostinil in IPF [197].

1.9.3.3 Emphysema/ Chronic Obstructive Pulmonary Disease

With the common risk factor of smoking, the prevalence of coexisting emphysema ranged from 6 to 67% [198]. The presence of both emphysema and pulmonary fibrosis was described in 2005 as combined pulmonary fibrosis and emphysema (CPFE), in which patients had radiological findings of upper zone emphysema and lower zone fibrosis. Lung function in these patients

were different from that of IPF or those with emphysema alone, where the presence of both often led to preserved lung volumes (TLC) but a significantly impaired gas transfer capacity (DLCO) [188]. CPFE is associated with poorer survival than those with emphysema alone. However, the evidence for mortality is somewhat mixed when compared to IPF, where some studies have noted poorer survival while some showed no significant difference when compared to patients just with IPF. CPFE remains poorly understood with variable terminology and diagnostic criteria being used. A recent international research task force proposed a criteria for a clinical syndrome based on emphysema extent of at least 15% of total lung volume and a disproportionate decrease in DLCO, while acknowledging that further research is needed to refine the criteria [199].

There is paucity of controlled data to inform specific treatment for CPFE. Currently, antifibrotic therapies are used since the landmark trials were published. However, given the unique physiology of IPF, more specifically the preserved FVC and slow rate of decline, there is a further need to study CPFE as a separate entity. For now, treatment is very much individualised based on the phenotype of patients, in which inhaled bronchodilators and corticosteroids may be used [199].

1.9.3.4 Lung Cancer

US and UK insurance claims and electronic medical record analyses show a prevalence of lung cancer to be 3-4% while others containing autopsy data in Asia elevate this rate to up to 23% [198]. Prevalence rates are often difficult to ascertain and often confounded by smoking, variable follow-up times, cancer types, stages and treatment. Median survival in patients with both lung cancer and IPF were shorter when compared to those with just IPF with a HR for death of 2.4

(95% CI 1.4 to 4.3, p=0.002) [200]. A retrospective Japanese study also showed that histopathological finding of IPF to be a significant negative prognostic factor for post-operative mortality and long-term survival in primary lung cancers undergoing surgical resection [201]. The coexistence of IPF may also limit the safety of potential therapeutic options for lung cancer. Studies on antifibrotic appear to be safe when used with lung cancer treatment and may even have a synergistic effect [202, 203] but further studies are needed.

1.9.3.5 Sleep Disordered Breathing

Sleep disordered breathing (SDB) is commonly observed in IPF patients with ranges of up to 91% [168, 204, 205]. As one would expect, obstructive sleep apnoea (OSA) were more common in patients with a higher BMI. Nocturnal hypoxaemia is also prevalent in IPF patients likely due to alveolar hypoventilation, ventilation and perfusion mismatch and apnoeas associated with OSA. Untreated, comorbid nocturnal hypoxaemia can be significantly associated with higher mortality risk in patients with IPF [167, 168]. Hence, further investigation and appropriate treatment is needed for SDB in patients with IPF to negate the development of secondary pulmonary hypertension (PH) and improve quality of life. Unfortunately, the standardised Epworth Sleepiness score (ESS) is a poor screening tool and has a poor sensitivity of identifying the presence of underlying OSA/SDB in the IPF population. Polysomnography can be considered in IPF patients deemed at potential risk of having OSA but referrals are often limited by available resources. Nonetheless, treatment with continuous positive airway pressure (CPAP) should be considered in IPF patients with comorbid OSA.

1.9.3.6 Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GORD) is defined as non-physiological aspiration of stomach contents leading to troublesome symptoms or complications of oesophagitis. Accurate diagnosis is difficult given the subjective and variable nature of symptoms. Gastroscopy or 24-hour ambulatory pH monitoring are commonly used for the diagnosis of GORD but findings of injury are not always present or in concordance with reported symptoms [206, 207]. While studies have suggested a higher prevalence of GORD in IPF patients compared to the general population, the causal relationship of GORD and IPF is not well defined and has been a contentious issue over the last few years. A recent bi-directional two-sample mendelian randomisation study showed that GORD increased the risk of IPF with an OR of 1.6 (95% CI 1.04 to 2.49, p=0.032).

Antacid therapies such as proton pump inhibitors (PPIs) are commonly used for the treatment of GORD. Studies have previously shown that treatment with PPIs in IPF was associated with a slower decline in FVC, fewer acute exacerbations and improved survival [208, 209]. However, other post-hoc studies have shown no benefit from antacid therapies over placebo in patients following treatment with nintedanib and pirfenidone [210, 211]. The current updated international guidelines made a conditional recommendation for the use of antacid therapies for the purpose of treating GORD symptoms and against the use of antacid therapy for the purpose of seeking an improvement in respiratory-related outcomes [35].

1.10 Acute Exacerbation of IPF

An attempt at a standardised approach to defining acute exacerbation (AE) of IPF was described in 2007, with the proposed criteria including subjective worsening over 30 days or less, new bilateral radiographic infiltrates and opacities in the absence of infection or other identifiable aetiology [212]. More recently, an international task force defined AE of IPF as an acute, clinically significant respiratory deterioration characterised by new, widespread alveolar infiltrates, not explained by cardiac failure or fluid overload [213]. While the aetiology of AE is often uncertain, many are likely triggered by infections or micro-aspirations. Risk factors for having an AE of IPF include physiologically worse disease, specifically lower FVC and DLCO [214, 215]. The prognosis of AE of IPF is generally poor. Median survivals have been shown to be only approximately three to four months with a 90-day mortality rate of up to 50% and AE of IPF accounting for 40% of IPF deaths [54, 216]. A recent meta-analysis identified that long term supplemental oxygen at baseline (adjusted HR 2.52, 95% CI 1.68 to 3.80), a diffuse radiological pattern (adjusted HR 2.61, 95% CI 1.32 to 2.90), and corticosteroid use prior to hospitalisation (adjusted HR 2.19, 95% CI 1.26 to 3.82) [217].

Despite the significant impact of AE of IPF, there remains no effective treatment. Moreover, there is significant global variability and no standardized management approach. For example, the previous ATS/ERS guidelines for the management of IPF cautioned against the use of mechanical ventilation for the treatment of respiratory failure due to IPF given the strikingly high mortality rates of above 80-90% but conceded with a weak recommendation on low quality evidence, that it may be used in a minority of patients [33]. Yet despite this, a recent US-based health database found that 21% of critically ill patients with a severe AE of IPF received invasive mechanical ventilation [218]. Ultimately the decision for mechanical ventilation is often

individualised and may be appropriate for specific situations following identification and treatment for specific reversible causes of AE of IPF and a bridge to lung transplantation [213, 219].

Most management strategies revolve around engagement of supportive and palliative care for symptom burden management, supplemental oxygen for hypoxaemia and broad-spectrum antibiotics to cover possible infections. While corticosteroids are often used in AE of IPF, there is still a lack of randomised controlled data to support this approach. Based on anecdotal evidence, the ATS/ERS management guidelines have given a weak recommendation for the use of corticosteroids in the majority of patients suffering an AE of IPF but was unable to provide specific recommendations on dosage, duration and route [33]. A recent retrospective study assessing in-hospital mortality, found that patients receiving corticosteroids were more likely to require ICU admissions and/or mechanical ventilation. While it may be possible to assume that the need for ICU-level care indicates more severe disease, the significantly reduced survival in those receiving corticosteroids (HR 6.17, 95% CI 1.35 to 28.14, p=0.019) begs the question as to whether corticosteroids are truly beneficial or harmful in AE of IPF. Other pharmacological approaches with immunosuppressive agents such as cyclophosphamide, tacrolimus, rituximab combined with plasma exchange and intravenous thrombomodulin have been described but there is insufficient evidence supporting routine clinical use [220]. There is some evidence to support the use of nintedanib to prevent occurrence of AE of IPF while data on pirfenidone are less robust in showing its effect on reducing risk of AE of IPF [215, 221].

1.11 Staging and Prognosis

The purpose of any staging system is a method able to identify patients most at risk of poor outcomes and predict prognosis, and in turn guide an appropriate management strategy. In the case of IPF, this may be the decision and initiation of antifibrotic therapies, referral for consideration of a lung transplant or conversely, the timing of end-of-life care discussions and referral to a palliative care service. To date, there is no standardised staging system that has been agreed upon for IPF [33].

1.11.1 Clinical Course

A potential hurdle to the development of a standardised staging system for IPF is the variability of the natural history of IPF. While the overall trajectory of IPF is one marked by relentless disease progression and lung function decline, the clinical course of IPF is highly variable. The classic phenotype of IPF is a slowly progressive decline in lung function with a long lead time of subclinical disease. However, other known phenotypes include those with rapid deterioration and patients whose clinical course are characterised by periods of stability interposed with rapid decline and acute respiratory events, often requiring hospitalisation [222].

1.11.2 Individual Prognostic Predictors

International standardised diagnostic criteria for IPF and epidemiological studies have allowed recognition of several clinical prognostic predictors. For example, studies have shown that patients with a younger age, higher BMI and lower dyspnoea scores have better survival [223, 224, 225]. While IPF appears to be more common in male, there are mixed data regarding the

prognostic effect of gender [226, 227]. Lower baseline forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) have been associated with poorer survival but such lung function measurements are inherently subject to variable patient effort and technique [227, 228]. Furthermore, given the vastly variable clinical course of IPF and other potential coexisting diseases such as emphysema, a true baseline lung function test may be difficult to ascertain and cannot be standardized across an entire cohort of patients. Instead, clinical trials have used serial changes in FVC and DLCO as study endpoints. Serial decline in FVC and DLCO have previously been shown to be associated with increased mortality [166, 229]. Radiological and histopathological features have also been shown to be important prognostic factors in IPF. The presence on honeycombing and traction bronchiectasis on CT imaging are associated with poorer prognosis [230, 231, 232]. However, the utility of serial changes on CT imaging is limited due to the subjectiveness of interpretation and scoring of changes.

1.11.3 Composite Staging Score/Models

Composite staging scores allows the incorporation of clinical, radiological and physiological assessments to develop a prognostic predictive model, rather than relying on individual tests, where their accuracy could be confounded by coexisting diseases. However, the lack of a standardised meaningful disease endpoint coupled with ongoing debate on newer and more reliable endpoints, multiple composite staging scores have been developed.

1.11.3.1 Clinical, Radiographic and Physiological (CRP) Score

The original iteration of the clinical, radiographic and physiological (CRP) was developed almost four decades ago and incorporated several variables including dyspnoea, chest

radiography, spirometry, lung volume, diffusing capacity, alveolar-arterial oxygen tension difference and arterial oxygen saturation during exercise [233]. While the score correlated well with the extent of histopathological findings seen on open lung biopsies, it failed to consistently predict survival in IPF patients. An updated CRP scoring system included a simplified physiological component, derived from TLC and arterial oxygen levels on maximal exertion. Increasing age, smoking status, digital clubbing, extent of interstitial opacities and the presence of pulmonary hypertension on chest radiography were found to predict survival in this model [227].

1.11.3.2 Composite Physiological index

The Compositive physiological index (CPI) score was developed based on the extent of disease on a high-resolution CT (HRCT) chest [234]. The scoring system accounts for concomitant emphysema which is reportedly present in more than 20% of IPF patients and artificially confound lung function results. The CPI score was found to independently predict mortality, more so than other univariate variables and individual lung function indices, with a regression coefficient of 0.092 (95% CI 0.043 to 0.141, $p<0.05$).

1.11.3.3 GAP Index

The GAP index is a prediction model and is score by a combination of individual variables of age, gender and physiology (FVC% predicted and DLCO% predicted) [223]. The total score was then divided into three severity stage (I, II and III) (Table 1.11). Stage I represented a low-risk group with mortality rates ranging from 1-16%, stage 2 had mortality rates of 16-42% and finally, stage 3 represented high-risk group with mortality rates of 39-77%. A further iteration

of the model is the CT-GAP score, in which a CT fibrosis extent score was incorporated to replace DLCO, considering the increased availability of automated CT scoring systems and the fact that every patient with IPF would have had an initial diagnostic CT scan [235]. The alternate model provided comparable accuracy in predicting mortality when compared to the original version.

Table 1.11. GAP Index

	Predictor variable	Points
G (Gender)	Female Male	0 1
A (Age)	≤ 60 61 – 65 >65	0 1 2
P (Physiology)	FVC% predicted >75 50 – 75 <50	 0 1 2
	DLCO% predicted >55 36 – 55 ≤35 Unable to perform	 0 1 2 3
GAP Stage	Points	
I	0 – 3	Low risk
II	4 – 5	Intermediate risk
III	6 – 8	High risk

Adapted from [223]. FVC: forced vital capacity, DLCO: diffusing capacity of the lung for carbon monoxide.

1.11.3.4 Risk stratification score

The Risk stratification ScorE (ROSE) was developed to determine 3-year survival based on clinical features at the time of diagnosis and subsequently at six months after diagnosis [236]. Using the Medical Research Council Dyspnoea (MMRC) score >3, six-minute walk distance <72% predicted and CPI>41, patients were stratified into low, intermediate and high risk groups. In a prospective study of 70 patients, the model showed a sensitivity of 39% and a specificity of 100% at predicting 3-year survival. Validation of this scoring system was limited by small study numbers and lack of assessment for pulmonary hypertension.

1.12 Thesis Goals

Despite advances in knowledge on idiopathic pulmonary fibrosis (IPF), there are still much unknown and areas of uncertainties revolving the diagnosis and management strategies. The interstitial lung disease multidisciplinary meeting (ILD MDM) remains pivotal in the diagnosis of IPF, but much uncertainty remains on the key elements and components of an efficient ILD MDM. To date, there is no international guidelines on how an ILD MDM should effectively be conducted. In addition, there has been an ongoing momentum to identify new diagnostic and prognostic biomarkers for IPF in recent years.

The discovery of pirfenidone and nintedanib as novel antifibrotic therapies, heralds a new therapeutic era for IPF, one that has been elusive for decades. As the true aetiology of IPF is still unknown, it remains unclear as to how such agents elicit their antifibrotic effect in IPF. In Australia, both pirfenidone and nintedanib were approved for the treatment of IPF in 2017. Little is known on their efficacy and safety in an Australian population. Furthermore, given their novelty, there are no local guidelines to guide physicians on the use of these agents or how to incorporate them into the management of patients with IPF. The overall goal of this thesis is to study the diagnostic process of IPF and to explore the impact of antifibrotic therapies on the management landscape of IPF.

Chapter Two aims to identify and to seek consensus on the essential features of an ILD MDM, as an initial step towards potential standardisation. Chapter Three explores the role of monocytes as a possible prognostic biomarker for patients with IPF and to investigate the effect of antifibrotic therapies on pathogenic pathways of IPF. Chapter Four aims to summarise the available evidence for the efficacy and safety of antifibrotic therapies for IPF and also

additionally, ILD with a progressive pulmonary fibrosis (PPF). Chapter Five and Six investigates the prescription of antifibrotics, the management strategies along with patient and physician experiences in an Australian national cohort.

Chapter One References

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Chapter Two: Essential features of an Interstitial Lung Disease Multidisciplinary Meeting: An International Delphi Survey

Essential Features of an Interstitial Lung Disease Multidisciplinary Meeting

An International Delphi Survey

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Abstract

Rationale: The interstitial lung disease (ILD) multidisciplinary meetings (MDM), composed of pulmonologists, radiologists, and pathologists, is integral to the rendering of an accurate ILD diagnosis. However, there is significant heterogeneity in the conduct of ILD MDMs, and questions regarding their best practices remain unanswered.

Objectives: To achieve consensus among ILD experts on essential components of an ILD MDM.

Methods: Using a Delphi methodology, semi-structured interviews with ILD experts were used to identify key themes and features of ILD MDMs. These items informed two subsequent rounds of online questionnaires that were used to achieve consensus among a broader, international panel of ILD experts. Experts were asked to rate their level of agreement on a five-point Likert scale. An *a priori* threshold for consensus was set at a median score 4 or 5 with an interquartile range of 0.

Results: We interviewed 15 ILD experts, and 102 ILD experts participated in the online questionnaires. Five items and two exploratory statements achieved consensus on being essential for an ILD MDM following two questionnaire rounds. There was consensus that the presence of at least one radiologist, a quiet setting with a visual projection system, a high-quality chest high-resolution computed tomography, and a standardized template summarizing collated patient data are essential components of an ILD MDM. Experts also agreed that it would be useful for ILD MDMs to undergo an annual benchmarking process and a validation process by fulfilling a minimum number of cases annually. Twenty-seven additional features were considered to be either highly desirable or desirable features based on the degree of consensus. Although our findings on desirable features are similar to the current literature, several of these remain controversial and warrant further research. The study also showed an agreement among participants on several future concepts to improve the ILD MDM, such as performing regular self-assessments and conducting research into shared practices to develop an international expert guideline statement on ILD MDMs.

Conclusions: This Delphi study showed consensus among international ILD experts on essential and desirable features of an ILD MDM. Our data represent an important step toward potential collaborative research into future standardization of ILD MDMs.

Keywords: interstitial lung disease; multidisciplinary meeting; Delphi; Essential features

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A complete list of ILD MDM Dephi Collaborators may be found before the beginning of the References.

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Interstitial lung disease (ILD) is a heterogeneous group of disorders that cause varying degrees of lung parenchymal inflammation and fibrosis. Although there is an array of specific ILD diagnoses, the clinical presentations of ILD are protean, and the precise recognition of specific ILD groups remains difficult (1). Over the last two decades, there have been increasing efforts to improve the accuracy of the diagnostic pathway for these diseases. In 2002, the American Thoracic Society (ATS) and European Respiratory Society (ERS) released a joint statement on the classification of idiopathic interstitial pneumonia (2) recommending the use of a multidisciplinary meeting (MDM) that included a respiratory clinician, a radiologist, and a histopathologist at its core. These recommendations have been echoed in several subsequent guidelines and position statements (3–5).

The ILD MDM allows for integration of available clinical, radiological and pathological data with the aim of rendering an accurate ILD diagnosis. Flaherty and colleagues reported significantly increased interobserver diagnostic agreement and confidence when relevant clinical, radiological, and pathological data were dynamically exchanged in an MDM setting (6). This approach has also been validated in several other studies (7–9). Furthermore, the diagnostic performances of physicians regularly attending ILD MDMs, irrespective of experience level, were greater than those without access to these meetings (10), suggesting an educational benefit of ILD MDMs. Although these findings demonstrate the integral role of ILD MDMs as the "gold standard" role for ILD diagnosis, many questions regarding the best practice for ILD MDMs remain unanswered (10). Although current international guidelines are able to recommend the basic membership of an ILD MDM, little beyond that is known (11). The member composition, level of expertise required, the amount of patient data required, and whether all ILD cases should be discussed at the MDM are just few of the many ambiguities left unanswered. Several studies have described significant heterogeneity in the manner in which ILD MDMs are conducted, making it difficult to recommend a "minimum standard" (12, 13). Given these inconsistencies, an international standardized approach or guide for conducting ILD MDMs is required to ensure high-quality discussions on the diagnosis and management of ILD.

We conducted a Delphi survey among international ILD clinicians to explore the necessary components of the ILD MDM. The aim of the study was to achieve consensus among ILD clinicians regarding the key components of an ideal ILD MDM. The Delphi model is a well-described approach frequently used to establish consensus among various health professionals on topics where an established evidence base does not exist (14, 15). This approach provides participant anonymity, ensuring that each individual input carries equal weight.

Methods

To inform development of the Delphi survey, recognized experts in the field of ILD were invited by e-mail to participate in individual interviews to identify potential key features of ILD MDMs. These experts were identified from the professional contacts of T.J., J.M. and S.W. Invited experts also had contributed to the field of ILD by research publications, participation in thoracic societies research working groups, or clinical contribution to the care of patients with ILD in their respective centers of practice. We aimed to have a wide geographical representation (North America: C.R., D.L., H.C., and M.S.; South America: J.E. and M.M.; Europe: J.B., K.A., T.M., and V.C.; Asia: Y.K. and Y.I.; and Australia and New Zealand: D.C., N.G., and M.W.) to ensure diversity of each participant's local ILD MDM experience. The interviews were conducted either in person or over the telephone in a semi-structured format. A.T. conducted all interviews, which were guided by a list of open-ended questions (Table 1). The interviews were digitally recorded and transcribed verbatim. Two reviewers analyzed the transcripts independently. The transcripts were analyzed using a qualitative approach to content analysis, allowing for common themes to be extracted and be used to identify key items or features of an ILD MDM (16). These items were used to form a list of statements for the first round of the modified Delphi survey. These statements were organized into major domains, reflecting a variety of aspects involved in the efficient running of an ILD MDM. We invited a broader international panel of ILD experts with a range of clinical and research experience in the field of ILD to participate in the Delphi surveys. Participants were identified to be attending an ILD MDM on at least a monthly basis, having previously consented to further research involvement from a previous study (10). ILD experts who participated in the semi-structured interviews were excluded from subsequent survey rounds. The ILD experts were invited by e-mail to participate in each round of the Delphi survey.

We conducted a two-round web-based survey between July 2019 and February 2020 in accordance with defined standards of the Delphi methodology (17). The surveys were published in English on a secure online survey platform (Qualtrics, LLC). An online platform was chosen for the ease of disseminating surveys to an international group of participants and allowing responses to be collected within a short period of time. Consent to the study was implied if the participants completed the questionnaires. Participants completed a short baseline demographic section regarding their medical practice and experience prior to the surveys. In the first round, participants were asked to rate their level of agreement on a list of statements detailing key features of an ILD MDM using a five-point Likert scale. Each item was scored as 1 (strongly disagree), 2 (disagree), 3 (neutral), 4

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(agree), and 5 (strongly agree). Experts were allowed to provide feedback following each statement and could add statements they considered relevant if they were not included in the original list. An *a priori* threshold of consensus was defined for the study as a median score of 4 or 5 with an interquartile range (IQR) of 0 for an essential feature of an ILD MDM. An interquartile range of 0 ensures that the distribution of responses truly reflects agreement and excludes a bimodal distribution where a smaller but important proportion of respondents may disagree. A median score of 4 or 5 with an IQR of 1 was considered to indicate desirable features. Other statements that did not meet these criteria were considered as "disagreement". In round 2, participants were given the distribution of group answers for statements that did not reach consensus. Participant comments and feedback for each statement were also provided. Participants were then asked to once again rate their level of agreement on a five-point Likert scale for statements that did not reach consensus and any additional statements identified in round 1.

We reported the results of this study according to the proposed methodological standards for Delphi studies (17). Participant responses remained anonymous during result analysis. STATA version 15.1 (StataCorp) was used for all statistical analyses. The study was approved by the human research ethics committee of Royal Prince Alfred Hospital, Sydney (Protocol No X18–0354 and LNR/18/RPAH/497).

Results

Expert Qualitative Interviews

Fifteen of 17 (88%) invited ILD experts agreed to participate in the semi-structured individual interviews. All experts were based in ILD referral centers across nine countries with 13 (87%) being involved in weekly ILD MDMs. Common themes were identified from the interview transcripts and informed development of the Delphi surveys (Table E1). These were subsequently organized into five major domains, namely "MDM team structure", "MDM infrastructure", "MDM organization and administration", "MDM clinical decision-making process", and "Future concept and directions".

Table 1. Questions for initial expert interview guide

Questions
1. Could you describe your experience in the field of ILD and your involvement in ILD MDM(s)?
2. What do you think the role of the ILD MDM is?
3. Who do you think should be involved in the ILD MDM?
4. What do you think are the key elements in an ILD MDM?
5. How much preparation goes into the ILD MDM?
6. How do you come to a consensus for each case discussed at the MDM?
7. What do you think are challenges that ILD MDM commonly face?
8. How do you think an ILD MDM could improve itself?

Definition of abbreviations: ILD = interstitial lung disease; MDM = multidisciplinary meeting.

Delphi Survey Results

A total of 134 ILD experts were invited by e-mail to participate in the Delphi survey, of whom 102 (76%) from 29 countries completed the first Delphi round. Subsequently, 94 out of 102 (92%) responded in the second round. In total, 91% of the experts actively participated in an MDM at an ILD referral center and 97% reported that their MDMs were attached to a university or academic hospital. Their characteristics are presented in Table 2.

First Round

Out of the 50 statements that were included in the first Delphi round, consensus was reached for a total of 5 statements (median 4 or 5 and IQR 0) (Table 3). Experts agreed that the presence of at least one radiologist is essential for an ILD MDM to function. Experts also agreed that it is essential that the ILD MDM has access to a visual projection system allowing real-time viewing of radiological images and that a high-quality chest high-resolution computed tomography (HRCT) scan is required for the discussion of cases. The two remaining statements that met consensus were considered to be explorative statements rather than current features of ILD MDMs (Table 6). A total of 36 statements met the threshold for being desirable features of an ILD MDM (median 4 or 5 and IQR 1), and 9 statements that did not meet either threshold were labeled as "disagreement".

Second Round

Out of the 45 statements that did not reach consensus in the first Delphi round, 39 were taken forward into round 2 without alterations. Five statements were rephrased to improve clarity based on study participants' feedback, and one statement was divided into two questions to enable a more accurate rating. Participants' feedback in round 1 generated four additional statements. The final list for round 2 contained 50 statements.

Two further statements achieved the *a priori* threshold for consensus in the second round (Table 3). Experts agreed that it was essential for an ILD MDM to be conducted in a quiet setting, allowing for easy interaction among its members. There was also consensus that it was essential for the ILD MDM to summarize collated patient data and information onto a standardized template. A total of 27 statements met the *a priori* threshold for being desirable features of an ILD MDM with a median score of either 4 or 5 and an IQR of 1. These statements were further subcategorized based on the level of agreement among experts. A total of 10 statements with a median score of 5 were considered "highly desirable" features of an ILD MDM (Table 4), whereas 13 statements with a median score of 4 were listed as "desirable" features (Table 5). Similar to round 1, the remaining four statements describing future concepts of ILD MDMs were listed separately.

Concepts and Future Direction

A total of six statements from both Delphi rounds fulfilled criteria for either being essential or desirable, were conceptual, and explored possible methods of improving the quality of ILD MDMs (Table 6). There was consensus among the experts that MDMs undergoing an annual benchmarking process once an international minimum standard has been established would be a useful approach to improve ILD MDMs. Experts also agreed

Table 2. Expert characteristics

Characteristics	Delphi Survey	
Sex, F, *n*/total (%)	39/102 (38%)	
Specialty, *n* (%)	Pulmonologist	95 (93%)
	Radiologist	2 (2%)
	Research/academic	2 (2%)
	Other	3 (3%)
Years of experience, *n* (%)	<5 yr	9 (8.8%)
	5–10 yr	27 (26.5%)
	11–15 yr	25 (24.5%)
	16–20 yr	16 (15.7%)
	21–30 yr	19 (18.6%)
	>30 yr	6 (5.9%)
Referral center MDM, *n*/total (%)	93/102 (91%)	
MDM attached to university/academic hospital, *n*/total (%)	99/102 (97%)	
Frequency of MDM, *n* (%)	More than once/weekly	8 (7.8%)
	Weekly	55 (53.9%)
	Fortnightly	26 (25.5%)
	Monthly	10 (9.8%)
	Other	3 (3.0%)
Duration of MDM, *n* (%)	30 min	6 (5.9%)
	31–60 min	48 (47.0%)
	61–90 min	30 (29.4%)
	91–120 min	16 (15.7%)
	>120 min	2 (2.0%)
Number of cases discussed per meeting, *n* (%)	1–5 cases	38 (37.3%)
	6–10 cases	19 (18.6%)
	11–15 cases	4 (3.9%)
	16–20 cases	39 (38.2%)
	>20 cases	2 (2.0%)

Definition of abbreviation: MDM = multidisciplinary meeting.

that ILD MDMs should undergo a validation process by fulfilling a minimum number of case discussions annually. Experts felt that it would be highly desirable for ILD MDMs to occur on a regular basis to maintain its members' expertise, to perform self-assessments using an internationally collated case database, and for further research to be conducted into shared practices among ILD MDMs to develop an internationally agreed minimum standard. Lastly, experts agreed that the development of an international expert statement or guideline would be useful to provide guidance on running an optimal ILD MDM.

Discussion

In this study, we conducted semi-structured interviews with a panel of ILD experts and identified items representing various aspects of an ideal ILD MDM, ranging from its member composition to the clinical decision-making process involved. Following a Delphi process involving an international panel of ILD experts, we identified seven items that achieved consensus as essential features of an ILD MDM. We also further identified a total of 27 items which experts considered to be desirable features that could be incorporated into an ILD MDM, allowing a standard set of criteria for an ideal ILD MDM to be constructed for standardization purposes.

The strong agreement among experts on the presence of at least one radiologist at an ILD MDM is in accordance with multiple iterations of international guidelines supporting radiologists as core members. Unsurprisingly, experts also strongly agreed that a high-quality HRCT scan was essential for all cases being discussed at the ILD MDM. This finding attests to the impact of having radiological data in rendering a consensus ILD diagnosis, with a previous study demonstrating that incorporation of HRCT

Table 3. Statements meeting consensus for essential features of an ILD MDM (median 4/5; IQR 0)

Consensus–Essential Items
It is essential to have at least one radiologist present at an ILD MDM.
It is essential for the ILD MDM to have access to a visual projection system allowing real time viewing of CT scan images.
A good quality high resolution CT scan is required for every case being discussed at the ILD MDM.
It is essential for the ILD MDM to be conducted in a quiet setting which allows for easy interaction among members.*
It is essential for the ILD MDM to summarize collated patient information onto a standardized template.*

Definition of abbreviations: CT = computed tomography; ILD = interstitial lung disease; IQR = interquartile range; MDM = multidisciplinary meeting.
*Statements that met consensus after second Delphi round.

Table 4. Items meeting criteria for highly desirable features of an ILD MDM (median 5; IQR 1)

Highly Desirable Items
More than one pulmonologist present at an ILD MDM.
At least one pathologist present at an ILD MDM when there are histopathological data available.
At least one member of the ILD MDM has at least five years ILD-focused experience/training.
ILD MDM to serve as an education platform for specialist trainees and fellows.
Pathologists should review biopsy specimens prior to the ILD MDM.
Clinical history, a high-resolution CT scan and autoimmune serology should be available as a minimum dataset before a case can be presented at the ILD MDM.
Pulmonary function testing comprising of at least spirometry and $D_{L_{CO}}$ is required for every case being discussed at the ILD MDM.
ILD MDM should report a consensus diagnosis.
ILD MDM should discuss initial treatment and management recommendations.
An ILD MDM diagnosis should be a provisional diagnosis that may require a representation at an MDM at a later date when new information is available.

Definition of abbreviations: CT = computed tomography; $D_{L_{CO}}$ = diffusing capacity for carbon monoxide; ILD = interstitial lung disease; IQR = interquartile range; MDM = multidisciplinary meeting.

data led to a change in more than 50% of clinicians' first-choice diagnoses and an improvement in diagnostic confidence (18). The technical requirements of an HRCT for the diagnosis of ILD have also been described by the Fleischner Society (19). The importance placed by experts on having a visual projection system for real-time review of HRCT images is also paramount, where the ability for radiologists to convey specific information of an image and the educational benefit obtained from other clinicians have been described in other medical MDMs (20). Similarly, the strong agreement on having the ILD MDM in a quiet setting likely stems from experts' recognition of the negative impacts of background noise on member interactions and discussions during an MDM (21). Although not specific to ILD MDMs, these have yet to be mandated in official guidelines or statements. Experts agreed on the importance of using a standardized template to be used to collate patient data for an ILD MDM. The Thoracic Society of Australia and New Zealand recently published a position statement advocating for a standardized format for data presentation, an approach that unfortunately remains variable (5).

Somewhat surprisingly, there was expert agreement on the merit of ILD MDMs undergoing a validation process by fulfilling a minimum number of case discussions annually and to undergo a benchmarking process against an international minimum standard. In the absence of a standardized validation process, an argument can be made that the expertise of an ILD MDM will increase over time with increasing numbers of case discussions. However, participant feedback from the survey highlighted concerns that validation of an ILD MDM merely by annual case numbers could deter smaller and newer ILD MDMs. Furthermore, case quantity as a sole criterion to validate ILD MDMs is surely inadequate. The ability of an ILD MDM to improve diagnostic agreement stems from a linked evidence approach, by which its efficacy is defined by its ability to change a clinical diagnosis and subsequent management, rather than direct evidence of its impact on patient health outcomes (22). However, Walsh and colleagues previously showed poor agreement between expert MDMs for hypersensitivity pneumonitis and nonspecific interstitial pneumonia (8). Quality assurance approaches such as using peer observers to

Table 5. Items meeting criteria for desirable features of an ILD MDM (median 4; IQR 1)

Desirable Items
Having more than one member from each discipline attending the ILD MDM to generate a more dynamic discussion.
ILD MDM should have a chair to moderate and guide its discussions.
The ILD MDM should allow the attendance of external physicians, either in person or via videoconferencing to present their cases.
The ILD MDM should be a stand-alone meeting dedicated to the discussion of ILD cases only.
A meeting coordinator should be present to collate essential information required for every case prior to the meeting.
Histopathology images are required for cases that are being discussed at the ILD MDM in which lung biopsies have been performed.
There should be processes in place for communicating MDM outputs to relevant stakeholders (i.e., referring physicians, other clinical service providers).
The ILD MDM should report on the degree of confidence of the diagnosis.
The ILD MDM should report a list of differential diagnoses if a confident diagnosis was not achieved.
The ILD MDM should adhere to current and available standardized diagnostic guidelines.
The ILD MDM should have a documented strategy on prioritizing urgent cases for the meeting.*
Research terminologies (e.g., IPAF) can be used as consensus final or provisional diagnoses.*
The ILD MDM should review its policies and protocols at least annually.*

Definition of abbreviations: ILD = interstitial lung disease; IPAF = idiopathic pneumonia with autoimmune features; IQR = interquartile range; MDM = multidisciplinary meeting.
*Items with interquartile range of 3–4.

Table 6. Future concepts that met criteria for either being essential or desirable features to be incorporated into ILD MDMs

Future Concepts and Direction	Median (IQR) Score
It would be useful for every MDM to undergo an annual benchmarking process once an international minimum standard has been established.	4 (0)
It would be useful for every ILD MDM to undergo a validation process by fulfilling a minimum number of case discussions annually.	4 (0)
It would be useful for every ILD MDM to occur on a regular basis to maintain its expertise.	5 (1)
It would be beneficial to conduct further research into shared practices in ILD MDM to develop an internationally agreed minimum standard.*	4 (1)
It would be useful for every ILD MDM to regularly perform a self-assessment using an internationally collated database of cases.*	4 (1)
It would be useful for an international expert statement/guideline to be developed to provide guidance on running an optimal ILD MDM.*	4 (1)

Definition of abbreviations: ILD = interstitial lung disease; IQR = interquartile range; MDM = multidisciplinary meeting.
*Items identified following round 2.

review the quality of MDMs have been explored in the field of oncology and could be explored in ILD MDMs (23, 24). However, the diagnostic accuracy of ILD MDMs has never been validated, and consequently, the best approach to benchmark an ILD MDM remains elusive. Nonetheless, the consensus among participants in our study highlights the strong international collective desire for the development of a validated minimum standard of an ILD MDM and a framework for a benchmarking process of ILD MDMs.

The degree of agreement seen with several highly desirable statements warrants further discussion. In our study, the presence of a pathologist at an ILD MDM was considered to be a highly desirable feature, whereas current guidelines recommend them as core ILD MDM members. A possible explanation is that experts viewed that clinicians and radiologists are more well-placed to contribute in discussions of a greater case spectrum in the ILD MDM, whereas pathologists contributed only in cases with available histopathological data. However, when the statement was rephrased in round 2 to address this, the degree of agreement did not change. A more likely explanation is the potential challenges encountered in smaller MDMs or geographically remote centers, where access to pathologists may be limited. Certainly, our findings should not imply a lack of importance of the crucial role of an expert ILD pathologist in the discussion of a patient with ILD for whom histopathology is available. Experts also agreed that it would be highly desirable to have at least one member with five years of ILD-focused experience attending the MDM. The proposed threshold of five years was derived from the expert interviews and has not been studied. Furthermore, the exact definition of experience and which ideal member requiring the additional experience have not been established.

Additionally, the finding that it was highly desirable for ILD MDM to deliver management recommendations is somewhat controversial. The role of MDMs in the management of oncological patients is clear where the diagnosis has already been established and evidence-based treatment options are available. In contrast, ILD MDMs have historically focused on disease characterization and diagnosis formulation (25). Major recent advances in therapeutic options may account for the expanded role of the ILD MDM, where clinicians may need more guidance in managing their patients. However, treatment often depends on individual patient factors such as frailty, comorbidities, and personal wishes, many of which cannot be addressed by an MDM panel that has not met the patient. However, our findings do suggest that there is a broad desire for cooperative assistance and advice in the development of therapeutic management plans for the complex ILD patient, although the potential role of the ILD MDM in this is yet to be established.

Experts also agreed that it was desirable for ILD MDMs to adhere to available standardized ILD clinical practice guidelines. These guidelines provide a framework that clinicians can use to evaluate patients presenting with ILD. However, it is important to recognize that the fundamental hallmark of the ILD MDM is the integration of multidisciplinary data to render a diagnosis, one that is particularly important in ILD cases that do not fit into clinical practice guidelines. Surprisingly, there was also agreement among experts that research terminologies such as idiopathic pneumonia with autoimmune features (IPAF), could be used as consensus diagnoses. IPAF was proposed as a standardized research term to define patients with overlapping features that do not fit established diagnostic criteria for a connective tissue disease–associated ILD (26). Our findings suggest that there is an international recognition of this IPAF cohort in clinical practice, and that clinicians are keen to use the term in their clinical practice. However, it remains uncertain whether IPAF does indeed represent a separate clinical entity, with implications on prognosis and management remaining unknown.

Nonetheless, the majority of desirable features are already present at ILD MDMs in varying degrees with similar findings reported in a recent systematic review on ILD MDMs (27). Despite the agreement seen in our study, standardization and incorporation of these features are very often constrained by geographical distances and local resource availability. This can potentially account for the small number of statements reaching consensus in our study. However, this could also reflect the collective notion among study participants that only a small number of features are truly essential to run a high-quality ILD MDM without hindering the applicability of these features to smaller and newer ILD MDMs. The burgeoning number and frequency of MDMs are likely to increase workloads of radiologists and pathologists involved, potentially impacting negatively on the MDMs' ability to function effectively (28). The recent coronavirus disease (COVID-19) pandemic has resulted in the rapid uptake of videoconferencing technologies in ILD MDMs (29). Our study findings on essential and desirable features are likely to remain relevant in such hybrid or virtual MDMs. Despite these recent advances in data sharing

and videoconferencing technologies providing viable platforms for MDMs, the ideal format remains unknown, and further research is needed to evaluate the benefits of virtual discussions (30, 31). Research into shared ILD MDM practices, collaborative data sharing, and self-assessments are suggested approaches that warrant further consideration. The UK's National Health Service is one example where an established program of national clinical audits informed a range of policy changes leading to improved patient health outcomes (32). However, successful audits require robust evidence-based guidelines, clinical leadership, and buy-in by professional bodies and stakeholders. Perhaps an initial approach is to explore the practicalities of performing self-assessments at an individual and local level, where resources may be more readily available.

Our study has several limitations. Participants recruited were predominantly pulmonologists (93%) with the remainder from other medical specialties (radiology, academic research, immunology, and rheumatology). Of note, no pathologists were recruited onto the study, and their absence as a recommended core member of an ILD MDM could potentially bias our results. Furthermore, we did not have demographic data from participants who did not respond to the invitation, hence will not be able to determine if potential bias was solely from the recruitment strategy or from a lack of response from other specialties. A majority of participants were from ILD referral centers and expert MDMs attached to academic hospitals. Hence, our study was unable to capture sentiments or opinions of clinicians participating in smaller or newer MDMs. However, we sought to establish consensus in an area with limited evidence, and we believe that our participant cohort enabled us to achieve this aim. We used a rigorous definition of consensus, which resulted in a small number of essential features and a larger number of desirable features. A more lenient definition of consensus would have resulted in more features classified as "essential"; however. this could deter establishment of MDMs in less resource-rich settings. Some potentially important aspects of an MDM were not included in the Delphi, such as the number of participants, level of expertise required, frequency of meetings, and number of case discussions per meeting. However, the experts did not identify these issues for inclusion in round 2. Lastly, opinions captured in a Delphi process are not equivalent to evidence-based facts. Expert opinions from the Delphi process should be subjected to further studies to validate any proposed future ILD MDM models, ideally by demonstrating impact on patient outcomes.

Conclusions

In conclusion, using a Delphi model in surveying an international panel of ILD experts, our study was able to identify the essential and desirable features of an ILD MDM. Our study is an important step toward standardization of ILD MDMs. Our data may guide future collaborative research into development of international guideline reco–mmendations for ILD MDMs, based on high-quality evidence. ■

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2.1 Supplementary Data

Table 2.1. Online Delphi questionnaire.

Team structure
It is essential to have more than one pulmonologist present at an ILD MDM.
It is essential to have at least one radiologist present at an ILD MDM.
It is essential to have at least one pathologist present at an ILD MDM when there are histopathological data available. *
It is essential to have a rheumatologist or immunologist present at an ILD MDM. †
Having more than one member from each discipline attending the ILD MDM will generate a more dynamic discussion.
It is essential that at least one member of the ILD MDM has at least five years ILD-focused experience/training. ‡
It is essential to maintain an attendance list at the ILD MDM.
It is essential for the ILD MDM to have a chair to moderate and guide its discussions.
It is essential for the ILD MDM to allow the attendance of external physicians, either in person or via video-conferencing to present their cases. §
It is essential for the ILD MDM to serve as an education platform for specialist trainees and fellows.
Infrastructure
It is essential for the ILD MDM to be a stand-alone meeting dedicated to the discussion of ILD cases only.

It is essential for the ILD MDM to be conducted in a quiet setting which allows for easy interaction amongst members.

It is essential for the ILD MDM to have access to a visual projection system allowing real time viewing of CT scan images.

It is essential for the ILD MDM to have access to a visual projection system or a multi-view microscope, allowing real time viewing of histopathological images.

It is essential for the ILD MDM to have access to videoconferencing equipment to allow remote access for offsite participants.

Organization and administration

It is essential for the ILD MDM to have a documented strategy on prioritising urgent cases for the meeting.

It is essential for the ILD MDM to have a meeting coordinator to collate essential information required for every case prior to the meeting.

It is essential for the radiologists to review the CT scans prior to the ILD MDM.

It is essential for the pathologists to review biopsy specimens prior to the ILD MDM.

It is essential for the clinical history, a high resolution CT scan and autoimmune serology to be available as a minimum dataset before a case can be presented at the ILD MDM.

It is essential for the ILD MDM to summarize collated patient information onto a standardized template.

It is essential for the primary treating physician present the case at the MDM.

It is essential for a meeting coordinator to document and capture discussions and outputs generated by the ILD MDM.

It is essential for the ILD MDM to have processes in place for communicating MDT outputs to relevant stakeholders (i.e. referring physicians, other clinical service providers).

It is essential for the ILD MDM to have processes in place to follow up on whether its recommendations were enacted.
Clinical decision-making process
A good quality high resolution CT scan is required for every case being discussed at the ILD MDM. A CT scan with expiratory views is required for every case being discussed at the ILD MDM. ‖ A CT scan with prone views is required for every case being discussed at the ILD MDM. ‖ A complete autoimmune and myositis serology panel is required for every case being discussed at the ILD MDM. Pulmonary function testing comprising of at least spirometry and DLCO is required for every case being discussed at the ILD MDM. ¶ A 6 minute-walk test is required for every case being discussed at the ILD MDM. Histopathology images are required for cases that are being discussed at the ILD MDM in which lung biopsies have been performed. It is essential for cases to be discussed at the ILD MDM prior to proceeding with a lung biopsy. It is essential for the ILD MDM to report a consensus diagnosis. It is essential for the ILD MDM to report on the degree of confidence of the diagnosis. It is essential for the ILD MDM to report a list of differential diagnoses if a confident diagnosis was not achieved. It is essential for the ILD MDM to discuss initial treatment and management recommendations. It is essential for the ILD MDM to report a disease behaviour category.

It is essential for the ILD MDM to adhere to current and available standardised diagnostic guidelines.

An ILD MDM diagnosis is a provisional diagnosis that may require a re-presentation at an MDM at a later date when new information is available.

Research terminologies (e.g. IPAF) can be used as consensus final or provisional diagnoses.

In cases where the MDM members did not agree on the diagnosis, it is essential to document the differing opinions and reasons in the final report.

Future concepts and directions

It is essential for each ILD MDM to have a documented policy statement, which clearly defines its purpose and intended outputs.

It is essential for the ILD MDM to discuss every ILD case seen at their centre.

It is essential for the ILD MDM to review its policies and protocols at least annually.

It would be beneficial to conduct further research into shared practices in ILD MDM to develop an internationally-agreed minimum standard.

It would be useful for every MDM to undergo an annual benchmarking process once an international minimum standard has been established.

It would be useful for every ILD MDM to regularly perform a self-assessment using an internationally-collated database of cases.

In an ILD MDM, a majority vote is required to allow a case discussion to achieve consensus.

It would be useful for every ILD MDM to undergo a validation process by fulfilling a minimum number of case discussions annually.

It would be useful for every ILD MDM to occur on a regular basis to maintain its expertise.

Additional statements
It is essential to have a thoracic surgeon attend the ILD MDM. **
It is essential to have a clinical nurse attend the ILD MDM. **
It is essential for cases to be presented at the ILD MDM prior to proceeding with a lung biopsy. **
It would be essential for an international expert statement/guideline to be developed to provide guidance on running an optimal ILD MDM. **

ILD MDM: interstitial lung disease multidisciplinary meeting; CT: computed tomography; DLCO: diffusing capacity for carbon monoxide; IPAF: idiopathic pneumonia with autoimmune features

* Statement rephrased in round 2 from; 'It is essential to have at least one pathologist present at an ILD MDM.'

† Statement rephrased in round 2 from; 'It is essential to have a rheumatologist present at an ILD MDM.'

‡ Statement rephrased in round 2 from: 'It is essential that at least one member of the ILD MDM has ILD subspecialty training.'

§ It is essential for the ILD MDM to allow the attendance of external physicians, either in person or via video-conferencing.

‖ Statement divided into two statements in round 2 from: 'A CT scan with expiratory and prone views is required for every case being discussed at the ILD MDM.'

¶ Statement rephrased in round 2 from: 'A full pulmonary function test is required for every case being discussed at the ILD MDM.'

** Additional statements incorporated in round 2.

Table 2.2. Geographical distribution of online questionnaire participants

Country	Number (n)	Percentage (%)
Argentina	3	2.9
Australia	12	11.8
Brazil	8	7.8
Costa Rica	2	2.0
Canada	2	2.0
Chile	2	2.0
Croatia	1	1.0
Czech Republic	2	2.0
Denmark	1	1.0
Egypt	1	1.0
France	3	2.9
Greece	2	2.0
Germany	3	2.9
India	1	1.0
Italy	6	5.9
Japan	5	4.9
Mexico	2	2.0
Netherlands	2	2.0
New Zealand	2	2.0
Poland	2	2.0
Portugal	1	1.0
Republic of Korea	1	1.0

Romania	3	2.9
Russia	2	2.0
Singapore	1	1.0
Spain	5	4.9
Turkey	5	4.9
United Kingdom	9	8.8
USA	13	12.7
Total	**102**	**100**

Table 2.3. Geographical distribution of invitees that did not complete the first Delphi round.

Region	Number of invitees
North America	8
South America	8
Europe	9
Asia	6
Australia & New Zealand	1

Chapter Three (Part A): Effect of Antifibrotic Therapies on the Extracellular Matrix in Idiopathic Pulmonary Fibrosis

3.1.1 Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial pneumonias (IIP) [1]. Prognosis remains poor with worsening quality of life in the setting of relentless lung function decline and resultant respiratory failure. The antifibrotic drugs, nintedanib and pirfenidone, have shown clinical efficacy in slowing lung function decline in patients with IPF, providing hope for people living with IPF [2, 3]. However, there is a need to better understand the mechanism of action of these antifibrotic medications, and to identify biomarkers indicating response to treatment.

The archetypal histological pattern in IPF is usual interstitial pneumonia (UIP), characterised by a heterogeneous distribution of architectural distortion, fibroblastic foci, and lung parenchymal destruction [4]. Fibroblastic foci are regions of densely packed fibroblasts, myofibroblasts and extracellular matrix (ECM), spatially and temporarily distributed across affected lung parenchyma. While pulmonary fibroblasts likely have a pivotal role in aberrant wound healing and dysregulated collagen metabolism, ECM proteins have been proposed to be a driver of fibrosis progression. Individual ECM proteins such as fibrin and fibronectin have been implicated as potentially fibrogenic with one model showing a profibrotic positive feedback loop between ECM and fibroblasts perpetuating aberrant ECM deposition and fibroblast activation [5, 6].

Literature review identified fibronectin, periostin, perlecan and tenascin-C as ECM proteins implicated in IPF pathogenesis. Fibronectin is important in ECM-cell interaction and myofibroblast differentiation in wound healing and fibrotic events. Fibronectin is increased in IPF lung tissue, suggesting it may play a pathogenic role [7]. Periostin binds to cells via integrin

molecules to promote cell adhesion, proliferation, migration and angiogenesis. It binds to type 1 collagen and fibronectin, and has also been shown to be more abundant in IPF lung tissue [8]. Perlecan, a ubiquitous heparan sulfate proteoglycan, has a central role in the regulation of ECM assembly and modulation of mitogenic growth factors that support fibroblast proliferation in fibrosis [9]. Lastly, Tenascin-C, a large hexametric glycoprotein, has been shown to be significantly upregulated in fibrotic lung compared to normal lungs, being mostly undetectable [10]. Our study aimed to evaluate the role of these ECM proteins in the pathogenesis of IPF, and to assess their responses to both nintedanib and pirfenidone in vitro.

3.1.2 Methods

In this study, patients who had received a lung transplant or had a surgical lung resection consented to the extraction of various cell lines. Pulmonary fibroblasts were harvested from ex-planted lungs, cultured and stored. Similarly, fibroblasts were harvested from lung tissue removed from patients requiring lobectomies or segmentectomies, forming the healthy comparator group. IPF and healthy/control fibroblasts were routinely cultured and maintained in Dulbecco's Modified Eagle Medium (DMEM, Gibco) supplemented with 5% foetal bovine serum (FBS, Gibco). We used an in-house developed enzyme-linked immunosorbent assay (ELISA) protocol, to assess changes in various ECM proteins using specific antibodies. IPF and control fibroblasts were seeded at a concentration of 4.2x104cells/ml in DMEM/ 5%FBS at 100µl/well in 96-well tissue culture (TC) plates for 72 hours. Cells were then washed with Hanks balanced salts solution (HANLS, Sigma). Media was replaced with DMEM/0.1% bovine serum albumin (BSA) to quiesce cells for 24 hours. Cells were treated with nintedanib and pirfenidone at concentrations of 100nM and 500nM, and 100uM and 500uM, respectively for 1hour prior to stimulating with transforming growth

factor – beta (TGF-β, 5ng/ml) for 72hours. We utilised TGF-β given its known role as a central regulator of cell differentiation, migration, proliferation and gene expression implicated in both normal reparative responses and fibrotic processes [11]. Fibroblasts were washed with PBS and lysed by incubating in 0.1M ammonium hydroxide (NH4OH) for 15 minutes at 37ºC, leaving deposited ECM on the plates. ECM plates were washed with phosphate-buffered saline (PBS) and were stored at -20°C for later use.

Prior to analysis, plates were defrosted at room temperature and incubated in blocking solution, 1% BSA-PBS, to counteract non-specific bound molecules. Primary antibodies for tenascin-C (Merck), fibronectin (Merck), perlecan (Invitrogen) and periostin (RnD systems) were diluted in 1% (w/v) BSA in PBS with 0.05% Tween-20 (v/v) (T-PBS) and added at 100 µL/well for 2 hours. Plates were washed four times with T-PBS and a rabbit anti-mouse monoclonal HRP-linked secondary antibody (Cell Signalling) was applied for 1 hour at 100 µL/well. An IgG isotype control was also included to account for any non-specific IgG binding. Plates were washed four times with T-PBS, and 100 µL of chromogenic 3,3',5,5'-tetramethylbenzidine (TMB) was added for 15 – 30 minutes. The reaction was stopped by the addition of 100 µL/well of 1M phosphoric acid. Absorbance was measured at 450 nm with background measured at 570 nm using Spectramax iD3 plate reader. Results were normalised against controls (i.e. cells lines which did not receive TGF-B stimulation).

A proliferation assay was performed with fibroblasts seeded in 96 well TC plates at $1x10^4$cells/ml, 100 µL/well in DMEM/5%FBS for 24 hours and treated with varying concentrations of nintedanib and pirfenidone. 72 hours post-treatment, 0.5% (w/v) MTT dye ((3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium) (Merck) in PBS was added at 10 µL/well under sterile conditions. All stimulations were performed in triplicate and plates were incubated at 37°C/ 5% CO_2 for 4 hours. The supernatant was then removed and 100 µL of

dimethyl sulfoxide (DMSO) was added to each well to dissolve the crystalline dye. After 1 min of vigorous shaking plates were read on the Spectramax iD3 plate reader at 570 nm with a background reading at 630 nm. To analyse the data, the untreated wells were considered to be 100% cell survival and treated wells were compared to the control wells to determine the percentage cell viability. Prism (version 10.2.2) was used for statistical analysis.

3a.3 Results

Six IPF patients and seven controls were included in the study. In the IPF group, mean age was 58 years (4.9), 83% were male and mean FVC% predicted was 43.0% (5.0), significantly lower than the control population. All four ECM proteins were increased following TGF-B stimulation when compared against unstimulated control samples (Figure 3.1). There was a significant reduction in tenascin C in IPF patients treated with 500nM nintedanib (mean difference -16.6, 95% CI 2.7 to 30.6; p=0.01) and in healthy controls (predicted LS mean difference -21.7, 95% CI 8.6 to 34.7; $p<0.05$). There were no significant changes following pirfenidone treatment. Periostin expression was significantly reduced in IPF patients treated with 500uM pirfenidone (mean difference -55.6, standard error of difference 17.8; p=0.03) but was not significant following treatment with 500nM nintedanib (MD -53.5, SE 68.0; p=0.45). There were no significant changes to periostin levels in the healthy comparator group. No significant changes in perlecan or fibronectin levels were seen following treatment with either nintedanib or pirfenidone. MTT assay showed no significant effect of pirfenidone and nintedanib on fibroblast activity in either IPF and controls.

3.1.4 Discussion

Our study showed a significant increase in tenascin-C expression in both IPF and healthy patients that received TGF-B stimulation. While expected in IPF, higher expression of tenascin-C in the healthy group differs from previous study results [10]. One possible explanation is the presence of malignancies in excised lung used in our healthy cohort where tenascin-C may have a role not only in fibrogenesis but also tumour growth and angiogenesis [12]. In addition, nintedanib significantly reduced tenascin-C in both IPF and healthy patients. This is in keeping with a previous in vitro study showing nintedanib preventing growth-factor induced proliferation of both IPF and non-fibrotic fibroblasts. Nintedanib was shown to inhibit expression of pro-fibrotic metalloproteinases, suggesting an effect on ECM proteins, though its effect on tenascin-C expression remains unclear [13, 14]. The lack of effect on pirfenidone on tenascin-C expression is in keeping with other studies, suggesting that pirfenidone has a a different mechanism of action, not involving tenascin-C [15].

Our findings of increased periostin expression in IPF are in keeping with previous work showing increased periostin levels in IPF lung and co-regulatory interaction with TGF-B in lung mesenchymal cells [8, 16]. In addition, our study demonstrated pirfenidone treatment led to a decrease in periostin expression in lung tissue of IPF patients. This supports a previous rat model showing attenuation in periostin expression following pirfenidone treatment, suggesting periostin as an integral component in fibrosis and pirfenidone's exerting its antifibrotic effect via the suppression of periostin [17]. Though not significant, our study showed a reduced periostin expression in IPF patients treated with nintedanib, which is in keeping with other data showing monomeric periostin to be associated with a suppressive effect on pulmonary function by nintedanib, [18].

We utilised an MTT assay to explore the effect of both antifibrotic agents on fibroblast activity and found no significant effect with varying doses of pirfenidone and nintedanib. Our findings differ from a previous study which showed both nintedanib and pirfenidone reduced in vitro fibroblast proliferation in a dose-dependent manner [19]. This could be attributed to proliferative properties of FBS on fibroblasts which may have masked the true effect of antifibrotics [20]. While no dose-dependent changes were seen, small mean reductions in fibroblast proliferation were seen following treatment with nintedanib (>83% viability vs 100% in controls) and pirfenidone (>92% viability vs 100% in controls), suggesting an antiproliferative effect [14, 21].

The strength of our study was the use of the ECM ELISA technique in studying suspect ECM proteins that have been previously linked to the pathogenesis of IPF. Study limitations included small sample numbers, and lack of a 'pure' control given the fact that the control lung was from those with lung resection for malignancy. Lastly, a fundamental factor in this model is that treatment was initiated before the stimulation of fibroblasts. This differs from current clinical practice where treatment is started after disease is established. Future treatment could prioritise prophylaxis or preventative approaches prior to disease development. Such models will still require a validated biomarker with good predictive and prognostic capabilities, one that still remains elusive in IPF.

3.1.5 Conclusion

In conclusion, tenascin-C and periostin levels in IPF lung were reduced following treatment with nintedanib, providing further insights into the potential mechanism of action of

nintedanib. Further studies evaluating the role of ECM proteins may provide insight into both the pathogenesis of IPF and the potential mechanism of action of future therapeutic agents.

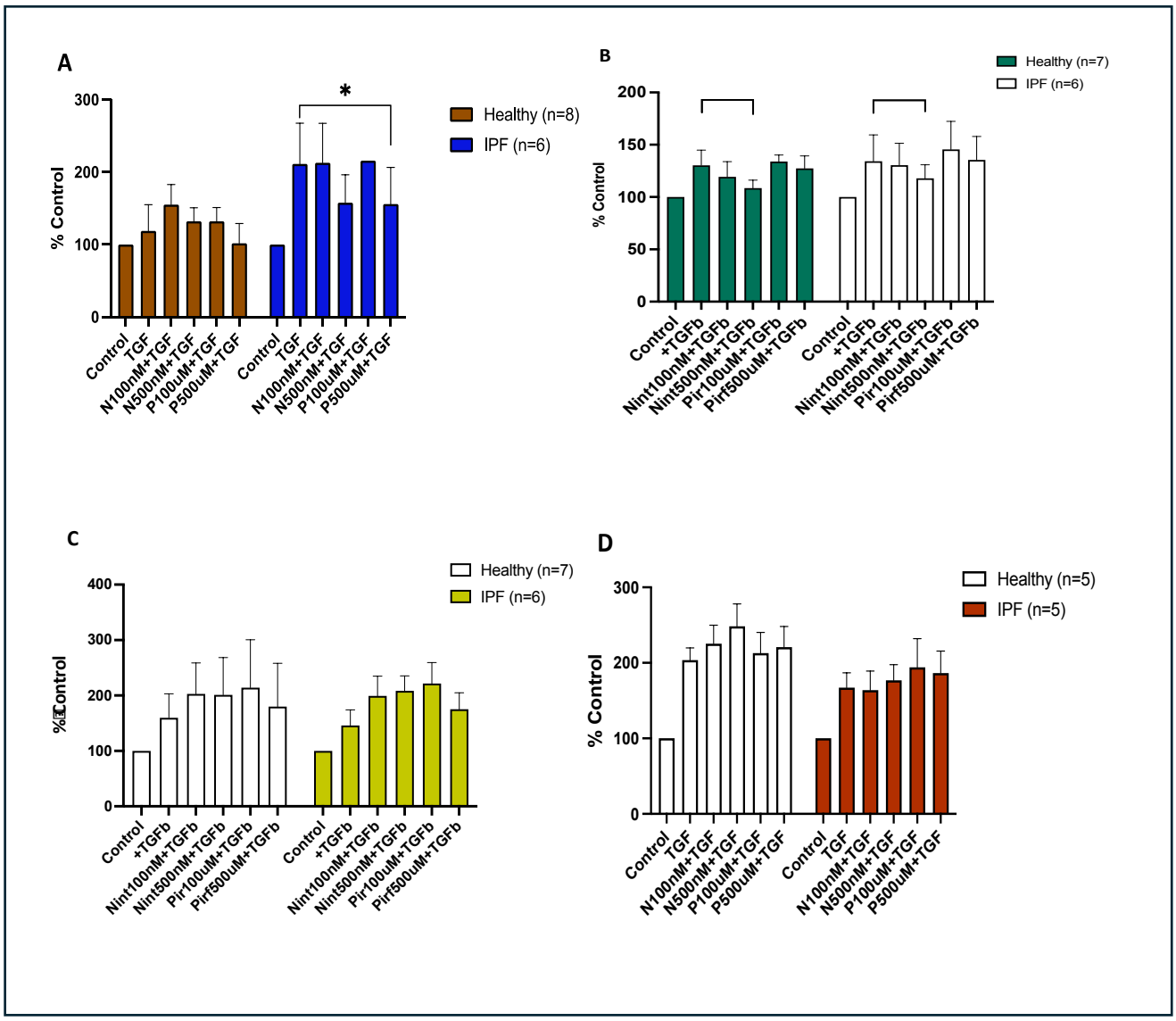

Figure 3.1. Expression levels of (A) periostin, (B) tenascin-C, (C) fibronectin and (D) perlecan in IPF patients and controls. TGF: transforming growth factor-beta; N100nM: nintedanib 100nM; N500nM: nintedanib 500nM; P100uM: pirfenidone 100uM; P500uM: pirfenidone 100uM. * $p<0.05$

3.1.6 Chapter Three (Part A) References

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Chapter Three (Part B): Blood Monocyte Counts as a Potential Prognostic Marker for IPF: Analysis from the Australian IPF Registry

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Early View

Research letter

Blood monocyte counts as a potential prognostic marker for IPF: Analysis from the Australian IPF registry

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Blood monocyte counts as a potential prognostic marker for IPF: Analysis from the Australian IPF registry.

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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing lung disease that leads to unrelenting dyspnea and chronic cough and ultimately respiratory failure.[1] IPF is characterized by a variable disease course that remains difficult to predict for an individual at diagnosis.[2] In the current era, with the advent of anti-fibrotic therapy which can slow disease progression, it is increasingly important to identify patients with early disease and to target those patients who are at most risk of rapid decline.[3] However, despite multiple studies proposing novel potential prognostic biomarkers, the current ATS/ERS/JRS/ALAT guideline statements dismissed the use of these biomarkers except in a research capacity.[3,4]

Recently, in this Journal, Scott and colleagues[5] have suggested that peripheral blood monocyte count may be a powerful biomarker capable of predicting poorer prognosis amongst IPF patients. In a retrospective analysis using transcriptome microarray data, the investigators found that estimated CD14+ monocyte percentages above the mean were associated with shorter transplant-free survival times. Using a threshold monocyte value of $0{\cdot}95*10^3/\mu L$ or greater, the investigators were able to validate their exploratory analysis using several independent cohorts. Higher absolute CD14+ monocyte counts were found in the COMET cohort in patients who had progressive disease and in those that were classified as high-risk in the Yale cohort. Higher absolute monocyte counts were found to be associated with increased risk of mortality in several other larger validation cohorts. This finding remained significant following adjustment for forced vital capacity (FVC) and the gender, age and physiology (GAP) index in each of the COMET, Stanford and Northwestern cohorts.

We sought to reproduce this finding using data from the Australian IPF Registry (AIPFR). The national AIPFR is investigator-led, prospectively acquired and was established in 2012 with the goal of facilitating research into IPF as well as to provide further insight into the epidemiology and management of IPF in Australia.[6] Baseline routine full blood count tests with cell differentials performed on patients recruited into the Registry were extracted for analysis. A total of 231 patients from three Australian states (New South Wales, Victoria and South Australia) were included.

Clinical data had been prospectively entered into the Registry with a follow up duration of 2·4 (1·3 – 3·3) years. The majority of patients were male (71%) with a mean age of 69·9 ± 8·3 years. Patients were found initially to have mild to moderate disease with a mean FVC of 80·3 ± 22·0 % predicted and a mean DLCO of 48·2 ± 16·8 % predicted. Mean blood monocyte counts were significantly higher in the 75 patients who died compared to the 156 patients who remained alive after the follow-up period, although the difference was clinically small [0·66 (0·5 – 0·9) versus 0·6 (0·4 – 0·7)$*10^3/\mu L$; p=0·006]. Additionally, neutrophil and total leucocyte counts were also significantly higher in the deceased patient cohort. A Cox proportional hazards model was used to evaluate the effect of an elevated serum monocyte count on survival of the IPF registry patients. 22 patients had monocyte counts equal to or greater than the value of $0{\cdot}95*10^9/L$, used in Scott and colleagues' study[5]. The Australian standardized upper limit of normal values for neutrophils and total leucocyte counts were used as threshold values at $7*10^9/L$ and $10*10^9/L$ respectively. There were 44 and 50 patients with neutrophil and total leucocyte counts equal or greater than the threshold values respectively. Univariate analysis for mortality showed that elevated monocyte, neutrophil and total leucocyte counts were associated with decreased survival (*Table 1*). Following a multivariate analysis adjusting for age, gender and baseline FVC% predicted, elevated monocyte count remained a significant predictor for poorer survival (HR 2·36, 95% CI 1·18 – 4·70, p=0·02). However, elevated neutrophil and total leucocyte counts also remained independently associated with poorer outcomes (HR 2.10, 95% CI 1.22 – 3.62, p=0.008 and HR 2.07, 95% CI 1.23 – 3.50, p=0.006, respectively).

The limitation of our study relates to the real-world nature of the Registry, in which peripheral blood sampling was dictated by individual physicians and was not necessarily the patients' true baseline at diagnosis. Additionally, there was limited data on the prescription of anti-fibrotic therapy as these agents were not readily available to the Australian public on subsidized government-funded programs prior to 2016. Despite this, one advantage of our Registry data is the availability of relatively longer follow-up time and mortality data of IPF patients recruited.

Our findings add further validity to the notion that a routinely measured blood cell population may have a potential as a biomarker, with elevated monocyte counts suggesting a worse prognosis in the individual patient presenting with IPF. Both monocytes and neutrophils have been postulated to play a role in the pathogenesis of IPF and have also been shown to correlate with disease progression.[7–9] We echo the commentary by Kreuter and Maher[10] in agreeing that there is a need for further detailed studies to provide better mechanistic insights into the role that monocytes and neutrophils have to play in IPF. Given the consistency of the association across several diverse cohorts, including ours, a crucial next step is to accurately delineate the nature of the monocytosis in poor prognosis IPF.

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	Hazard ratio (HR)	95% CI	p value
Age	1.0	1.0 - 1.1	0.11
Gender	1.1	0.7 - 1.9	0.64
FVC% *	0.7	0.7 - 0.9	<0.0001
DLCO% *	0.6	0.5 - 0.8	<0.0001
Monocytes ¶	3.2	1.4 - 7.4	0.005
High monocytes (≥0.95x10^9/L)	2.4	1.3 - 4.4	0.004
Neutrophils ¶	1.2	1.1 - 1.2	<0.0001
High neutrophils (≥7x10^9/L)	2.5	1.5 - 4.1	<0.0001
Total WCC ¶	1.2	1.1 - 1.2	<0.0001
High total WCC (≥10x10^9/L)	2.6	1.6 - 4.1	<0.0001

Table 1. Univariate cox analysis for mortality. *: every 10% change. ¶: Continuous variable. WCC: white cell count.

Chapter Four: Antifibrotic Therapy for Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis: A Systematic Review and Meta-Analysis

Antifibrotic Therapy for Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis: A Systematic Review and Meta-Analysis

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4.1 Abstract

Idiopathic pulmonary fibrosis (IPF) is characterised by irreversible, declining lung function leading to worsening quality of life and a poor prognosis. A similar progressive disease course is seen in progressive pulmonary fibrosis (PPF). Antifibrotic agents have changed the management landscape with newer agents continue being studied. This systematic review and meta-analysis aim to review and summarise the efficacy and safety of antifibrotic agents for IPF and PPF treatment.

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Randomised controlled trials comparing antifibrotic agents to placebo in adults aged ⩾ 18 years with IPF and PPF were included. Primary outcomes were change in percentage predicted forced vital capacity from baseline, progression-free survival and health-related quality of life. Secondary outcomes included adverse events, mortality outcomes, six-minute walk distance and diffusing capacity of lungs for carbon monoxide changes from baseline. The study was registered at PROSPERO (CRD42020211151).

22 studies (n=7117 participants) were included for meta-analysis. For IPF, change in ppFVC favoured nintedanib and pirfenidone. For PPF, change in FVC favoured both nintedanib and pirfenidone. Although not clinically significant, pooled analyses of St Georges Respiratory Questionnaire score favoured nintedanib. Nintedanib and pirfenidone significantly reduced respiratory but not all-cause mortality in IPF. Safety analysis of nintedanib and pirfenidone were comparable with open-label extension and real-world cohort studies.

While our study showed both nintedanib and pirfenidone reduced lung function decline, their effects on patient reported outcome remain uncertain. Though antifibrotics have been a huge

step in the right direction for the treatment of IPF and PPF, further development of novel agents is needed.

4.2 Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial pneumonia of unknown cause with a prevalence of 10-60 cases per 100,000 people, increasing to 400 per 100,000 people in those over 65 years [1, 2, 3, 4]. Prognosis is poor with a median survival time from IPF diagnosis of merely 2-5 years [5] and the natural history is highly variable with some developing rapid progressive decline, and others having slower disease trajectories [6].

IPF represents only one of the spectrum of interstitial lung diseases (ILD), many of which can follow a similarly progressive disease course. It is now understood that approximately 40% of fibrotic ILD will progressively decline [7, 8, 9, 10]. Recent international clinical practice guidelines have coined the term progressive pulmonary fibrosis (PPF) to describe this progressive phenotype [11].

Recent studies of two antifibrotic medications, nintedanib and pirfenidone, herald a new era in the management of IPF [12, 13]. As longer-term data on their tolerability and efficacy continue to emerge, uncertainties still remain for certain cohorts of patients with IPF. Furthermore, their role in treating other fibrotic ILD is emerging. With further novel agents being studied, comprehensive understanding of the role of antifibrotic therapies, their efficacy and potential adverse effects in the management of IPF and other fibrotic ILD is needed, providing clarity for both patients and physicians.

This systematic review and meta-analysis aimed to evaluate and summarise the efficacy and safety of antifibrotic therapies in the treatment of individuals with IPF and PPF.

4.3 Methods

The study protocol was registered at PROSPERO (CRD42020211151). This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

4.3.1 Types of studies

We included randomised controlled trials (RCT) where antifibrotic agents were compared to placebo or best supportive care in individuals with IPF and non-IPF fibrosing ILD.

4.3.2 Participants

We included adults aged⩾18 years with a diagnosis of IPF, defined by diagnostic criteria at the time the studies were identified. We also included adults aged⩾18 years with non-IPF, progressive and fibrotic ILD, irrespective of disease severity. There were no further exclusion criteria.

4.3.4 Search strategy

This systematic review aimed to assess the efficacy and safety of antifibrotic therapies, including pirfenidone and nintedanib in the treatment of individuals with IPF and other fibrotic ILD separately. We searched the Cochrane Airways Trial Register and the Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Register of Studies, MEDLINE (OvidSP) and EMBASE (OvidSP), from inception to April 2023. Only studies in English

language were included. Database search strategies are listed in the supplementary appendix. We also reviewed the US National Institute of Health Ongoing Clinical Trials Register (www.clinicaltrials.gov) and World Health Organisation International Clinical Trials Registry (apps.who.int/trialsearch). Study authors were contacted for additional information or any clarification on missing data where possible.

4.3.5 Outcomes

The primary outcomes were the change in percentage predicted forced vital capacity (ppFVC) at 12 months from baseline, either as absolute or relative change or rate of decline at 12 months, progression-free survival (PFS) defined by investigators, and health-related quality of life (HrQOL) scores, determined from generic or respiratory-specific HrQOL questionnaires. Secondary outcomes included adverse events, all-cause and respiratory-specific mortality, change in six-minute walk distance (6MWD) and change in percentage predicted diffusing capacity of lungs for carbon monoxide (ppDLCO) from baseline.

4.3.6 Study selection, data extraction and risk of bias assessment

Two authors (A.T and L.G.) independently identified eligible citations by sequentially reviewing titles, abstracts and full text manuscripts. A.T. extracted data using standardised forms. Data was sequentially reviewed and cross-checked by L.G. independently. Risk of bias assessment were independently performed by both reviewers. Disagreements were resolved either by consensus or a third reviewer if required. Assessments were performed based on the information from articles and available study protocols.

4.3.7 Data analysis and synthesis

As anti-fibrotic agents may have different mechanisms of action and effects, they were each analysed separately. The effects of anti-fibrotic agents on IPF were analysed separately to non-IPF fibrotic ILD. Meta-analyses were performed if adequate data were available in at least two independent studies with comparable outcome of interest using Review Manager (RevMan, version 5.3; the Cochrane Collaboration). Where a study included multiple dose comparisons, the number of participants in the control group was divided by the number of comparisons. Continuous variables were recorded as mean values and standard deviation (SD). Dichotomous data were analysed as risk ratios (RR) and continuous data, as mean difference (MD). Skewed data were described narratively. The magnitude of heterogeneity was measured through the I^2 statistic described in the Cochrane Handbook. Thresholds for I^2 values were as follows: low (25–49%), moderate (50–74%) and high ($\geqslant$75%).

4.4 Results

Following the removal of duplicate records, 10085 records from our literature search were screened. 9661 records were excluded based on titles and abstracts not meeting the inclusion criteria, leaving 374 records that were assessed for eligibility. A total of 22 RCTs were included in the final meta-analysis (Figure 4.1).

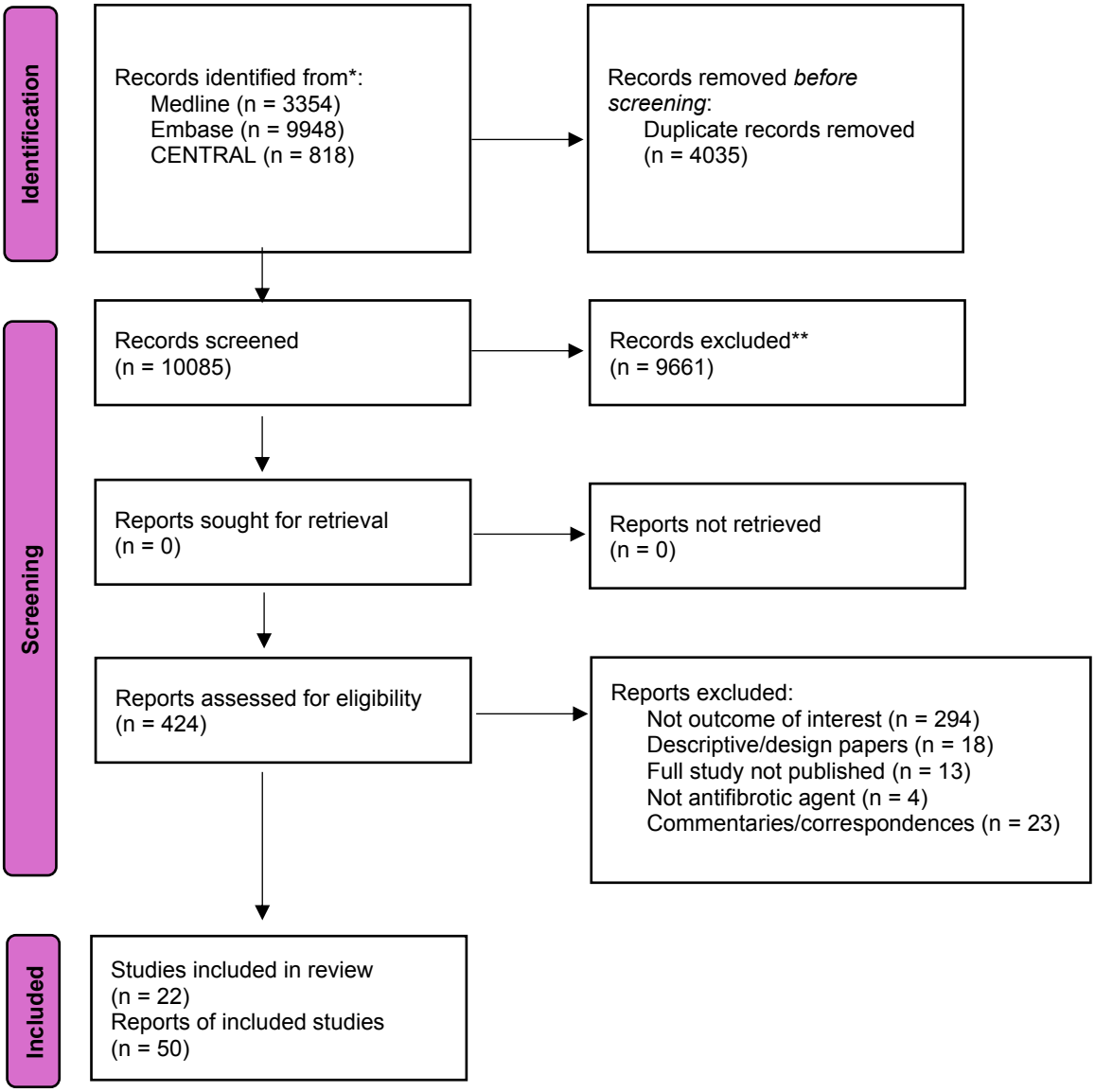

Figure 4.1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) diagram.

4.4.1 Study characteristics

A total of 3906 individuals received antifibrotics and 3211 received placebo from the 22 RCTs included (Table 4.1) [12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33]. Of these, five studied pirfenidone, four studied nintedanib and seven studied other agents in the treatment of

IPF. One study compared pirfenidone to placebo in IPF patients receiving background N-acetylcysteine [17]. Another study comprised of two separate cohorts where lebrikizumab was compared to placebo with and without background pirfenidone. Four studies examined multiple different doses of antifibrotics. The remaining six RCTs studied pirfenidone and nintedanib (four and two studies, respectively) in the treatment of non-IPF progressive fibrotic ILD. Most studies were multi-centred with study duration ranging between 12 weeks to 254 weeks. 11 of 16 IPF studies used the 2011 international consensus statement [1] while the remainder used the 2000 statement [34]. Both RCTs in SSc-ILD used the same international classification criteria [35]. Two studies included patients with non-IPF progressive fibrotic ILD of various aetiology, one included rheumatoid arthritis associated-ILD and the last included fibrotic unclassifiable ILD. While three studies required evidence of disease progression, different definitions were used.

Table 4.1. Summary of included studies.

Authurs	Year	Location	Duration	Study population	Antifibrotic (n)	Comparator (n)	Primary Outcome	Secondary Outcome
Azuma *et al.* (16)	2005	Japan, multicentre	9 months	IPF	Pirfenidone	Placebo	Change in the lowest SpO2 during a 6-minute steady-state exercise test (6MET).	Changes in lung function, disease progression by HRCT patterns, acute exacerbation, serum biomarkers, HrQOL.
Acharya *et al.* (29)	2020	India, single centre	6 months	Ssc-ILD	Pirfenidone	Placebo	Proportion of subjects with either improvement or stabilization in FVC at 6 months.	Changes in FVC, 6MWD, MRSS, serum biomarker levels, and adverse events.
Behr *et al.* (31)	2021	Germany, multicentre	48 weeks	Progressive fibrotic ILD	Pirfenidone	Placebo	Absolute change from baseline in FVC% predicted	Time to disease worsening and time to progression-free survival. Change from baseline in pulmonary function variables and HrQOL
Distler *et al.* (32)	2019	Multinational	52 weeks	Ssc-ILD	Nintedanib	Placebo	Annual rate of decline in FVC (mL)	Absolute change in HrQOL scores, lung function and digital ulcer net burden. Time to all-cause mortality. Proportion of patients with relative decline in FVC >5% and >10% predicted.
Flaherty *et al.* (33)	2019	Multinational	52 weeks	Fibrosing ILD	Nintedanib	Placebo	Annual rate of decline in FVC (mL)	Absolute change from baseline in HrQOL scores and lung function. Time to first acute exacerbation, death, progression. Proportion of patients with absolute/relative decline in FVC>5% and >10% predicted
Huang *et al.* (19)	2015	China, multicentre	48 weeks	IPF	Pirfenidone + NAC	Placebo + NAC	Change in FVC, maximal 6MWD and lowest SpO2.	Change in lung function, arterial blood gas, HrQOL scores, CT fibrosis. Progression of fibrosis, acute exacerbations and adverse events.
King *et al.* (15)	2014	Multinational	52 weeks	IPF	Pirfenidone	Placebo	Change FVC% predicted from baseline to week 52	All-cause mortality, IPF-related mortality, change in HrQOL score from baseline, adverse effects
Lancaster *et al.* (21)	2020	Multinational	6 months	IPF	Nintedanib	Placebo	Relative change from baseline in QLF score (%)	Change in lung function, 6MWD, HrQOL scores. Time to mortality event, hospitalisation and acute exacerbations
Maher *et al.* (24)	2018	Multinational	12 weeks	IPF	GLPF1690	Placebo	Safety and tolerability profile	Change in lung function, exploratory blood and broncheoalveolar lavage biomarkers and HrQOL scores
Maher *et al.* (22)	2019	Multinational	12 weeks	IPF	Nintedanib	Placebo	Rate of change in blood CRPM	Proportion of patients with disease progression. Rate of lung function decline, Time to progression and acute exacerbation. Safety analysis.

Maher *et al.* (30)	2020	Multinational	24 weeks	Unclassifiable ILD	Pirfenidone	Placebo	Rate of decline in FVC in mL measured by handheld spirometry.	Decline in FVC measured by site spirometry. Change in lung function, 6MWD, HrQOL. Hospitalisation, acute exacerbation, PFS, adverse events and time to death.
Maher *et al.* (27)	2021	Multinational	52 weeks	IPF	Lebrikizumab	Placebo	Annualised rate of decline in FVC% predicted	PFS, anualised rates of decline in lung function, 6MWD and HrQOL. Time to death.
					Lebrikizumab + Pirfenidone	Placebo + Pirfenidone		
Noble *et al.* (18)	2011	Multinational	72 weeks	IPF	Pirfenidone	Placebo	Change in FVC% predicted from baseline	PFS, 6MWD, HrQOL, lung function, mortality
Parker *et al.* (25)	2017	Multinational	52 weeks	IPF	Tralokinumab	Placebo	Absolute change from baseline in FVC% predicted	Percentage of patients with disease progression, lung function, HrQOL scores, mortality, adverse events, pharmacokinetics.
Raghu *et al.* (23)	2017	Multinational	up to 254 weeks *	IPF	Simtuzumab	Placebo	PFS	Overall survival, lung function, HrQOL, 6MWD, acute exacerbation, mortality, adverse events.
Raghu *et al.* (26)	2018	Multinational	28 weeks	IPF	Pentraxin-2	Placebo	Change in FVC% predicted from baseline	Change in lung function, proportion of patients with lung function decline, 6MWD, HrQOL.
Richeldi *et al.* (20)	2011	Multinational	52 weeks	IPF	Nintedanib	Placebo	Annual rate of decline in FVC (mL)	Change in lung function, 6MWD, HrQOL scores, oxygen saturation levels. Mortality and acute exacerbations.
Richeldi *et al.* (14)	2014	Multinational	52 weeks	IPF	Nintedanib	Placebo	Annual rate of decline in FVC (mL)	Time to acute exacerbation, mortality, change in lung function, oxygen saturations and HrQOL.
Richeldi *et al.* (28)	2019	Multinational	48 weeks	IPF	Pamrevlumab	Placebo	Change in FVC% predicted from baseline	Disease progression. change in lung function, quantitative lung fibrosis score and HrQOL scores. Adverse events
Richeldi *et al.* (35)	2022	Multinational	12 weeks	IPF	BI 1015550	Placebo	Change in FVC from baseline	Change in lung function and HrQOL. Adverse events.
Solomon *et al.* (34)	2023	Multinational	52 weeks	RA-ILD	Pirfenidone	Placebo	Composite endpoint of decline in FVC>10% or death	Change in lung function, HrQOL scores and proportion of patients with progressive disease. Time to composite endpoint of decline in FVC>10% or death, hospitalisation, mortality, acute exacerbations and lung transplantation. Adverse events.
Taniguchi *et al.* (17)	2010	Japan, multicentre	52 weeks	IPF	Pirfenidone	Placebo	Change in VC from baseline	PFS, change in lowest oxygen saturation during 6MET.

4.4.2 Risk of bias assessment

Studies included in the systematic review generally scored well for domains related to random sequence generation, allocation concealment, outcome assessment blinding and reporting bias. However, 50% of studies were at high or unclear risk of bias due to incomplete outcome data (Figure 4.2).

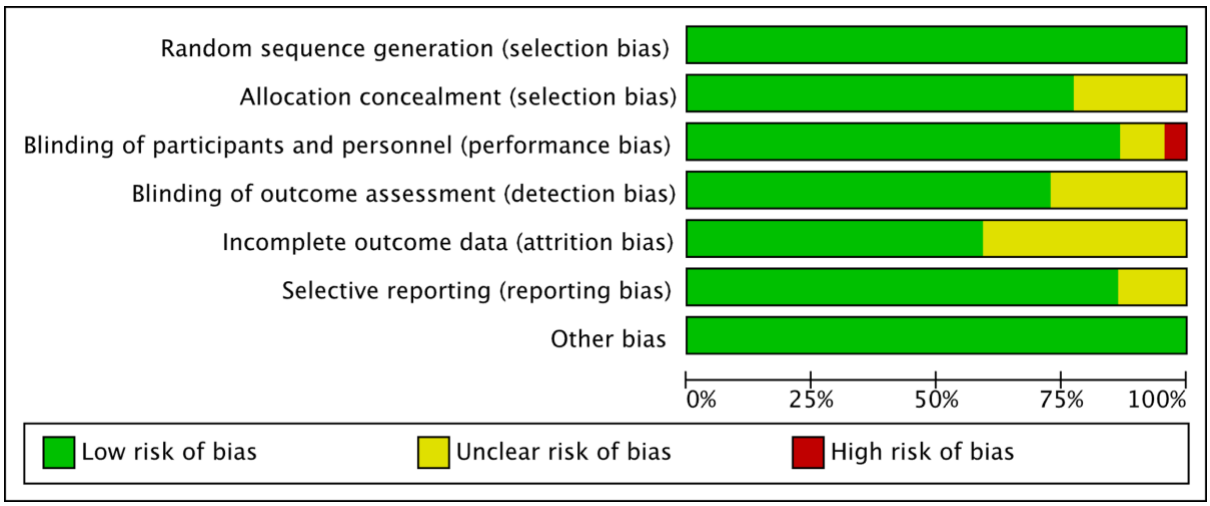

Figure 4.2. Risk of bias

4.4.3 Primary outcomes

4.4.3.1 FVC Change

IPF

Nintedanib:

The mean difference in change in ppFVC from baseline favoured nintedanib over placebo by 2.69% predicted (95% CI 1.63-3.75, 3 studies, 1597 participants) [12, 18, 19]. Multiple different

doses of nintedanib were used across studies and heterogeneity was high (I^2=96%) (Figure 4.3A).

Pirfenidone:

Pooled analysis of the effect of pirfenidone on the change in ppFVC was limited due to insufficient data and variable endpoints. Based on available data (Table 4.2), mean difference in ppFVC change from baseline significantly favoured pirfenidone over placebo by 2.96% predicted (95% CI 0.73 to 5.18% predicted, 3 studies, 768 participants, I^2=0%) [16, 17] (Figure 4.3B).

Table 4.2. FVC outcome variables in studies of pirfenidone for IPF.

Study	**Outcome**	**Pirfenidone**	**Placebo**	**Comment**
King 2014 [13]	ppFVC change from baseline to week 52	n/a	n/a	(p<0.001)
	Proportion of patients with decline ppFVC≥10%/death:	46 patients (16.5%)	88 patients (31.8%)	p<0.05*
	Proportion of patients with no decline ppFVC	63 patients (22.7%)	27 patients (9.7%)	
	Mean decline FVC (mL)	235mL	428mL	Relative difference 45.1%, p<0.001)
	Linear slope of FVC decline (mL)	-164mL	-280mL	Relative difference (41.5%, p<0.001)

Huang 2015 [17]	Mean decline FVC (L) at 24 weeks	-0.08 ± 0.20L	-0.22 ± 0.29L	p=0.02
	Mean decline FVC (L) at 48 weeks	-0.15 ± 0.25L	-0.25 ± 0.28L	p=0.11
	Mean ppFVC decline at 24 weeks	0.68 ± 7.66%	6.11% ± 7.70%	p=0.004
	Mean ppFVC change at 48 weeks	-1.95 ± 9.99%	-5.40 ± 6.56%	p=0.10
Noble 2011 (study 004) [16]	Mean ppFVC change	-8% (16.5)	-12.4% (18.5)	P=0.001 *
	Proportion of patients with ppFVC decline ≥10%	35 (20%)	60 (35%)	Absolute difference 14.4 (95% CI 7.4 to 21.3), p=0.001
Noble 2011 (study 006) [16]	Mean ppFVC change	-9% (19.6)	-9.6% (19.1)	p=0.501 *
	Proportion of patients with ppFVC decline ≥10%	39 (23%)	46 (27%)	Absolute difference 3.8 (95% CI -2.7 to 10.2), p=0.44
Noble 2011 (pooled) [16]	Mean ppFVC change	-8.5%	-11.0%	p=0.005 *
	Proportion of patients with ppFVC decline ≥10%	74 (21%)	106 (31%)	Absolute difference 9.1 (95% CI 4.3 to 13.9), p=0.003
Taniguchi 2010 (high dose) [15]	Mean VC change from baseline	-0.09L ± 0.02 †	-0.16L ± 0.02 †	P=0.0416

Taniguchi 2010 (low dose) [15]	Mean VC change from baseline	-0.08L ± 0.03 †	-0.16L ± 0.02 †	P=0.0394
Azuma 2005 [14]	Mean VC change from baseline	-0.03L ± 0.22	-0.13L ± 0.19	P=0.0366

Continuous variable data expressed as mean ± standard deviation, unless stated otherwise.

ppFVC: forced vital capacity percent predicted, mL: millilitres, L: litres, VC: vital capacity

* Rank ANCOVA (pirfenidone vs placebo)

† Adjusted mean ± standard error

Other agents:

The least-squares (LS) mean change in ppFVC from baseline favoured recombinant human pentraxin 2 over placebo by 2.3% predicted (95% CI 1.1 to 3.5% predicted) [24]. The mean change in ppFVC from baseline also favoured the agent GLPG1690 over placebo by 2.8% predicted (95% CI -0.71 to 6.31% predicted) [22]. In a phase 2 trial of tralokinumab, the LS mean change in ppFVC from baseline favoured placebo over tralokinumab 400mg and 800mg by -2.02% (95% CI -6.00 to 1.96% predicted) and -1.99% (95% CI –5.58 to 1.60) [23]. The LS mean change in ppFVC from baseline favoured pamrevlumab over placebo by 4.3% (95% CI 0.4 to 8.3% predicted) [26]. A study of simtuzumab reported a relative change in ppFVC from baseline of -6.26% (95% CI -10.85 to -1.68% predicted), favouring placebo [21]. When lebrikizumab was compared to placebo, the rate of annualised ppFVC decline non-significantly favoured lebrikizumab by 1% (95% CI -1.58 to 3.58) and in a separate cohort of participants concomitantly receiving background pirfenidone by 0.5% (95% CI -1.18 to 2.18) [25]. In a study of a preferential phosphodiesterase-4B inhibitor, Bayesian analysis of the median change in FVC over 12 weeks showed a favourable difference of 88.4ml (95% CI 29.5 to 154.2) in

participants without background antifibrotics and 62.4ml (95% CI 6.3 to 125.5) in those using background therapy.

Non-IPF ILD

Nintedanib:

The adjusted annual rate of decline in FVC favoured nintedanib over placebo by 73.36mL (95% CI 8.59 to 138.13mL, 2 studies, 1239 participants) [30, 31] (Figure 4.3C). Study heterogeneity was high (I^2=81%), which may have been related to dose reductions permitted in both studies, different population cohorts and different regression model covariates.

Pirfenidone:

The mean change in ppFVC from baseline favoured pirfenidone over placebo by 2.10% predicted (95% CI 1.04 to 3.17% predicted, 4 studies, 497 participants, I2=0%) [27, 28, 29, 32] (Figure 4.3D).

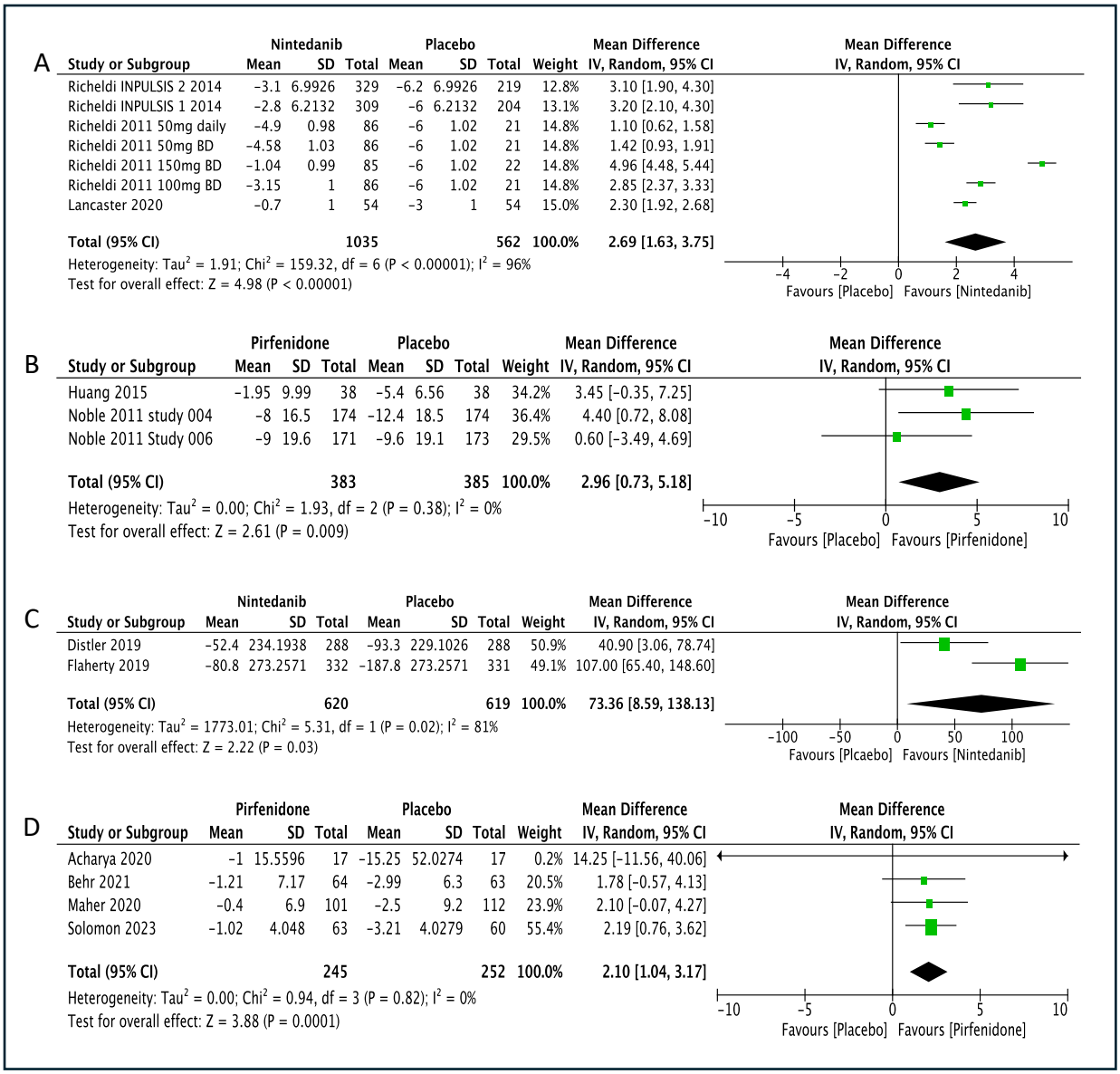

Figure 4.3. Mean difference of change in ppFVC (A) between nintedanib and placebo in patients and (B) between pirfenidone and placebo in patients with IPF; (C) Mean adjusted rate of change in FVC between nintedanib and placebo in patients with non-IPF fibrosing ILD; (D) Mean difference in ppFVC change from baseline between pirfenidone and placebo in patients with non-IPF fibrosing ILD.

4.4.3.2 Progression-free survival (PFS)

Pooled analysis of PFS could not be performed due to variations in PFS definitions used. Nonetheless, pirfenidone appeared to significantly prolong PFS in IPF studies, though this effect was not seen in non-IPF studies. Individual studies of simtuzumab, lebrikizumab and tralokinumab showed no significant effect on PFS. Studies reporting PFS are summarised in Table 4.3.

Table 4.3: Progression free survival in patients with IPF and non-IPF ILD

Study (drug)	**Definition**	**Timepoint**	**Outcome**
	IPF		
King *et al.* 2014 [13] (Pirfenidone)	Time to the first occurrence of any one of the following: - A confirmed decrease of ≥10% points in ppFVC - A confirmed decrease of ≥50meters in the 6MWT distance - Death	52 weeks	HR 0.57 (95% CI 0.43 to 0.77, p<0.001)
Noble *et al.* 2011 (study 004 and study 006)[16] (Pirfenidone)	Time to any of the following: - Confirmed ≥10% decline in ppFVC - ≥15% decline in ppDLCO - Death	72 weeks	Pooled HR 0.74 (95% CI 0.57 to 0.96, p=0.025)
Taniguchi *et al*. 2010 [15] (Pirfenidone)	Time to: - Death AND/OR	52 weeks	High dose cohort (1800mg/day): Log-rank test p=0.028*

	- ≥10% decline in absolute changes in measured VC - VC could not be obtained due to worsening respiratory symptoms, including acute exacerbation		Low dose cohort (1200mg/day): Log-rank test p=0.0655*
Huang *et al.* 2015 [17] (Pirfenidone)	Time until the first occurrence of any one of the following: - A confirmed ≥10% decline in ppFVC - A confirmed ≥15% decline in ppDLCO - A confirmed progression of fibrosis defined by the HRCT fibrosis score, acute exacerbation of IPF or death	48 weeks	HR 1.88 (95% CI 1.09 to 3.24, p=0.02) †
Raghu *et al.* 2017 [21] (Simtuzumab)	Time between randomisation and: - All-cause death OR - A categorical decrease from baseline in ppFVC (ie, a patient with ≥10% relative decrease and ≥5% absolute decrease)	Up to 148 weeks	HR 1.13‡ (95% CI 0.74 to 1.43, p=0.851)
Maher *et al.* 2020 [25] (Lebrikizumab)	Time from randomisation to:	Up to 122 weeks	Cohort A (no background pirfenidone): HR 0.65 (95% CI 0.39 to 1.09; p=0.097)

	- First occurrence of death from any cause - Non-elective hospitalisation for any cause - Relative decline in ppFVC		Cohort B (background pirfenidone): HR 1.01 (95% CI 0.72 to 1.42; p=0.934)
Parker *et al.* 2017 [23] (Tralokinumab)	Percentage of patients with disease progression defined as: - FVC decline ≥ 10% - 6MWT distance decline ≥ 50m - Adjudicated respiratory-related mortality - Adjudicated hospitalisation due to IPF exacerbation	52 weeks	Tralokinumab 800mg: 35.1% Tralokimumab 400mg: 28.8%
Non-IPF ILD			
Maher *et al.* 2020 [28] (Pirfenidone)	Time to: >10% decline ppFVC>50m decline 6MWD or death	24 weeks	HR 0.84 (95% CI 0.56 to 1.24; p=0.366)
	Time to: >10% relative decline ppFVC, non-elective respiratory hospitalisation or death		HR 0.79 (95% CI 0.52 to 1.2; p=0.273)
Behr *et al.* 2021 [29] (Pirfenidone)	Time to first occurrence of: - > 10% absolute ppFVC decline - > 15% absolute ppDLCO decline - Death	48 weeks	Data unavailable (logrank p=0.20)

*HR not reported

† Study participants received background N-acetylcysteine

‡ Stratified log-rank test, adjusted for screening post-bronchodilator FVC % predicted, serum Lysyl oxidase-like 2 (LOXL2) level categories and concomitant use of pirfenidone or nintedanib (P/N) at time of screening.

4.4.3.3 Health-related Quality of Life (HrQOL)

IPF

Pooled analysis of change in HrQOL scores was not possible for studies examining the effect of pirfenidone due to different questionnaires used and insufficient data available. The mean difference in change of St George's Respiratory Questionnaire (SGRQ) total score from baseline favoured nintedanib over placebo by -2.13 points (95% CI -3.69 to -0.57, 3 studies, 1561 participants, I^2=23%), with a lower score indicating better quality of life (Figure 4.4A) [12, 18, 19]. Neither mean difference nor the lower end of the confidence interval exceeded the minimal important difference (MID) of 4 points [36]. Table 4.4 summarises HrQOL scores for individual studies.

Non-IPF ILD

Pooled analysis of SGRQ total scores in 2 studies of non-IPF ILD favoured pirfenidone with a mean difference of -1.05 points (95% CI -4.23 to 2.13, 2 studies, 253 participants, I^2=0%) (Figure 4.4B) [28, 29]. Different HrQOL scores prevented pooled analyses of studies nintedanib studies.

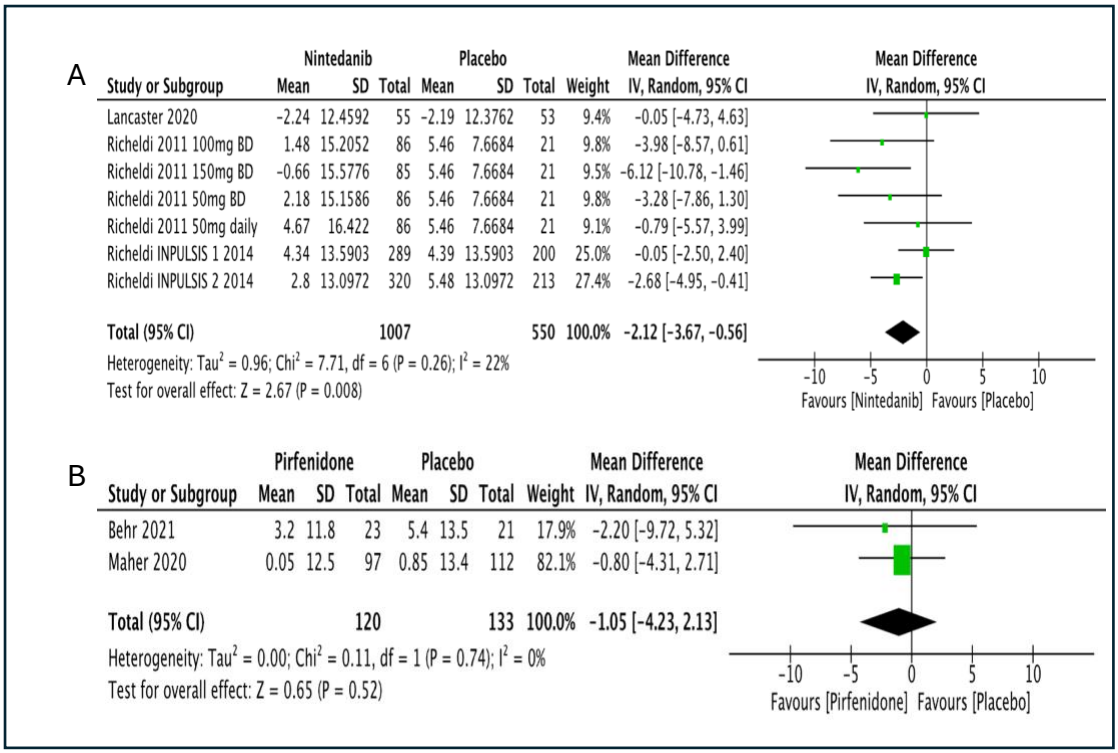

Figure 4.4. (A) Pooled mean absolute change in total SGRQ score from baseline between nintedanib and placebo in patients with IPF; (B) Pooled mean absolute change in total SGRQ score from baseline between pirfenidone and placebo in patients with non-IPF ILD.

Table 4.4. Health-related quality of life scores in patients with IPF and PPF.

Study (drug)	QOL score	Timepoint	Outcome
IPF			
King *et al.* 2014 [13] (Pirfenidone)	UCSD-SOBQ	52 weeks	Absolute between-group difference (dyspnoea score increase ≥ 20 points) 7%, relative reduction 19.3%, p=0.16
Noble *et al.* 2011 (study 004 and study 006) [16] (Pirfenidone)	UCSD-SOBQ	72 weeks	Study 004: Absolute difference -3.1 (95% CI -8.5 to 2.3, p=0.509) Study 006: Absolute difference -2.0 (95% CI -7.6 to 3.6, p=0.604)

Taniguchi *et al*. 2010 [15] (Pirfenidone)	Hugh-Jones classification	52 weeks	Data unavailable
Azuma *et al.* 2005 [14] (Pirfenidone)	Chronic Respiratory Disease Questionnaire	9 months	Data unavailable p=0.6367
	Hugh-Jones classification		Data unavailable p=0.8720
Huang *et al.* 2015 [17] (Pirfenidone)	Total SGRQ	48 weeks	Mean difference -6.37 points (95% CI -4.72 to 1.70)
	Borg dyspnoea score		Mean difference -0.96 points (95% CI -2.25 to 0.33)
Richeldi *et al.* 2014 [12] (Nintedanib)	Total SGRQ	52 weeks	Mean pooled difference -1.43 points (95% CI -3.09 to 0.23, p=0.09)
Richeldi *et al.* 2011 [18] (Nintedanib)	Total SGRQ	52 weeks	Change in total SGRQ score from baseline 150mg BD: -0.66 (95% CI -4.02 to 2.71) 100mg BD: 1.48 (95% CI -1.78 to 4.75) 50mg BD: 2.18 (95% CI -1.07 to 5.43)

			50mg daily: 4.67 (95% CI 1.17 to 8.16)		
Lancaster *et al.* 2020 [19] (Nintedanib)	Total SGRQ	6 months	Mean difference -0.05 (95% CI -4.89 to 4.79)		
	UCSD-SOBQ		Mean difference 4.89 (95% CI -1.47 to 11.25)		
Raghu *et al.* 2017 [21] (Simtuzumab)	Total SGRQ	Up to 148 weeks	Data unavailable		
Maher *et al.* 2021 [25] (Lebrikizumab)	ATAQ-IPF	52 weeks	Annualised rate of decline		
			Cohort A: Absolute difference -2.10, relative difference -30.5%		
			Cohort B: Absolute difference -0.16, relative difference -2.9%		
	Borg scale		Only baseline data available		
	Total SGRQ (Cohort A)		HR 0.84 (95% CI 0.54 to 1.31)		
Maher *et al.* 2018 [22] (GLPG1690)	SGRQ	12 weeks	Symptom domain: mean difference -8.35		
			Activity domain: mean difference -6.46		
			Impact domain: mean difference -7.12		
Parker *et al.* 2018 [23] (Tralokinumab)		72 weeks	Placebo	400mg	800mg
	UCSD-SOBQ		12.9 ± 14.7	-0.4 ± 18	10.9 ± 23.3
	Total SGRQ		2.91 ± 14.92	3.16±15.11	3.38 ± 14.88
	EXACT-IPF		1.95 ± 7.46	0.63±7.5	1.81 ± 10

	EQ-5D-3L		-3.0 ± 17.9	2.5 ± 20.9	0.6 ± 14.3
	PGI-C CGI-C CGI-S		Number of participants per score available		
Richeldi *et al.* 2019 [26] (Pamrevlumab)	Total SGRQ	48 weeks	Mean difference -5.4 (95% CI -11.7 to 1.0)		
	UCSD-SOBQ		LS mean -13.32 (95% CI -26.39 to -0.25)		
Non-IPF ILD					
Maher *et al.* 2020 [28] (Pirfenidone)		24 weeks	Mean change from baseline		
			Pirfenidone	Placebo	
	Leicester Cough Questionnaire		0.36 ± 2.9	0.04 ± 3.7	
	SGRQ		0.05 ± 12.5	0.85 ± 13.4	
	UCSD-SOBQ		5.21 ±18.7	5.30 ± 22.1	
	Cough VAS		-2.52 ± 26.7	0.78 ± 30.1	
Solomon *et al.* 2023 [32]	Dyspnea-12 Questionnaire	52 weeks	Pirfenidone	Placebo	
			0.46 (0.71)*	1.38 (0.72)*	
Behr *et al.* 2021 [29] (Pirfenidone)	SGRQ	48 weeks	Hodges-Lehman estimate for difference between treatment: -3.30 (95% CI -10.7 to 4.1)		
Flaherty *et al.* 2019 [31] (Nintedanib)	K-BILD	52 weeks	Mean difference 1.34 points (95% CI -0.31 to 2.98)		
Distler *et al.* 2019 [30]		52 weeks	Mean difference (95% CI)		

(Nintedanib)	SGRQ		1.69 (95% CI -0.73 to 4.12)
	HAQ-DI		0.032 (95% CI -0.035 to 0.099)
	FACIT-Dyspnea		0.64 (95% CI -0.51 to 1.79)

UCSD-SOBQ = University of California San Diego Shortness of Breath Questionnaire; SGRQ = St George's Respiratory Questionnaire; ATAQ-IPF = A Tool to Assess the Quality of Life in IPF; EXACT-IPF = Exacerbations of Chronic Pulmonary Disease Tool diary; PGI-C = Patient Global Impression of Change; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; VAS = Visual analogue scale; K-BILD = King's Brief Interstitial Lung Disease Questionnaire; HAQ-DI = Health Assessment Questionnaire–Disability Index; FACIT = Functional Assessment of Chronic Illness Therapy

* Mean (Standard error)

4.4.4 Secondary outcomes

4.4.4.1 All cause and respiratory mortality

IPF

Pooled analysis of all-cause mortality at various timeframes favoured pirfenidone over placebo, RR of 0.69 (95% CI 0.48 to 0.99, 5 studies, 1697 participants, I^2=0%), (Figure 4.5A) [13, 14, 15, 16, 17]. Pooled analysis for all-cause mortality significantly favoured nintedanib over placebo, RR 0.22 (95% CI 0.10 to 0.49, 3 studies, 1604 participants, I^2 = 0%, p=0.0002) (Figure 4.5B) [12, 18, 19]. There was no difference in all-cause mortality in individual studies of lebrikizumab, pentraxin 2, simtuzumab, tralokinumab and pamrevlumab.

Analysis of 4 studies (1430 patients) comparing pirfenidone to placebo showed a non-significant reduction in pooled respiratory-cause mortality rate, RR of 0.61 (95% CI 0.37 to 1.00, $I^2 = 0\%$), favouring pirfenidone [13, 14, 16, 17]. Pooled analysis of respiratory-cause mortality from two studies (1491 patients) significantly favoured nintedanib (RR 0.17, 95% CI 0.06 to 0.44, $I^2 = 79\%$) [12, 18]. There was no significant difference in respiratory mortality when comparing lebrikizumab, pentraxin 2 and tralokinumab to placebo in their respective studies [23, 24, 25].

Non-IPF

There was no significant difference in pooled all-cause mortality in three studies comparing pirfenidone to placebo in non-IPF fibrosing ILD, RR 0.47 (95% CI 0.14 to 1.59, $I^2=0\%$) [28, 29, 32] (Figure 4.5C) and in two nintedanib studies, RR 1.00 (95% CI 0.59 to 1.70, $I^2 =0\%$) [30, 31] (Figure 4.5C). No significant difference in respiratory-cause mortality were reported in two separate studies comparing pirfenidone and nintedanib versus placebo respectively [29, 30].

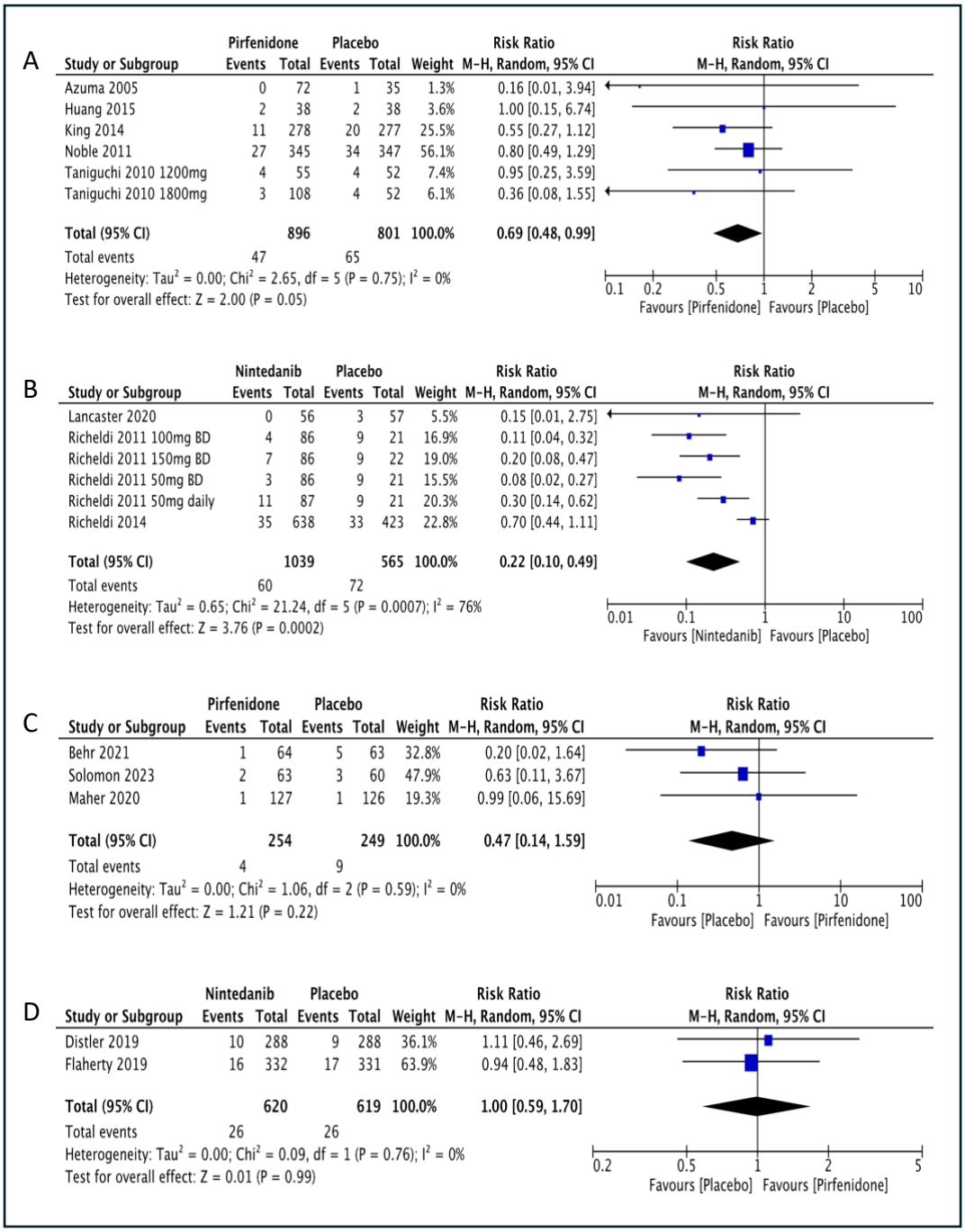

Figure 4.5. Pooled risk ratio for all-cause mortality in IPF (A) comparing pirfenidone versus placebo in IPF, (B) comparing nintedanib versus placebo in IPF, (C) comparing pirfenidone versus placebo in non-IPF fibrosing ILD and (D) comparing nintedanib versus placebo in non-IPF fibrosing ILD.

4.4.4.2 Change in 6MWD

IPF

The mean change in 6MWD from baseline in two studies showed a significantly higher 6MWD in those treated with pirfenidone compared to placebo with a mean difference of 23.05m (95% CI 4.78 to 41.33, I^2 = 0%) [16, 17]. Only one study compared nintedanib to placebo, mean difference of 18m (95% CI 13.83 to 22.17) [19].

There was no significant change in 6MWD over various timepoints in studies comparing pentraxin 2, simtuzumab and tralokinumab each to placebo [21, 23, 24]. A study favoured lebrikizumab to placebo with an absolute difference of 21.9m/year in annualised rate of 6MWD decline but was conversely worse at -21.4m/year in a cohort with background pirfenidone treatment [25].

Non-IPF

Pooled data from two studies in non-IPF fibrosing ILD favoured pirfenidone over placebo, mean 6MWD difference of 25.98m (95% CI 7.92 to 44.05, I^2=0) [28, 29].

4.4.4.3 Change in ppDLCO

IPF

Pooled analysis of available data showed the mean difference in ppDLCO change from baseline non-significantly favouring pirfenidone by 0.9% (95% CI -0.84 to 2.64, 3 studies, 768 participants, I^2=8%) [16, 17]. Another study reported a mean absolute DLCO change from baseline

at 0.62ml/min/mmHg (95%CI -0.29 to 1.53) [14]. Mean change in absolute DLCO from baseline showed no significant difference between nintedanib and placebo at -0.01 mmol/min/kPA (95%CI -0.12 to 0.09) [12, 18]. There was no significant difference seen in studies of simtuzumab, tralokinumab and pentraxin 2 [21, 23, 24].

Non-IPF

In a study comparing pirfenidone to placebo in unclassifiable ILD, the mean difference in change of ppDLCO from baseline was 1.8% (95% CI -0.37 to 3.97) [28]. Another study of progressive, fibrosing ILD reported a mean difference in absolute DLCO change from baseline of 0.4 mmol/kPa/min (95% CI 0.1 to 0.7) [29]. The mean difference in ppDLCO change from baseline was -0.44% (95% CI -1.94 to 1.06) in a nintedanib study in Ssc-ILD [30].

4.4.5 Adverse events

IPF

Compared to placebo, IPF participants receiving pirfenidone had an increased risk of nausea, photosensitivity reaction, rash and anorexia (Table S3). Risk of elevated alanine and/or aspartate aminotransferase (ALT and/or AST) of three or more times the upper limit of normal (⩾3 ULN) were higher with those receiving pirfenidone (RR 2.32, 95% CI 0.42 to 12.86, 4 studies, 1430 participants, I^2=77%). Pooled analysis of studies comparing nintedanib to placebo showed a higher relative risk of diarrhoea, nausea, vomiting, decreased appetite and transaminitis (Table 4.5).

Non IPF

Participants with non-IPF ILD receiving pirfenidone had higher risk of nausea. There were no significant differences in the relative risk of rash, weight loss, dizziness, fatigue, diarrhoea and decreased appetite (Table S3). The risk of diarrhoea, nausea, vomiting, weight loss, abdominal pain and elevated AST and/or ALT ⩾3 ULN were greater in participants receiving nintedanib. (Table 4.5).

Table 4.5. Pooled analyses of most common adverse events of pirfenidone and nintedanib in patients with IPF and PPF.

Adverse event	**Studies (n)**	**Participants (n)**	**Risk Ratio (95% CI)**	**I^2**	**p value**
Pirfenidone in IPF					
Fatigue	4	1441	1.42 (1.09 – 1.84)	31%	0.009
Anorexia	7	1788	2.82 (1.97 – 4.03)	0%	<0.05
Transaminitis elevation	4	1430	2.32 (0.42 – 12.86)	77%	0.34
Nausea	5	1432	2.31 (1.88 – 2.84)	0%	<0.05
Diarrhea	4	1410	1.31 (1.01 – 1.71)	33%	0.04
Dizziness	5	1519	1.58 (1.20 – 2.08)	0%	0.001
Reflux	5	1519	1.70 (1.03 – 2.79)	35%	0.04
Photosensitivity	5	1072	2.95 (2.15 – 4.05)	38%	<0.05
Rash	4	1410	2.83 (2.21 – 3.63)	0%	<0.05
URTI	4	929	1.10 (0.80 – 1.49)	0%	0.56
Dyspnoea	2	631	0.84 (0.58 – 1.22)	0%	0.36
Dyspepsia	3	1323	2.66 (1.91 – 3.70)	0%	<0.05
Vomiting	3	1334	2.26 (1.31 – 3.88)	49%	0.003
Weight loss	3	1323	1.85 (1.24 – 2.75)	0%	0.003
GORD	5	1519	1.70 (1.03 – 2.79)	35%	0.04

Insomnia	3	1334	1.63 (1.13 – 2.35)	0%	<0.05
Back pain	2	631	0.83 (0.53 – 1.30)	0%	0.41
Nasopharyngitis	3	827	0.84 (0.70 – 1.01)	0%	0.07
Nintedanib in IPF					
Diarrhoea	8	1948	2.68 (2.14 – 43.37)	38%	<0.05
Nausea	8	1948	2.43 (1.72 – 3.42)	26%	<0.05
Vomiting	8	1948	3.22 (2.06 – 5.05)	0%	<0.05
Transaminase >3x ULN	8	1948	4.71 (1.94 – 11.45)	0%	<0.05
Transaminase >5x ULN	3	1407	6.27 (1.17 – 33.67)	0%	0.03
Transaminase >8x ULN	3	1407	2.39 (0.39 – 14.61)	0%	0.35
Cough	8	1948	0.88 (0.69 – 1.13)	0%	0.32
Decreased appetite	8	1948	2.01 (1.40 – 2.89)	0%	<0.05
Weight loss	3	1407	4.11 (0.80 – 21.07)	82%	0.09
IPF progression	7	1602	0.67 (0.50 – 0.91)	0%	<0.05
Dyspnoea	6	1489	0.73 (0.53 – 1.00)	0%	0.05
Bronchitis	6	1489	0.97 (0.71 – 1.32)	0%	0.84
Upper abdominal pain	4	428	1.81 (0.59 – 5.53)	0%	0.30
Headache	6	887	1.62 (0.92 – 2.85)	0%	0.09
Fatigue	5	541	1.18 (0.64 – 4.35)	0%	0.59

Pirfenidone in PPF					
Rash	3	411	1.63 (0.85 – 3.13)	0%	0.14
Weight decrease	2	378	3.17 (0.41 – 24.32)	63%	0.27
Fatigue	2	378	1.17 (0.69 – 1.99)	0%	0.57
Nausea	3	411	2.51 (1.35 – 4.68)	50%	0.004
Dizziness	2	378	1.72 (0.81 – 3.64)	0%	0.16
Diarrhea	2	160	1.17 (0.56 – 2.44)	0%	0.67

Decreased appetite	2	160	3.16 (0.86 – 11.66)	0%	0.08
Nintedanib in PPF					
Diarrhea	2	1239	2.57 (2.20 – 3.00)	20%	<0.05
Nausea	2	1239	2.65 (2.02 – 3.49)	16%	<0.05
Vomiting	2	1239	2.81 (1.88 – 4.20)	36%	<0.05
Cough	2	1239	0.70 (0.52 – 0.93)	0%	0.01
Nasopharyngitis	2	1239	0.90 (0.61 – 1.33)	48%	0.54
Weight loss	2	1239	3.24 (2.06 – 5.10)	0%	<0.05
Abdominal pain	2	1239	2.48 (0.93 – 6.60)	78%	0.07
AST and/or ALT ≥3 ULN	2	1239	7.11 (3.43 – 14.75)	0%	<0.05

AST: aspartate transaminase, ALT: alanine transaminase

4.5 Discussion

This systematic review and meta-analysis summarised available data of 6849 patients across 22 RCTs for the efficacy and safety of antifibrotic agents for the treatment of IPF and PPF. In patients with IPF, we found that the relative effect of nintedanib on slowing the rate of decline of ppFVC from baseline was consistent across three studies, with a pooled difference of 2.69% predicted (95% CI 1.64-3.74% predicted). Despite individual studies of pirfenidone in the treatment of IPF showing efficacy, pooled analysis could not be performed. For the treatment of PPF, pooled analysis of nintedanib showed efficacy, with an adjusted annual rate of FVC decline by 73.39mL/year (95% CI 8.62 to 138.15mL) while pirfenidone also showed a pooled mean ppFVC change of 2% (95% CI 0.41 to 3.59% predicted).

Our results are in keeping with other studies and the global experience from cohort studies [37, 38, 39, 40, 41, 42]. It has taken almost a decade for nintedanib and pirfenidone to be widely accepted

as a treatment for IPF. This highlights the difficulties in running IPF trials, let alone successful, paradigm-changing ones. Though the successes of nintedanib and pirfenidone appear to extend to the treatment of PPF, these remain non-curative [27, 28, 29, 30, 31]. Other antifibrotic agents, despite some promising results, have yet to impact the management landscape significantly [43].

One major factor delaying progress has been the lack of reliable clinical trial endpoints. FVC is accepted as a clinically meaningful endpoint for IPF clinical trials [44, 45]. Over time, changes in FVC have repeatedly been shown to be an important and reliable endpoint and continue to being used in ILD clinical trials [46, 47, 48, 49, 50]. However, in both IPF and PPF where disease progression is often associated with poorer survival and irrecoverable lung function, reliance on a 12-month FVC trend is less than ideal. A recent individual participant data meta-analysis from IPF trials showed that FVC changes over 3 months were not only associated with poorer outcomes but also highly predictive of 12-month change [51]. These findings could potentially streamline future clinical trials to a shorter timeframe, being more cost-effective and mitigating the issue of missing data from patient death and loss to follow-up. More research is needed to refine endpoints for IPF and PPF trials, for the sake of patients living with such devastating progressive diseases.

Patient-reported outcomes measures (PROMs) and patient-centred approaches are an urgent priority for ILD trials [52, 53, 54, 55]. Despite the need of PROMs to measure HrQOL in patients, the lack of consensus in the optimal way of measuring HrQOL have resulted in different PROMs being used across IPF trials. Our study reflects this, as meta-analysis could only be performed on a limited number of studies. Although total SGRQ scores for nintedanib in IPF studies are numerically better, they do not reach MID of -4 points and hence, do not reflect a clinically important improvement. In PPF, only the lower CI endpoint in pooled analysis

reached the MID (Figure 8) making the benefit uncertain. The SGRQ, being first developed for COPD and asthma, may not necessarily capture all relevant aspects of IPF [56]. While an IPF-specific variation of SGRQ is available, evaluation of PROMs remains challenging in rarer diseases because of fewer patients and lack of power in clinical trials [57]. Furthermore, capturing precise patient perception may be limited in a heterogenous population with a wide range of disease severity, symptom perception, cultural and socioeconomic factors [56]. The development of IPF-specific PROMs such as the K-BILD and Living with IPF (L-IPF) questionnaires are early steps in the right direction but more high-quality, standardised PROMs are needed in future clinical trials [58, 59].

Some have proposed all-cause mortality as an ideal primary endpoint for IPF trials [60]. Our study showed that nintedanib in IPF significantly reduced all-cause and respiratory-cause mortality, but this effect was less significant with pirfenidone. However, other studies which included cohort studies showed a significant reduction in mortality with both agents [61, 62]. In the pooled studies of PPF, no significant differences were seen in all-cause mortality with pirfenidone and nintedanib when compared to placebo. This is likely due to fewer trials, some of which were hampered by recruitment difficulties and lower participant numbers. In keeping with another study [63], our findings suggest that a higher number of patients are needed to show significant differences in all-cause mortality from antifibrotic treatment. This supports the notion that it would be impractical to use all-cause mortality as a primary trial endpoint, without subjecting trials to longer follow-up periods, higher costs and larger participant numbers [64, 65].

Wide variations in PFS definitions prevented pooled analysis of the effects of nintedanib and pirfenidone on PFS in both IPF and PPF. Definitions were a combination of variables such as time to (i) $\geqslant$10% decrease in ppFVC, $\geqslant$50meters decrease in 6MWD or death, (ii) $\geqslant$10%

relative decline ppFVC, non-elective respiratory hospitalisation or death and (iii) >10% absolute ppFVC decline, >15% absolute ppDLCO decline or death. Progression was defined in the INBUILD study as (i) ⩾10% relative decline ppFVC, (ii) 5-10% relative decline ppFVC with worsening respiratory symptoms or increased radiological fibrosis, or (iii) worsening respiratory symptoms and increased fibrosis (31). An international consensus defined PPF as having at least two of three criteria occurring within the last year; (i) worsening respiratory symptoms, (ii) either ⩾5% absolute decline ppFVC or ⩾10% absolute decline ppDLCO and (iii) radiological evidence of disease progression. However, a recent multicentred, retrospective study showed that ⩾10% relative decline ppFVC strongly predicted reduced survival in non-IPF ILD across multinational cohorts, irrespective of ILD subtypes [66]. Six additional PPF criteria derived from previous trials were associated with reduced transplant-free survival (TFS), three of which required combinations of physiological, radiological and symptomatic worsening. When their stand-alone components were used, similar TFS prediction were still seen but in fewer patients. The study highlights that although the consensus PPF definition is a major step forward, more research is needed before widespread implementation.

Our study summarised pooled safety data on pirfenidone and nintedanib. We showed that pirfenidone was associated with higher rates of adverse events compared to placebo, with the most frequent being nausea, photosensitivity, rash, anorexia and transaminitis. Similarly, nintedanib was associated with more frequent diarrhoea, nausea, vomiting, decreased appetite and transaminitis. Our findings are consistent with open-label extension studies and real-world cohort data [67, 68, 69, 70, 71, 72]. Similar rates of adverse events were seen in PPF studies [27, 28, 29, 30, 31]. Despite global uptake of antifibrotic agents, it is envisaged that novel agents with fewer side effects may be on the horizon.

There were limitations to this meta-analysis. First, not all raw data were available for complete meta-analysis for several endpoints. Second, a major problem encountered was the lack of consistency in clinical trial endpoints of interest in our study, such as physiological data, PROMs and PFS definitions. Though unfortunate, our study aimed to summarise available data predating any attempt to standardize trial endpoints. It is hoped that with a standardised approach, improved trial designs with more meaningful clinical outcomes will follow. Third, our approach to analyse antifibrotic agents and conditions separately limited our ability to pool more data for analysis. However, we chose this design *a priori* over performing a network meta-analysis given the different pharmacological profile of each agent and possibly their effect on different ILD subtypes. Lastly, our study only included publications in English language and may have limited the scope of our search.

In conclusion, our meta-analysis shows both nintedanib and pirfenidone are effective in slowing ppFVC decline in both IPF and PPF, while nintedanib reduces mortality risk in IPF. Nintedanib was shown to improve HrQOL scores in IPF and pirfenidone in PPF. Their impact in the treatment of IPF and PPF is reflected in current international guidelines. While such achievements have changed the management paradigm of IPF and PPF, more work is needed. A recent survey of patients living with PF and their carers identified the need for better, more effective therapies and interventions designed to alleviate symptoms as top research priorities [73]. As antifibrotic agents were akin to the light at the end of a long tunnel, ongoing clinical trials are needed to continue providing a tangible sense of hope for our patients living with this condition.

4.6 Chapter Four References

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4.7 Chapter Four Supplementary Data

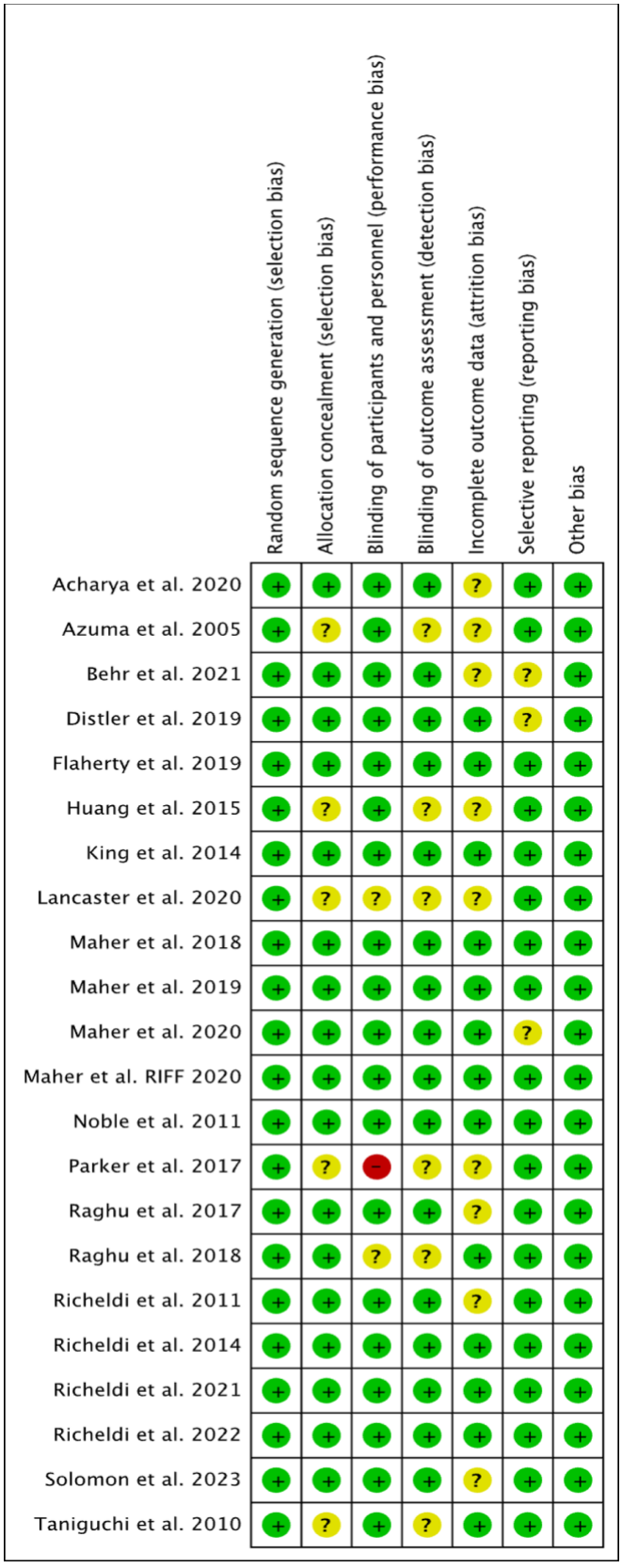

Figure 4.6. Risk of bias summary.

1 exp Lung Diseases, Interstitial/

2 (interstitial$ adj lung$ adj disease$).mp.

3 (interstitial$ adj (fibros$ or pneumonitis or pneumonia or pneumopathy)).mp.

4 alveolitis.mp.

5 exp Bronchiolitis Obliterans/ or (bronchiolitis adj obliterans).mp.

6 (goodpasture$ adj syndrome$).mp.

7 granulomatosis.mp.

8 exp Histiocytosis/ or histiocytosis$.mp.

9 exp Pneumoconiosis/ or pneumoconiosis.mp. or pneumokoniosis.mp. or pneumonoconiosis.mp.

10 bagassosis.mp.

11 (pulmonary$ adj sarcoid$).mp.

12 (pulmonary$ adj fibros$).mp.

13 (wegener$ adj granuloma$).mp.

14 (lung$ adj purpura).mp.

15 ((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$) adj (lung$ or disease$)).mp.

16 (asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis).mp.

17 Idiopathic Pulmonary Fibrosis/

18 IPF.mp.

19 Cryptogenic fibrosing alveolitis.mp.

20 Pulmonary Fibrosis/

21 Idiopathic Interstitial Pneumonias/

22 unclassifiable interstitial lung disease.mp.

23 progressive fibrotic interstitial lung disease.mp.

24 progressive fibrosing interstitial lung disease.mp.

25 non-specific adj3 interstitial adj pneum*.mp.

26 nonspecific adj3 interstitial adj pneum*.mp.

27 (((usual or ordinary) adj3 interstiti$) and pneumo$).mp.

28 chronic interstitial pneumonia.mp.

29 or/1-28

30 exp Scleroderma, Systemic/

31 scleroderma.mp.

32 exp Rheumatic Diseases/

33 rheumatic$.mp.

34 Connective Tissue Diseases/

35 Autoimmune Diseases/

36 or/30-35

37 36 and (lung$ or pulmonary$ or respiratory$).mp.

38 29 or 37

39 antifibro*.mp.

40 anti-fibro*.mp.

41 antifibro* adj agent*.mp.

42 antifibro* adj therap*.mp.

43 anti-fibro* adj agent*.mp.

44 anti-fibro* adj therap*.mp.

45 nintedanib*.mp.

46 pirfenidone*.mp.

47 or/39-46

48 38 and 47

49 progressive pulmonary fibrosis.mp.

50 48 or 49

Figure 4.7. MEDLINE and EMBASE (Ovid) search strategy

#1 MeSH descriptor Lung Diseases, Interstitial explode all trees

#2 interstitial* near lung* near disease*

#3 (interstitial*) near (fibros* or pneumonitis or pneumonia or pneumopathy)

#4 alveolitis*

#5 bronchiolitis near obliterans

#6 goodpasture* near syndrome*

#7 granulomatosis

#8 histiocytosis*

#9 pneumoconiosis or pneumokoniosis or pneumonoconiosis or pneumonokoniosis

#10 pulmonary* near sarcoid*

#11 pulmonary* near fibros*

#12 wegener* near granuloma*

#13 lung* near purpura

#14 (bird* near lung*) or (bird* near disease*)

#15 (farmer* near lung*) or (farmer* near disease*)

#16 (pigeon* near lung*) or (pigeon* near disease*)

#17 (avian* near lung*) or (avian* near disease*)

#18 (budgerigar* near lung*) or (budgerigar near disease*)

#19 asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis

#20 Idiopathic Pulmonary Fibrosis

#21 MeSH descriptor: [Idiopathic Pulmonary Fibrosis] explode all trees

#22 (Cryptogenic fibrosing alveolitis)

#23 MeSH descriptor: [Idiopathic Interstitial Pneumonias] explode all trees

#24 (unclassifiable interstitial lung disease)

#25 (progressive fibrotic interstitial lung disease)

#26 (progressive fibrotic interstitial lung disease)

#27 (usual interstitial pneumonia)

#28 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR#23 OR #24 OR #25 OR #26 OR #27)

#29 MeSH descriptor: [Scleroderma, Systemic] explode all trees

#30 scleroderma

#31 MeSH descripto: [Rheumatic Diseases] explode all trees

#32 rheumatic*

#33 #29 OR #30 OR #31 OR #32

#34 (#33 AND (lung* OR pulmonary* OR respiratory*))

#35 (#28 OR #34)

#36 antifibrotic*

#37 anti-fibrotic*

#38 anti-fibrotic agent*

#39 antifibrotic agent*

#40 anti-fibrotic therapy*

#41 antifibrotic therapy*

#42 nintedanib

#43 pirfenidone

#44 (#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43)

#45 (#35 AND #44)

Figure 4.8. CENTRAL search strategy

Chapter Five: Diagnosis and Antifibrotic Choice for Idiopathic Pulmonary Fibrosis: Analysis from the Australian Idiopathic Pulmonary Fibrosis Registry

Diagnosis and Antifibrotic Choice for Idiopathic Pulmonary Fibrosis: Analysis from the Australian Idiopathic Pulmonary Fibrosis Registry

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5.1 Abstract

Introduction: Nintedanib and pirfenidone are two antifibrotic therapies currently approved for the treatment of idiopathic pulmonary fibrosis. Their comparable efficacies have resulted in the absence on clear guidelines on the choice of agents for the treatment of IPF. The study aimed to describe the IPF diagnostic process and antifibrotic choice in an Australian cohort.

Methods: Participants with IPF were recruited from multiple Australian ILD centres into the Australian IPF registry (AIPFR). Participants without a recent multidisciplinary meeting case discussion and unable to consent were excluded. Participants and their respective physicians completed a proforma questionnaire at baseline, three, six and 12 months. Participants were also invited to participate in semi-structured telephone interviews.

Results: Between July 2017 and January 2021, 166 participants completed baseline questionnaires. Time to diagnosis from symptom onset was reported to be mostly between three to 12 months, with 27.4% reported a duration of over two years. Despite various reasons for diagnostic delays, majority of participants were satisfied with their overall care. Prescription rates were similar for nintedanib (51%) and pirfenidone (48%). While most physicians (43.5%) perceived equal shared decision-making in medication choice, only 42% of respective participants had similar perceptions. 86.7% participants reported potential side effects as at least a moderately important factor driving agent choice. Participants requested for further education on treatment, management and prognosis of their disease.

Conclusion: Our study described the diagnostic process and baseline antifibrotic choices for IPF in Australia. Future strategies to improve diagnostic delays and provide patient education are needed.

5.2 Introduction

Idiopathic pulmonary fibrosis (IPF), the most common chronic, fibrosing interstitial pneumonia, is characterised by relentless disease progression, worsening quality of life and ultimately, a guarded prognosis [1]. While reported incidence and mortality rates are highly variable, global incidence of IPF has increased over the last decade, suggesting an increasing burden of disease [2, 3].

Antifibrotic therapies have dramatically changed the global management landscape of IPF. In 2014, placebo-controlled randomised trials of pirfenidone, a novel antifibrotic agent and nintedanib, a multiple tyrosine kinase inhibitor, demonstrated reduction in annual FVC decline at 12 months compared to placebo [4, 5]. Consequently, IPF management guidelines include recommendations for both agents for IPF treatment [6]. Post-hoc and real-world cohort studies showed relatively good tolerability of both agents [7, 8, 9, 10]. However, the lack of head-to-head trials and near comparable efficacy have resulted in the absence of clear guidelines on which agent should be chosen. Decisions on treatment initiation and medication choice often stem from discussions between patient and their treating physician [11].

Disease registries have been established worldwide to collate real-world data on people diagnosed with IPF. While clinical trials assess treatment efficacy in well-defined and prespecified study populations, disease registries allow for longitudinal assessments of treatment efficacy in a broader, more diverse cohort, providing complementary insight into the management of conditions [12]. The Australian IPF registry (AIPFR) is a multicentred, prospective and observational disease registry established by the Lung Foundation Australia (LFA) in 2012 aimed at fostering collaborative research and providing epidemiological insight

on IPF in Australia [13]. Following federal regulatory and payer approval of antifibrotic agents for the treatment of IPF in Australia in 2016, there was a need to understand the impacts of such therapies on the management of people living with IPF across Australia.

In this study, we describe the characteristics and management pathways of newly diagnosed IPF patients, specifically exploring the decision-making process to commencing patients on antifibrotics.

5.3 Methods

5.3.1 AIPFR design

Data collection methodology for the AIPFR was previously described [13]. In stage 2 of the AIPFR, participants were recruited through 13 ILD centres with a multidisciplinary team meeting (MDM) following local position statement recommendations [14]. The study was approved by the human research ethics committee of Royal Prince Alfred Hospital, Sydney (HREC/11/RPAH/ X19-0476 &2019/ETH13556).

5.3.2 Registry Recruitment

Consecutive patients diagnosed with IPF at participating centres were invited to join the AIPFR between July 2017 and January 2021. Participants agreeing to join provided written consent. Exclusion criteria included participants with a historic diagnosis of IPF without a recent MDM discussion and those unable to provide written consent. Participants were deidentified and linked to individual unique registry ID numbers. Participants were included as part of a larger

study, with follow up at three, six and 12 months. We report the results of the baseline evaluation.

5.3.3 Study protocol

AIPFR co-ordinators in each state collected baseline participant data through standardized proforma questionnaires. Baseline data collected include anthropologic data, medical history, lung function and patient reported outcome measures (PROMs). A questionnaire specific to the AIPFR was designed to capture data on antifibrotic therapy prescription and management strategies for IPF. Separate questionnaires were administered for participants and respective treating physicians (Figure 5.2 and Figure 5.3). Data were collected at prespecified timepoints (zero months/time of consent, three months, six months and 12 months).

Participants who had consented to take part in this study were invited by e-mail to participate in semi-structured telephone interviews. The purpose of the interview was to explore participants' opinions and experiences regarding the process leading to a diagnosis of IPF and their subsequent management. Interviews were conducted by A.T., a study researcher and clinician involved in the care of people with IPF, guided by a list of open-ended questions (Table 5.6). The interviews were audio-recorded and transcribed verbatim.

5.3.4 Analysis

Categorical data in questionnaires were analysed descriptively as *n* (% of total). Continuous data were recorded as mean values and standard deviations (SD). Missing data were excluded. Interview response transcripts were analysed using a qualitative approach to content analysis,

allowing for common themes to be extracted. STATA v15.1 (StataCorp, College Station, TX,USA) was used for all statistical analyses.

5.4 Results

5.4.1 Baseline characteristics

185 participants were recruited into the Registry. Of these, 166 participants (90%) had completed the baseline questionnaires as part of the study protocol. Participant baseline characteristics are outlined in Table 5.1. Participants were typical for IPF with a median age of 73.1 (67.9 - 77.5) years and predominantly males (n=124; 75%). The majority of participants were either current or ex-smokers (67.7%). The most common comorbidities included gastroesophageal reflux disease (GORD) (42.7%), ischaemic heart disease (24.4%), diabetes mellitus (22.5%) and depression and/or anxiety (14.6%).

Mean forced vital capacity (FVC) was 87.6% predicted (SD 20.9) and mean diffusing capacity of the lungs for carbon monoxide (DLCO) was 53.3% predicted (SD 15.4). 120/156 (77%) participants responded to the questionnaire that they have symptoms of cough and/or dyspnoea.

Table 5.1. Baseline characteristics of the Australian Idiopathic Pulmonary Fibrosis Registry

Participants		n= 166
Age (years)		73.1 (67.9 - 77.5)
Gender	Male	124 (75%)
	Female	42 (25%)
BMI (kg/m^2)		29 (4.5)
Smoking status	Current smoker	4 (2.5%)
	Ex-smoker	103 (65.2%)
	Never smoker	51 (32.3%)
Comorbidities	GORD	67 (42.7%)
	Diabetes Mellitus	36 (22.5%)
	IHD	39 (24.4%)
	CCF	5 (3.2%)
	Lung cancer	3 (1.9%)
	Pulmonary hypertension	12 (7.6%)
	Depressionand/or Anxiety	23 (14.6%)
Lung function	FVC (L)	2.85 (0.8)
	FVC % predicted	87.6 (20.9)
	TLC (L)	4.39 (0.92)
	TLC % predicted	72.9 (0.14)
	DLCO	13. 15 (4.71)
	DLCO % predicted	53.3 (15.4)
PROM	SGRQ	38.8 (19.9)
	UCSD SOBQ	36.1 (26.0)
	HADS-A	5.0 (3.8)
	HADS-D	3.9 (3.2)
WHO functional class	I	63 (52.1%)
	II	47 (38.8%)
	III	10 (8.3%)
	IV	1 (0.8%)

Symptoms	SOB	120 (77%)
	Cough	120 (77%)

Data presented as mean (SD) or n (%). Age expressed as median (interquartile range). BMI: body mass index; GORD: gastroesophageal reflux disease; IHD: ischaemic heart disease; CCF: congestive cardiac failure; FVC: forced vital capacity; TLC: total lung capacity; DLCO: diffusing capacity of the lung for carbon monoxide; PROM: Patient reported outcome measures; SGRQ: St George's Respiratory Questionnaire; UCSD SOBQ: University California San Diego Shortness of Breath Questionnaire; HADS: Hospital Anxiety and Depression Scale, WHO: World Health Organisation; SOB: Shortness of breath

5.4.2 Participant-specific Questionnaire

5.4.2.1 Diagnostic process

Table 5.2 reports the participants' perspectives of the diagnostic process. Participants reported being diagnosed by a general respiratory physician (30.6%), a physician subspecialising in ILD or an ILD clinic (50.9%) and their general practitioner (GP) (15.3%). 3.2% reported that other physicians, such as their cardiologists, made the diagnosis.

18.3% participants reported receiving a diagnosis within 3 months from first symptoms. While the majority of participants received their diagnosis within 12 months, 27.4% reported a prolonged duration of over 2 years. 27.7% reported that the delay in diagnosis was due to time taken for them to see their GP following symptom onset, while 33.1% reported the time taken to be seen by a specialist after seeing their GP was the main reason for diagnostic delay. Other periods of potential delay were the time taken to receiving results from specialists following the initial review (14.5%) and time taken for specialists to discuss results at an MDM (19.9%). Other reasons raised by participants were time taken to have a lung biopsy and being misdiagnosed with another condition (n=2). (Table 5.2).

Table 5.2. Participants' perceptions on diagnostic process

Diagnosis made by	
GP	24 (15.3%)
Local Respiratory Physician	48 (30.6%)
ILD Physician/Clinic	80 (50.9%)
Other	5 (3.2%)
Duration of time from first symptoms to IPF diagnosis	
Less than 3 months	28 (18.3%)
3 – 6 months	33 (21.6%)
6 – 12 months	32 (20.9%)
1 – 2 years	18 (11.8%)
> 2 years	42 (27.4%)
Reason for diagnostic delay	
Symptoms to GP	46 (27.7%)
GP to specialist	55 (33.1%)
Specialist to results	24 (14.5%)
Results to MDT discussion	33 (19.9%)
Satisfaction with time taken to make diagnosis	
Very satisfied	40 (25.8%)
Satisfied	65 (43.9%)
Neither	27 (15.5%)
Dissatisfied	9 (5.8%)
Very dissatisfied	14 (9%)
Satisfaction in process of receiving diagnosis	
Very satisfied	47 (30.3%)
Satisfied	68 (43.9%)
Neither	24 (15.5%)
Dissatisfied	9 (5.8%)
Very dissatisfied	7 (4.5%)

Data presented as n (%). GP: general practitioner; ILD: interstitial lung disease; MDT: multidisciplinary team

The majority of participants were either very satisfied (25.8%) or satisfied (42%) with the time taken to achieve the diagnosis (Figure 5.1a). Similarly, most participants were very satisfied (30.3%) or satisfied (43.9%) with the process of receiving the diagnosis (Figure 5.1b).

Figure 5.1. Patient satisfaction level on (a) time taken to reach diagnosis, (b) experience of process of receiving diagnosis and (c) overall care received.

5.4.2.2 Antifibrotic therapies

121/135 (89.6%) participants were commenced on antifibrotic therapies. Of those who were not started on treatment (n=14), eight participants reported it to be their personal choice, two failed to qualify for subsidised antifibrotic therapies through the Australian Pharmaceutical Benefits Scheme (PBS), while the remainder reported that it was their physician's recommendation.

The choice of antifibrotic agents is shown in Table 5.3, with a near even distribution between the pirfenidone (n= 64/133; 48%) and nintedanib (n=68/133; 51%). While 57/134 (42.5%) participants reported an equal input from themselves and their physicians into antifibrotic choice, 24/134 (17.9%) patients perceived that the decision was made for them either mostly or completely by their physician, while 53/134 (39.6%) of patients perceived the decision on medication choice was made mostly or completely by themselves.

Table 5.3 shows the relative importance of various factors thought to impact on the choice of antifibrotic agent. Most patients reported that the concern of potential drug-related side effects was moderately to very important (111/128; 86.7%) as a factor influencing their choice of treatment. Fewer participants reported the number of tablets (51.2%) and comorbidities (52.9%) to be of at least moderate importance impacting treatment choice. While antifibrotics for IPF are supported by government subsidy, 42/131 (32%) and 23/131 (17.6%) reported cost to still be either a very important or important factor, respectively.

Table 5.3. Participants' perspective on antifibrotic therapies for IPF.

Antifibrotics recommended		n = 135
	Yes	121 (89.6%)
	No	14 (10.4%)
Reasons for not starting antifibrotic		n = 14
	Chose not to	8 (57.1%)
	Did not qualify	2 (14.3%)
	Doctor's recommendation	4 (28.6%)
Antifibrotic choice		n = 133
	Nintedanib 100mg BD	1 (0.75%)
	Nintedanib 150mg BD	67 (50.4%)
	Pirfenidone 2403mg	62 (46.6%)
	Pirfenidone 534-2402mg	2 (1.5%)
	Clinical trial	1 (0.75%)
Input into choice		n = 134
	Completely patient	32 (23.9%)
	Mostly patient	21 (15.7%)
	Equal	57 (42.5%)
	Mostly doctor	17 (12.7%)
	Completely doctor	7 (5.2%)
Factors impacting choice		
Side effects (n=128)	Very important	48 (37.5%)
	Important	45 (35.2%)
	Moderately important	18 (14%)
	Slightly important	11 (8.6%)
	Not important	6 (4.7%)
Tablet number (n=129)	Very important	13 (10.1%)
	Important	28 (21.7%)
	Moderately important	25 (19.4%)
	Slightly important	18 (13.9%)
	Not important	45 (34.9%)
Tablet frequency (n=128)	Very important	14 (10.9%)

	Important	31 (24.2%)
	Moderately important	27 (21.1%)
	Slightly important	13 (10.2%)
	Not important	43 (33.6%)
Comorbidities (n=157)	Very important	46 (29.3%)
	Important	16 (10.2%)
	Moderately important	21 (13.4%)
	Slightly important	23 (14.6%)
	Not important	51 (32.5%)
Cost (n=131)	Very important	42 (32%)
	Important	23 (17.6%)
	Moderately important	16 (12.2%)
	Slightly important	11 (8.4%)
	Not important	39 (29.8%)
Participant understanding		
Rationale for antifibrotics (n=124)	Completely understand	59 (47.6%)
	Almost completely understand	59 (47.6%)
	Moderate understanding	5 (4%)
	Little understanding	1 (0.8%)
Potential side effects (n=119)	Completely understand	55 (46.2%)
	Almost completely understand	55 (46.2%)
	Moderate understanding	8 (6.7%)
	Little understanding	1 (0.9%)
Prognosis (n=137)	Completely understand	45 (32.9%)
	Almost completely understand	57 (41.6%)
	Moderate understanding	18 (13.1%)
	Little understanding	14 (10.2%)
	No understanding at all	3 (2.2%)
Further information		
	Reasons for medication	60/135 (44.4%)

	Potential side effects	63/135 (46.7%)
	Usual progression and outcome	83/138 (60.1%)
	Cost	62/137 (45.3%)
	Management of potential side effects	78/132 (59.1%)

Data presented as n (%).

5.4.2.3 Patient Understanding and Education

When participants were asked to self-assess their degree of understanding of the rationale for starting antifibrotics, most participants (95.2%) reported complete or near complete understanding. Similarly, 92.4% participants reported at least a near complete understanding of the potential side effects associated with antifibrotics. 87.6% participants reported at least moderate degree of understanding on the prognosis of their condition at baseline appointments (Table 5.3).

Despite most participants report a good understanding of the rationale for treatment and potential side effects, 60/135 (44.4%) participants reported an interest or need for further education on the rationale for being offered antifibrotic therapies. 63/135 (46.7%) participants requested further education and information pertaining to potential drug-related side effects. Furthermore, 78/132 (59.1%) participants requested more information on management strategies for such side effects. Despite most reporting at least a moderate understanding of their prognosis, 83/138 (60.1%) participants reported the need for more education on the usual progression and outcomes of their disease (Table 5.3).

5.4.3 Physician-specific questionnaire

5.4.3.1 Diagnostic confidence and therapy selection

Of the 160 physicians who completed the baseline questionnaire, 46 (28.8%) reported a definite diagnosis of IPF from their respective ILD MDM, 90 (56.3%) reported a high confidence and 24 (15%) reported a low confidence in the diagnosis of IPF in their respective patients (Table 5.4).

57/131 (43.5%) physicians perceived that the choice of antifibrotic agents was made with equal input from their respective patients. However, only 24 (42%) of respective patients perceived the choice to be mutually made. 27/131 (21%) physicians perceived medication choice was made by completely or mostly by themselves while only 11/27 (41%) respective patients perceived the same. Similarly, 47/131 (36%) physicians perceived that the medication choice were mostly or completely decided by their respective patients, but only 24/47 (51%) of respective patients responded with similar perceptions. Among physicians, the side effect profile of antifibrotics weighed more heavily as a factor impacting the choice of agents. Physicians also perceived tablet burden to be an important factor (Table 5.4). Of the patients who were not prescribed antifibrotics, physicians reported the rationale to be: minimal functional impairment (n=3), lack of progression (n=5), did not meet PBS criteria (n=2) and the remaining four declined treatment.

Apart from being offered antifibrotics for IPF, 63/151 (41.7%) participants were offered referrals to pulmonary rehabilitation, 49/150 (32.7%) were referred to a pulmonary fibrosis support group and 54/137 (39.4%) for clinical trials. Seven patients were offered referrals to a lung transplant clinic and two were referred to a palliative care service.

Table 5.4. Physicians' perceptions on diagnosis and management of IPF

Diagnostic confidence		n = 160
	Very confident	46 (28.75%)
	High confidence	90 (56.25%)
	Low confidence	24 (15%)
Reasons for not starting antifibrotic		n = 16
	Minimal functional limitation	3 (18.75%)
	No disease progression	5 (31.25%)
	Did not qualify	2 (12.5%)
	Patient declined	6 (37.5%)
Input into choice (physician)		n = 131
	Completely patient	8 (6.1%)
	Mostly patient	39 (29.8%)
	Equal	57 (43.5%)
	Mostly doctor	25 (19.1%)
	Completely doctor	2 (1.5%)
Factors impacting choice		
Side effects (n=125)	Very important	40 (32%)
	Important	55 (44%)
	Moderately important	17 (13.6%)
	Slightly important	11 (8.8%)
	Not important	2 (1.6%)
Tablet number (n=125)	Very important	5 (4%)
	Important	37 (29.6%)
	Moderately important	33 (26.4%)
	Slightly important	31 (24.8%)
	Not important	19 (15.2%)
Tablet frequency (n=125)	Very important	5 (4%)
	Important	37 (29.6%)
	Moderately important	30 (24%)
	Slightly important	34 (27.2%)
	Not important	19 (15.2%)

Comorbidities (n=124)	Very important	14 (11.3%)
	Important	32 (25.8%)
	Moderately important	31 (25%)
	Slightly important	27 (21.8%)
	Not important	20 (16.1%)
Drug interactions (n=125)	Very important	16 (12.8%)
	Important	27 (21.6%)
	Moderately important	27 (21.6%)
	Slightly important	32 (25.6%)
	Not important	23 (18.4%)
Other services offered		
	Pulmonary rehabilitation*	73 (45.4%)
	Lung transplant clinic	7 (4.3%)
	Palliative care	2 (1.2%)
	PF support group	29 (17.9%)
	Dietician	0 (0%)
	Psychologist	4 (2.5%)
	Advanced care planning	9 (5.6%)
	Smoking cessation**	3 (2%)
	Pulmonary hypertension clinic	0 (0%)

Data presented as n (%). PF: pulmonary fibrosis.

* n=161, ** n=151

5.4.4 Qualitative interviews with participants

28 participants were interviewed. geographically spread across Australia, from New South Wales (n=16), Victoria (n=8) and Queensland (n=2), South Australia (n=1) and Tasmania (n=1). 10 patients (36%) were from rural townships. Once data saturation was reached, the following themes were identified.

Theme 1: First impressions and responses to receiving diagnosis.

The feeling of being overwhelmed by the gravity of their diagnosis was commonly reported among participants, where they described '*having a lot to digest'* during the consultation (P008). Participants described being '*stunned'* throughout the consultation and having a '*feeling of disbelief*' where they initially did not expect to be given a diagnosis of an incurable disease (P010). In some cases, they were surprised by the perceived disconnect from having minimal symptoms to the seriousness of their diagnosis of IPF (P011). Participants commonly expressed themselves being concerned and *'terrified'* upon receiving their diagnosis. One participant reported being on an '*emotional roller coaster'* and impacting their mental health, describing their '*head going to a space where it shouldn't have'*. Patients also sought additional information by *'looking on the Internet'* as a response to being told of the diagnosis. However, information they encountered failed to alleviate their concerns with patients recounting that *'the information on the Internet was horrendous'* (P011). Nonetheless, some participants were accepting of the diagnosis and were keen to carry on with management, citing that they are willing to *' face it and work with it'* (P004) and *'At least it gave a sense of ease…I know exactly what it is so therefore we can take the right course of medication'* (P013) (Table 5.5).

Theme 2: Response to Initial discussions about antifibrotic therapy

Participants reported that a core element within the initial discussion with their physicians focused on the goals of antifibrotic therapies. Participants recalled the role of antifibrotic agents to *'slow it down and prolong the inevitable'* (P001). Many also recalled being told that antifibrotics will *'not cure their condition'* (P005, P020). Most participants recalled being given *'a choice of two medications and were told of their side effects'* (P009). Several

participants recalled being given written information on treatment options in the form of brochures or pamphlets. These were received differently with one participant describing them to be *'pretty useful'*, often serving as a point of reference to *'refresh his mind'* and remarking that *'it was the most information given about any medication'* (P007). In contrast, another remarked that drug information pamphlets needed to be *'taken with a pinch of salt'* as they perceived that writers of the pamphlets probably never had the drug themselves and don't truly understand the drug side effects (P008).

Several participants poorly recollected the discussion with their physicians. Some felt that all *'they heard were about the different side effects'* (P011). Rather than poor communication, participants suggested that it was the complexity of the condition making them feel *'lost a little bit from time to time'* (P018) and that *'there was a lot to take in'* (P010) (Table 5.5).

Theme 3: Autonomy of medication choice

Most participants were pleased that they were given a choice on antifibrotics. Many cited that the final decision were often left to them and that '*it was a perfectly valid approach*' (P017). However, some participants reported being both surprised and uneasy on this approach, citing that *'it was the first time ever that a doctor invited me to choose'*, that there *'was absolutely no direction from a medical point of view'* and *'not what they would normally expect from the medical profession'* (P008).

While some participants reported that the decision was made by their physician and that they *'weren't given a choice'* (P022), others preferred to *'leave it to their physicians' capable hands'* (P018). (Table 5.5)

Table 5.5. Themes identified from participant interviews.

Major Themes	Sub-themes	Quotes from participants
1. First impressions and responses when receiving the diagnosis of IPF.	1.1Being overwhelmed	*"I just went and had an interview after the testing and the doctor just told me what I had. He didn't say how long I had got to live but he said an indication of this disease is you know probably two years, could be five years… I was fractured…I wasn't sort of stunned until I got home, and I read up about it cause I had never even heard of the disease before" P005*
		"It was a lot to digest and initially I did not tell anyone about it and for quite a few weeks, because I was still digesting the information, trying to work out what I should do about it. That was my immediate reaction." P008
		"I didn't know what it was. And being me, I looked into Google, said most people with that only last 18 months. This is not too good… when they're first talking about it was a little bit overwhelming. You think you're healthy, and next minute they're telling me that you're not at all. So it was a little bit overwhelming." P026
	1.2 Being shocked/surprised	*"I don't know that I was in shock or upset by it. In any way, I knew there was something wrong." P007*
		"Probably a little bit of disbelief. Didn't expect it to be obviously a condition that would end up with me lying horizontal." P010
		"My emotion at the time was one of surprise. I didn't realize that I was unwell. I did have symptoms, but I didn't know about that. I just thought that that was just getting older. So the actual fact that it was a disease was a real shock, and it worried me because I looked on the Internet straight away. And the information on the Internet was horrendous." P011

		"Well, I was surprised in one sense, because I knew nothing about the condition at all…I suppose some apprehension in terms of well, what's the prognosis?" P017
	1.3 Acceptance of diagnosis	*"To me it just was the way of life. Whatever happens, happens." P001*
		"If I've got something, well I face it, and work with it. So my attitude towards sickness is, well, if I have it, so be it. I just have to do what's right." P004
		"At least it gave a sense of ease that it's okay now I know exactly what it is so therefore we can take the right course of medication because at that time we didn't know which course of medication to go down" P013
	1.4 Being concerned/fearful	*"It concerns me that I'm going to lose the ability to get around and do a lot of things as time goes on." P009*
		"Over weeks, I went very quickly from thinking, oh, this is okay, to, oh, I'm going to die tomorrow. So the emotional roller coaster was not matching the reality that I was living. My head went in a space that it shouldn't have. I think that was just because I tried to process it on my own." P011
		"When I was told of the condition, I certainly became a little more concerned…I then went to Dr google and I looked up the life expectancy and the prognosis was not all that cheerful." P020
		"I was terrified. I was convinced my days were limited." P024
2. Initial discussion on antifibrotic therapy for IPF.	2.1 Goals of therapy	"What we got out of it was to maybe slow it down and prolong the inevitable" P001
		"I remember that it was going to be something that had to be monitored so closely, that it could have all these multiple side effects." P004
		"They won't cure your condition, but he said research has shown that they would certainly slow it down." P005

		"The doctor indicated that the medication was not a cure, but the medication hopefully would stop the actual build-up of scarring." P020
	2.2 Use of written information	"I got a little paperwork I was given at the time about it. I thought it was all pretty useful stuff. I kept it all. I sometimes go back and have a bit of a quick squeeze through to refresh my mind. It was probably the most information I've ever given about any medication I've ever had." P007
		"They gave me a brochure written by the manufacturers and so you take this with a pinch of salt…probably the people who are writing it probably never had the drug themselves, so they don't really know what you're going through or what's happening to you and some of these side effects are quite distressing. "P008
	2.3 Treatment options	"There was a choice of two medications. Both have side effects. I was told it was up to me. I could take it or I could not take it." P009
		"There were two drugs on the market and they both were enablers to just slow the fibrosis down. And to what extent, but possibly up to 50% to slow the fibrosis. And obviously there was a choice, and he mentioned the side effects." P012
	2.4 Poor recall of discussion	"During the conversation I think all I heard was that there were side effects." P011
		"Not that I can recall clearly. I'm guessing that it helps to slow it down. In my meeting with him I was still getting the grips of the fact that I have IPF. There was a lot to take in" P010
		"I can't recall, I have to say. Whether the information came from her or it was stuff that I'd read, so it's a bit difficult to distinguish." P014

		““They tried to explain it as best as possible. I understood most of what they were saying, but every now and again. They lost me a little bit from time to time” P018
3. Autonomy on medication choice.	3.1 Pleased that choice was given	“The doctor left it completely up to me. It was an option that I could choose.” P016
		“He gave me the facts on the medications and pamphlets to read. I would read them and then make my own decision. I thought it was brilliant. If they give me all the facts and I make the wrong decision, that's my choice. And it is my life after all. “ P009
		“I was pleased. I was quite amazed at the discussion, and the decision was up to me, basically.” P024
		“It was largely my choice. I mean, they weren't recommending one over the other one…I could have asked for advice. I didn't. There wasn't any particular need to… I thought it was a perfectly valid approach” P017
	3.2 Uncertain on concept of being provided options to choose	“That was the first time ever a medic has invited me to choose. What was even more interesting was they could not tell me which was preferred, so it was just sort of a take your pick.” P008
		“The recommendation from the hospital was to pick which ever one that you like between them. So, absolutely no direction from a medical point of view…it’s your body, you pick one. Which is not perhaps what you would normally expect from the medical profession.” P008
		“Well, I really didn't have much insight in there, so I left it in their capable hands..so I had to trust that and didn't have much choice.” P018
		“I'm the patient and I have to rely upon what they tell me. I have to rely upon the medication they prescribe.” P009
	3.3 Decision made by physician	“Well I didn’t choose it, the doctor chose it, he said I would like you to try this one first is what I recall his words. He said it is just one that they had a better understanding

		of…he said we believe this one may be a good one to start with…" P005
		"I didn't feel the doctor gave me a choice. I didn't feel that the explanation was well understood by me at the time." P011
		"Well, he just suggested I go on that particular one at the time to start with. I wasn't given a choice of any others." P022

5.5 Discussion

In this study using data from the AIPFR, we described the diagnostic processes and management strategies of people with IPF living in Australia. Despite many participants reporting satisfaction with the time taken to reach a diagnosis and their overall care, our study identified significant diagnostic delays, and a need for better patient education. Our study showed that close to 90% of participants were offered treatment with antifibrotic agents. Of these, the prescription of both pirfenidone and nintedanib were similar at 64 (48.1%) and 68 (51.2%) respectively. Medication side effects were the biggest factor impacting the choice of antifibrotic agent. The choice of agents was mostly made with input from patients and their respective physicians, with both parties reporting an equal partnership in the decision-making process.

In our cohort, 60.8% of participants reported a duration of less than 12 months from the onset of symptoms to the diagnosis of IPF. This is comparable to the IPF-PRO registry in the USA where only 51% of patients with IPF were diagnosed within a year of their symptom onset [16]. Another registry cohort reported a mean duration of up to 21.8 months from self-reported

symptom onset to an IPF diagnosis [17]. The most commonly encountered reason for diagnostic delay was the time taken for patients to be referred to a specialist physician, followed by the duration taken for patients to see their GP from the symptom onset, time taken for an MDM case discussion and lastly, time taken for them to receive results from their physicians. Similar reasons were reported in a Danish study, including the time taken for patients to see a health care professional with their symptoms, time taken for a referral to a secondary physician from their general practitioner and referral to an ILD centre [18]. Lancaster et al. surveyed IPF patients and physicians from several countries showing that up to 45% of patients with early IPF were misdiagnosed and needing seven to 10 diagnostic investigations as compared to the mere three to four suggested by current guidelines, likely accounting for the delay reported in their study [19]. Such diagnostic delays highlight the importance of strategies to facilitate early diagnosis and improve access to specialist centres and disease-modifying therapies. Improved referral pathways to ILD centres, easy access to ILD MDMs, regular GP and respiratory physician engagement and education, increasing the number and frequency of available ILD MDMs, and utilising media resources for national awareness campaigns are potential strategies that may help. Strategies similar to the recent Pulmonary Fibrosis Awareness Month campaign run by the LFA, should be utilised to educate patients on early recognition of their symptoms and how best to seek medical reviews, and to highlight the importance of a multidisciplinary diagnostic approach through the ILD MDM.

Our study showed that medication side effect profile was the most important factor for both patients and physicians impacting the choice of antifibrotic therapies. This was expected given the potential impact of side effects on quality of life for patients with an incurable, progressive disease. The near equal divide in drug choice could reflect the different opinions among patients on which side effects are less concerning. This is in keeping with other studies showing

that medication side effects were the most frequent reported reason for treatment cessation [20]. Fewer participants expressed tablet numbers (31.8%) and comorbidities (39.5%) as important or very important factors impacting antifibrotic choices. Conversely, a recent study showed that high baseline concomitant medication burden was consistently associated with intolerance of antifibrotic therapies within six months of initiation [21]. A possible explanation for our findings could simply be that discussions on antifibrotic therapies are often dominated by the potential side effects rather than the impact of tablet numbers and other medical comorbidities. This is frequently cited in patient interviews, and physician questionnaire responses suggesting an overwhelming importance placed on medication side effects over other factors. While both agents have been shown to be generally safe, the high uptake of antifibrotic therapies despite importance placed on drug tolerability, suggests that patients may ultimately be willing to tolerate a degree of side effects [9, 22, 23, 24, 25, 26].

Another important aspect our study demonstrated, is the concept of shared decision-making in antifibrotic choices, with majority of participants (42.5%) and physicians (43.5%) reporting equal contribution to the final medication choice. However, of equal importance is the disparity in perception where merely half of participants compared to their respective physicians perceived an equal contribution. Participant interviews reflect this where some find the concept of choosing their treatment both foreign and confronting, hence possibly preferring the decision being made by their respective physicians. While impossible to eliminate opinion differences, clear communication lines between both parties are paramount to minimise misperceptions that may delay or negatively affect treatment. Furthermore, despite most patients reporting a good understanding of their diagnosis and the role of antifibrotics, nearly half of them requested further information detailing the rationale for treatment, side effects and strategies to manage them. Up to 60% of patients also desired more information on the prognosis of their condition.

This highlights that patients newly diagnosed with IPF may benefit from more consultation time spent with their physicians or clinical team. This was highlighted in a survey of ILD patients where many respondents reported the importance of understanding their condition, in particular their disease progression and prognosis. Education provided by physicians and ILD specialist nurses were highly valued and further education sessions were the most common suggested improvement strategy [27]. The utility of a peer support program allowing patients to share experiences and provide mutual support, have also been explored [28]. Regular education webinars for doctors, patients and carers, the use of standardized education written materials and continued input from patient advocacy organisations should be considered strategies.

Our study's strength lies with the prospective recruitment of participants onto the well-established AIPFR. The unique questionnaire used in our study sought to capture nuances in physicians' clinical practice and improve our understanding of patient perceptions on their diagnostic and treatment journey of IPF, of which are unlikely to be captured in current available patient reported outcome measure tools. Phone interviews were used to further tease out such nuances in patient experiences in their initial consultations with their physicians. Study recruitment took place in major leading ILD centres, allowing us to capture diagnostic and management processes in expert centres and patients' experiences through them. As no definitive guidelines were in place to guide physicians on managing IPF with antifibrotic therapies, our study findings may provide some guidance needed for smaller centres and physicians who lack experience in the use of antifibrotic therapies.

This study has several limitations. Data collected for this study were predominantly questionnaire based and are subject to missing data and potential misunderstanding of line of questioning. While the questionnaire was purposefully designed to capture data on patient

experiences, most were not open-ended questions and hence, responses from participants may be constrained within the limits of questions used in the survey. We employed qualitative interviews to overcome this limitation. Recruitment centres were tertiary ILD referral centres predominantly on the eastern seaboard of Australia. Our results may be biased and not representative of smaller, rural or regional hospitals or private practices. However, as the use of antifibrotic therapies at the time of the study was fairly new in Australia, the decision to recruit participants at larger ILD centres was due to greater experience levels in antifibrotic therapies with the hope that our study findings may serve as a guide for physicians with less experience. Lastly, majority of participants had only mild disease and responses from participants cannot be generalised across the spectrum of patients living with IPF, particularly those with more severe disease.

In conclusion, data from the AIPFR demonstrate that patients with newly diagnosed IPF report a mostly satisfactory experience with receiving their diagnosis and overall care. Despite a potential delay of more than a year in achieving a diagnosis, satisfaction levels with their care remained high. Antifibrotic therapies were frequently started in patients despite the potential side effects, suggesting that patients were eager for treatment for their disease. Participants also actively took part in the decision-making process on which the choice of medications and wanted more education on their condition and management strategies, behaviours that would be in keeping with a desire for self-management [29]. Improvement in diagnostic processes to hasten access to available treatment and development of education material resources are strategies that may help improve the patient experience with antifibrotic therapies in the management of IPF.

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5.7 Chapter Five Supplementary Data

Table 5.6. Phone interview guide.

Q1. Can you tell me about any discussions you may have had with your doctor about starting medications for your IPF? <what information where you given?>
Q2. What factors did you consider when deciding if you would take any antifibrotic medication? < To what extent did you feel these things were included in your doctor's decision about whether you should take an antifibrotic? >
Q3. Can you tell me about your experiences in taking an antifibrotic medication? a. May need to ask about positive and negative experiences b. <*additional prompt*> What support have you received/are you receiving in the management of your IPF?
Q4. What aspects of the care you are receiving, are you happy with? What aspects do you feel could be improved?

AIPFR STAFF: IPF ID#: _____ Date Sent: _____ Date Received: _____Database Entry: _____

Initial Treatment Questionnaire

IPF REGISTRY AUSTRALIAN IDIOPATHIC PULMONARY FIBROSIS REGISTRY | LUNG FOUNDATION AUSTRALIA

1.Date when you completed this questionnaire:			
Date today, when you completed the questionnaire		Date:	**_ _ / _ _ / 20_ _**
2.Symptom onset:			
A. Do you have breathlessness?	Yes ☐ No ☐	*If yes, answer the question 2B. If no go to question 2C.*	
B. When was the first time you experienced shortness of breath?		Year of onset:	_ _ _ _
C. Do you have cough?	Yes ☐ No ☐	*If yes, answer the next question, 2D. If no, go to Q3.*	
D. When was the first time you experienced cough (with or without phlegm)?		Year of onset:	_ _ _ _
3.Diagnostic process:			
A. Date when your Pulmonary Fibrosis was diagnosed:		Month and year:	_ _ / 20_ _
B. Who made the diagnosis?			*Please select only one answer*

i.General Practitioner (GP) ☐	Local respiratory specialist ☐	Pulmonary fibrosis specialist physician ☐	Other ☐	ii. If other who?

C. How long was the time between when you first developed symptoms, and when you were given a diagnosis of Pulmonary Fibrosis? *For the following questions please select only one answer*

Less than 3 months ☐	3-6 months ☐	6-12 months ☐	1-2 years ☐	More than 2 years ☐

D. What was the main reason/s for the time taken to diagnose your Pulmonary Fibrosis? *Select 1 or more*

i. Time between your symptoms beginning and seeing your GP ☐	Time between seeing your GP and seeing your specialist ☐	Time between seeing your specialist and getting your test results ☐
Time taken for your specialist to discuss your results at a meeting ☐	Other ☐	Not applicable ☐

ii. If "Other" please give the main reason for the time taken to diagnose your Pulmonary Fibrosis?

E. How satisfied are you with the time taken to make your diagnosis of Pulmonary Fibrosis?

Very dissatisfied ☐	Dissatisfied ☐	Neither satisfied nor dissatisfied ☐	Satisfied ☐	Very satisfied ☐

F. How satisfied are you with your experience of the process to receive your diagnosis?

Very dissatisfied ☐	Dissatisfied ☐	Neither satisfied nor dissatisfied ☐	Satisfied ☐	Very satisfied ☐

G: What aspects of the manner in which you were informed of your diagnosis do you feel could be improved upon?

4.Therapy selection I:			
Treatment specifically for your pulmonary fibrosis is called "anti-fibrotic therapy". Currently in Australia, two anti-fibrotic therapies are available on prescription: pirfenidone ("Esbriet") and nintedanib ("Ofev"). Other anti-fibrotic therapy is available to some patients in clinical trials.			
A. Are you already on anti-fibrotic therapy?	Yes ☐ No ☐	*If yes, go to **Q5.** below. Continue to answer the questionnaire but ALSO answer Questions 10,11 and 12 at the end of this questionnaire. If no, go to Q4B.*	
B. If you are NOT already on treatment, has your doctor recommended that you START taking anti-fibrotic therapy?			Yes ☐ No ☐
			If you answered yes, please go to question 5

C. If you are not going to start anti-fibrotic therapy, what is the main reason for this?

Please select only one answer

i. I was told I do not qualify ☐	I chose not to take it ☐	I have already tried previously and stopped ☐	Your doctor recommended that I not start it ☐
Other ☐			

ii. If you selected "Other" please give reason:

D. If you chose not to take anti-fibrotic therapy, what was the main reason for this? *Please select only one*

i. Possible side effects ☐	I didn't want to take any more tablets ☐	I didn't think it would benefit me ☐	Cost ☐	Other ☐

ii. If you selected "Other" please give reason:

Only complete Questions 5 and 6 if you are starting or are already using anti-fibrotic therapy.
If you are not taking anti-fibrotic therapy please go to Question 7.

5.Therapy selection II:

A. How much input did you have in the choice of your anti-fibrotic therapy? *Please select only one answer*

Completely your choice ☐	Mostly your choice ☐	Equal input from me and your doctor ☐	Mostly your doctor's choice ☐	Completely your doctor's choice ☐

B. How important were the following factors in your choice of anti-fibrotic therapy?

For the following questions please tick only one box per line

	Not important	Slightly important	Moderately important	Important	Very important
i. The side effects of the medication	☐	☐	☐	☐	☐
ii. The number of tablets to take per day	☐	☐	☐	☐	☐
iii. The frequency of medication (how often the tablets are taken per day)	☐	☐	☐	☐	☐
iv. Your other medical problems (e.g. bowel problems, blood clots etc)	☐	☐	☐	☐	☐

v. If other factors influenced your choice of anti-fibrotic therapy please describe:

6.Therapy selection III:

A. How well would you rate your understanding of the following:

*For the following questions please select **only one** answer for each question*

	Don't understand at all	Understand a little	Moderate understanding	Understand almost everything	Understand completely
i. The reasons for taking anti-fibrotic therapy?	☐	☐	☐	☐	☐
ii. The potential side effects of the anti-fibrotic therapy which you are taking?	☐	☐	☐	☐	☐
iii. The usual progression and outcome of pulmonary fibrosis?	☐	☐	☐	☐	☐
	Not important	Slightly important	Moderately important	Important	Very important
iv. How important is the cost of the anti-fibrotic therapy to you?	☐	☐	☐	☐	☐

B. Do you think that further education/information on the following topics may have been valuable?		
	Yes	**No**
i. The reasons for taking anti-fibrotic therapy	☐	☐
ii. The potential side effects of the anti-fibrotic therapy which you are taking	☐	☐
iii. The usual progression and outcome of pulmonary fibrosis	☐	☐
iv. The cost of the anti-fibrotic therapy to you	☐	☐
v. Management of potential side effects of your anti-fibrotic therapy	☐	☐

7. Other therapies: ALL participants to answer

A. Since your diagnosis of pulmonary fibrosis have you been involved in any of the following?

For the following questions please select an answer in each column, up to four responses in each row.
If you are unsure of what the question is referring to please select "No".
If in the first column you answer "No" or "Not applicable" please just move to the next question (row).

	Have you been offered/referred to this service?	**Are you currently attending this service?**	**Have completed this service?**	**Have you decided not to attend this service?**
i. Pulmonary rehabilitation	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
ii. Lung transplant clinic	Yes ☐ No ☐	Yes ☐ No ☐	NA	Yes ☐ No ☐
iii. Palliative care specialist	Yes ☐ No ☐	Yes ☐ No ☐	NA	Yes ☐ No ☐
iv. PF support group	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
v. Dietician	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
vi. Psychologist	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
vii. Advance care planning	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
viii. Smoking cessation	Yes ☐ No ☐ Not applicable ☐	Yes ☐ No ☐ Not applicable ☐	Yes ☐ No ☐ Not applicable ☐	Yes ☐ No ☐ Not applicable ☐
ix. Clinical trial participation	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

B. Are you on any of the following therapies? *Please answer each question either yes or no*

	Yes	**No**
i. Anticoagulation (blood thinners including warfarin)	☐	☐
ii. Reflux medications (e.g. Somac, Nexium, Losec, Zantac)	☐	☐
iii. Anti-depressants	☐	☐
iv. Anti-anxiety medications	☐	☐
v. Inhalers	☐	☐
vi. Prednisone (steroids)	☐	☐
vii. Other immune suppressants (e.g. methotrexate, azathioprine, cyclophosphamide, mycophenolate)	☐	☐
viii. Oxygen (Continuous or most of the day, e.g. a stationary concentrator)	☐	☐
ix. Oxygen (Ambulatory, for use only during physical activity e.g. cylinders for walking or a portable concentrator)	☐	☐
x. CPAP therapy	☐	☐
xi. Medication to help relieve or prevent severe breathlessness or coughing (e.g. morphine syrup, tablets or patches)	☐	☐

8. Hospital admission history:	
A. In the last 12 months have you been admitted to hospital?	Yes ☐ No ☐ *If no go to Q9.*
B.If yes, what was the date or dates you were admitted to hospital? *(Please list a date for every hospital admission in the last 12 months, but do not include clinic appointments or visits)*	**Date (s):**
C. If yes, was this for your pulmonary fibrosis?	Yes ☐ No ☐

9. How satisfied are you with your overall care? *For the following question please select only one answer*

	Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
How satisfied are you with your overall care?	☐	☐	☐	☐	☐

Only complete the following Questions 10, 11 and 12 if you are already on anti-fibrotic therapy (if you answered Yes to Question 4A):

10. Therapy IV:

A. What anti-fibrotic therapy are you currently taking? *Please select **only one** answer for the following*

Nintedanib (OFEV)	Pirfenidone (Esbriet)	Pirfenidone (Pirfenex)	Clinical trial with Nintedanib	Clinical trial with Pirfenidone	Other Clinical trial
☐	☐	☐	☐	☐	☐

B. Approximately when did you first start this treatment?	**Date:**	

C. In the last 3 months, has there been any change to therapy?

i. Permanently stopped taking anti-fibrotic	Yes ☐ No ☐	
ii. Paused (temporarily stopped anti-fibrotic therapy)	Yes ☐ No ☐	iii. Length of time without any treatment Approx._____ days *or if no* Not applicable ☐
iv. Dose of anti-fibrotic therapy was changed	Yes ☐ No ☐	v. New dose *or if no* _____mg Not applicable ☐
vi. Changed to alternative anti-fibrotic therapy	Yes ☐ No ☐	vii. Name of new therapy _____ *or if no* Not applicable ☐

D. Who made the change to your anti-fibrotic therapy? *Please select **ONLY one** answer (the main one)*

i.	Pulmonary fibrosis specialist	☐	
	Local respiratory specialist	☐	
	Local doctor (GP)	☐	
	The change was made by the hospital	☐	
	I made the change yourself	☐	
	Other	☐	
	Not applicable	☐	

ii. If "other" please state who made the change:

E. Why was the change made? *Please select any number of relevant options*

i. Side effects ☐	Abnormal blood test ☐	It wasn't working ☐	Other ☐	Not applicable ☐

ii. If you selected "other" give reason/s:

F. How regularly do you take your anti-fibrotic therapy? *For the following please select **only one** from 5 options*

Never (0-19% of the time) ☐	Infrequently (20-39% of the time) ☐	Sometimes (40-59% of the time) ☐	Often (60-79% of the time) ☐	Always (80-100% of time) ☐

G. Why do you miss doses?

i. I forget to take the therapy ☐	I have side effects ☐	I ran out of tablets ☐	Other ☐	Not applicable (I don't forget) ☐

ii. If you selected "Other" please describe the reason/s you miss your dose.

11. Side effects:

In the last 3 months, how severe were your side effects? *For each side effect please select only one option per row*

	Very severe	Severe	Moderate	Mild	I did not have this side effect
A. Diarrhoea	☐	☐	☐	☐	☐
B. Nausea	☐	☐	☐	☐	☐
C. Vomiting	☐	☐	☐	☐	☐
D. Reduced appetite	☐	☐	☐	☐	☐
E. Abdominal pain	☐	☐	☐	☐	☐
F. Weight loss	☐	☐	☐	☐	☐
G. Liver function abnormality (blood test)	☐	☐	☐	☐	☐
H. Skin problems (e.g. rash, sunburn)	☐	☐	☐	☐	☐
I. Fatigue	☐	☐	☐	☐	☐
J. Bleeding	☐	☐	☐	☐	☐
K. Other side effect	☐	☐	☐	☐	☐
L. If "other" please describe					

	More than 7 stools/day compared to pre-treatment	4-6 stools/day compared to pre-treatment	Up to 4 stools/day compared to pre-treatment	Slight increase, but not daily	Not applicable (none)
M. Approximately, how frequently did you have diarrhoea?	☐	☐	☐	☐	☐

	More than 10 kg	5-10kg	2-5kg	Less than 2 kg	Not applicable
N. How much weight have you lost in the last 3 months?	☐	☐	☐	☐	☐

12. Monitoring and additional therapy:

For the following please select only one answer for each question.

	1-2 times a week	Monthly	Every 3-6 months	Yearly or less often	Never
A. How frequently are you having blood tests to monitor your anti-fibrotic therapy?	☐	☐	☐	☐	☐

AIPFR STAFF:	IPF ID#: _____

	Multiple times per day	Daily	A few times a week	A few times a month or less often	Never
B. Approximately how often are you taking anti-nausea medications?	☐	☐	☐	☐	☐
C. Approximately how often are you taking anti-diarrhoeal medications?	☐	☐	☐	☐	☐
D. Approximately how often are you using sunscreen?	☐	☐	☐	☐	☐
	Very unlikely	**Somewhat unlikely**	**Not sure**	**Somewhat likely**	**Very likely**
E. Overall, how likely are you to continue to take your anti-fibrotic therapy?	☐	☐	☐	☐	☐

Are you happy to be contacted by a researcher from the Registry team for a telephone interview on these topics?	
Yes	☐
No, thanks	☐

Thank you for taking the time to complete this questionnaire. We appreciate your time and effort

All information provided to the Australian IPF Registry is bound by Commonwealth and State privacy legislation and guidelines, including the Health Records and Information Privacy Act and the NSW Health Privacy Manual. The Australian IPF Registry is committed to providing a high standard in handling personal information. Your information will only ever be used for health research. The researchers conducting any study will not have access to your identifying information unless you give your consent to participate.

CHECKLIST

Please take a moment to check you have completed all the relevant sections on this Questionnaire.

	Participant		
Question number	**On anti-fibrotic therapy already**	**STARTING to take anti-fibrotic therapy**	**NOT taking anti-fibrotic therapy**
1. Date - **ALL Participants**	☒	☒	☒
2. Symptoms - **ALL Participants**	☒	☒	☒
3. Diagnostic process - **ALL Participants**	☒	☒	☒
4. Therapy I (anti-fibrotic)	Only A	A and B	A, B, C, D
5. Therapy II (anti-fibrotic)	☒	☒	
6. Therapy III (anti-fibrotic)	☒	☒	
7. Other therapies - **ALL Participants**	☒	☒	☒
8. Hospital admissions - **ALL Participants**	☒	☒	☒
9. Care – satisfaction - **ALL Participants**	☒	☒	☒
10. Therapy IV (anti-fibrotic)	☒		
11. Side-effects of anti-fibrotic therapy	☒		
12. Monitoring of anti-fibrotic therapy	☒		

Figure 5.2. Patient-specific Questionnaire.

AIPFR STAFF: IPF ID#: _____ Date Sent: _____ Date Received: _____ Database Entry: _____

Patient name:_____ Patient DOB: _ _ / _ _ / _ _ _ _

Initial Treatment Physician Form

IPF REGISTRY
AUSTRALIAN IDIOPATHIC PULMONARY FIBROSIS REGISTRY
LUNG FOUNDATION AUSTRALIA

Name of Respiratory physician:

Date this patient attended clinic

1.Date of Clinic Visit: _ _ / _ _ / 20_ _

2. Are you happy to be contacted by a researcher from the Registry team for a telephone interview on this topic?		Yes ☐ No ☐	
3. Is this a new patient to your clinic?		Yes ☐ No ☐	
A. Date of MDM	Date:		
B. Date of HRCT	Date:		
C. Surgical biopsy (if performed)	Date:	Not done	☐

D. Diagnostic confidence at MDM: *Select one answer*

Unclassifiable (≤50%)	Provisional -Low confidence (51-69%)	Provisional – high confidence (70-89%)	Very confident (≥90%)
☐	☐	☐	☐

5. Therapy selection:

A. Is this patient already on anti-fibrotic therapy? Yes ☐ No ☐

*If you answered **yes,** please continue to answer the questionnaire **including** Questions 10- 15 at the end.*
*If you answered **no**, and you are NOT prescribing anti-fibrotic therapy today please go to Q6.*

For the following questions please select only one answer for each question

	Completely patient choice	Mostly patient choice	Equal input from patient and physician	Mostly physician choice	Completely physician choice
B. How much input did you have in the choice of anti-fibrotic therapy?	☐	☐	☐	☐	☐

C. How important were the following factors in your choice of anti-fibrotic therapy?

	Not important	Slightly important	Moderately important	Important	Very important
i. Side effect profile	☐	☐	☐	☐	☐
ii. Number of tablets	☐	☐	☐	☐	☐
iii. Frequency of medication	☐	☐	☐	☐	☐
iv. Drug interactions	☐	☐	☐	☐	☐
v. Co-morbidities	☐	☐	☐	☐	☐

vi. Were other factors important in your choice of treatment selection? Yes ☐ No ☐

vii. If yes, what were they?

D. What anti-fibrotic treatment has been prescribed the patient? *Please select only one*

Nintedanib (OFEV) 150mg BD ☐	Pirfenidone (Esbriet) 2403mg/day ☐	Pirfenidone (Pirfenex) ☐
Nintedanib (OFEV) 100mg BD ☐	Pirfenidone (Esbriet) 534-2402mg mg/day ☐	Pirfenidone clinical trial ☐
Nintedanib clinical trial ☐	Pirfenidone (Esbriet) <534mg /day ☐	Other clinical trial ☐

Please now go to Q7

AIPFR STAFF: IPF ID#: _____

6. Patient NOT on anti-fibrotic treatment

A. If the patient is not on anti-fibrotic treatment, have you offered anti-fibrotic therapy to the patient? Yes ☐ No ☐

B. If no, please select the reasons why this patient was not offered anti-fibrotic therapy?

Please select all reasons of relevance to your decision for this patient

i. Limited functional impairment ☐	ii. Severe functional impairment ☐	iii. Too much concurrent emphysema ☐	iv. Patient declined anti-fibrotic therapy ☐	v. Disease is non-progressive ☐
vi. Advanced age ☐	vii. Did not meet PBS prescribing criteria ☐	viii. Other comorbidities ☐	ix. Contraindicated with other medications ☐	x. Other ☐

xi. If "other" selected please provide details.

7. Comorbidities:

A. Does the patient have any of the following comorbidities?

If yes, please give the date of diagnosis, if no select not applicable

	Yes	No	Year of diagnosis	Not applicable
i. COPD	☐	☐		☐
ii. GORD	☐	☐		☐
iii. Pulmonary Hypertension	☐	☐		☐
iv. Sleep apnoea	☐	☐		☐
v. Lung Cancer	☐	☐		☐
vi. Diabetes Mellitus	☐	☐		☐
vii. Chronic heart failure	☐	☐		☐
viii. Depression and/or anxiety	☐	☐		☐
ix. Coronary heart disease (or atherosclerotic heart disease) including a history of MI	☐	☐		☐
x. Arterial hypertension	☐	☐		☐

B. Have you offered/referred any of the following?	**Yes**	**No**
i. Pulmonary rehabilitation	☐	☐
ii. Lung transplant clinic	☐	☐
iii. Palliative care specialist	☐	☐
iv. Pulmonary Fibrosis support group	☐	☐
v. Dietician	☐	☐
vi. Psychologist	☐	☐
vii. Advance care planning	☐	☐
viii. Smoking cessation	☐	☐
ix. Pulmonary hypertension clinic	☐	☐

C. Is the patient on any of the following therapies?	**Yes**	**No**
i. Anticoagulation	☐	☐
ii. Reflux (PPI or H2)	☐	☐
iii. Anti-depressants	☐	☐
iv. Anti-anxiolytics	☐	☐
v. Inhalers	☐	☐
vi. Pulmonary vasodilators	☐	☐
vii. Prednisone	☐	☐
viii. Other immunosuppression	☐	☐
ix. Oxygen: LTOT	☐	☐
x. Ambulatory oxygen	☐	☐
xi. Overnight oxygen	☐	☐

AIPFR STAFF: IPF ID#: _____

8. Exacerbation History:				
	Yes	**No**	**B. Date/s of Exacerbation**	**Not applicable**
A. In the last 12 months, has the patient had an acute exacerbation?	☐	☐		☐

C. Aetiology of exacerbation?

i. Unknown	Infective	PE	Cardiac	Other
☐	☐	☐	☐	☐

ii. If "Other" selected please describe.

D. Treatment of Acute exacerbation *(Select all relevant options)*

i. Hospitalisation	☐
ii. Antibiotics	☐
iii. Prednisone	☐
iv. ICU	☐
v. Supportive ventilation (NIV, CPAP etc)	☐
vi. Other	☐

vii. If "Other" selected please describe.

9. Physical Findings:				
	Room air	Oxygen		
A. SpO2	☐	☐	ii. Resting O_2 saturation	___%
If Oxygen selected			iii. O_2 flow rate	___L/min
B. WHO FC (I-IV)	___			
	Yes	**No**		
C. Crackles	☐	☐		
D. RHF	☐	☐		
E. Clubbing	☐	☐		
F. CTD features	☐	☐		

Only complete Q10 - 15 if the patient is already on anti-fibrotic treatment (if you answered yes to question 5A):

10. Anti-fibrotic medication that your patient is currently taking		
A. What anti-fibrotic medication is your patient currently taking? *Please select only one*		
Nintedanib (OFEV) 150mg BD ☐	Pirfenidone (Esbriet) 2403mg/day ☐	Pirfenidone (Pirfenex) ☐
Nintedanib (OFEV) 100mg BD ☐	Pirfenidone (Esbriet) 534-2402mg mg/day ☐	Pirfenidone clinical trial ☐
Nintedanib clinical trial ☐	Pirfenidone (Esbriet) <534mg /day ☐	Other clinical trial ☐
B. When did you first prescribe treatment?	**Date:**	
C. Changes to anti-fibrotic therapy		
i. In the last 3 months have there been any changes to therapy?	Yes ☐ No ☐	*If no please go to Q11.*
ii. Stopped	Yes ☐ No ☐	
iii. Paused	Yes ☐ No ☐	iv. Length of time without any treatment Approx._____ days *or if no* Not applicable ☐
v. Changed dose of anti-fibrotic	Yes ☐ No ☐	vi. New dose _____mg *or if no* Not applicable ☐

AIPFR STAFF: IPF ID#: _____

vii. Changed to alterative anti-fibrotic therapy	Yes ☐ No ☐	viii. Name of new therapy _____ *or if no* Not applicable ☐

11. Anti-fibrotic medication changes

A. Who made the change *Please select **ONLY one** answer (the main one)*

i.	ILD specialist	☐	
	Local respiratory specialist	☐	
	Local doctor (GP)	☐	
	Hospital	☐	
	Patient	☐	
	Other	☐	
	Not applicable	☐	

ii. If "other"please state who made the change:

B. Why was the change made? *Please select one answer for the following question*

i. Side effects	☐	Perceived loss of efficacy/ progression	☐
Abnormal blood test	☐	Not applicable	☐
Patient choice	☐	Other	☐

ii. If you selected "other" give reason:

12. Anti-fibrotic medication compliance

A. How often do you think your patient takes their dose? *For the following please select **only one** from 5 options*

Never (0-19% of the time)	Infrequently (20-39% of the time)	Sometimes (40-59% of the time)	Often (60-79% of the time)	Always (80-100% of time)
☐	☐	☐	☐	☐

B. Why do you think that your patient misses their dose?

i. Forget	Side effects	Ran out of tablets	Other	Not applicable (They don't forget)
☐	☐	☐	☐	☐

ii. If you selected "Other" please describe the reason/s you think they miss the dose.

13. Side effects

How severe do you think the patient's side effects were in the last 3 months? *Select only one option for each row*

	Very severe	Severe	Moderate	Mild	Pt did not have this side effect
A. Diarrhoea	☐	☐	☐	☐	☐
B. Nausea	☐	☐	☐	☐	☐
C. Reduced appetite	☐	☐	☐	☐	☐
D. Vomiting	☐	☐	☐	☐	☐
E. Abdominal pain	☐	☐	☐	☐	☐
F. Weight loss since starting medication	☐	☐	☐	☐	☐
G. Liver function abnormality	☐	☐	☐	☐	☐
H. Skin problems	☐	☐	☐	☐	☐
I. Fatigue	☐	☐	☐	☐	☐
J. Bleeding	☐	☐	☐	☐	☐
K. Other side effect	☐	☐	☐	☐	☐

L. If "other" please describe

AIPFR STAFF: IPF ID#: _____

14. Monitoring

For the following please select only one answer for each question.

	1-2 times a week	Monthly	Every 3-6 months	Yearly or less often	Never
A. Approximately how frequently is your patient having blood tests for IPF medication?	☐	☐	☐	☐	☐

15. Additional therapy

For the following please select only one answer for each question.

	Multiple times per day	Daily	A few times a week	A few times a month or less often	Never
A. Approximately how often is your patient needing anti-nausea medications?	☐	☐	☐	☐	☐
B. Approximately how often is your patient needing anti-diarrhoeal medications?	☐	☐	☐	☐	☐
C. Approximately how often is your patient using sunscreen?	☐	☐	☐	☐	☐

	Very unlikely	Somewhat unlikely	Not sure	Somewhat likely	Very likely
D. Overall, how likely are you to continue to recommend ongoing treatment with anti-fibrotic therapy?	☐	☐	☐	☐	☐

16. Patient follow-up

A. Patient to return to clinic in 3 months — Yes ☐ / No ☐ *If no, go to B*

B. Patient will return to referring physician — Yes ☐ Name Dr_____ / No ☐ If no, go to C

C. Advise Coordinator plan of action for follow- up of this patient.

Figure 5.3. Physician-specific Questionnaire.

Chapter Six: Antifibrotic Therapies and the Management of Idiopathic Pulmonary Fibrosis: Longitudinal Analysis from the Australian Idiopathic Pulmonary Fibrosis Registry

Antifibrotic Therapies and the Management of idiopathic Pulmonary Fibrosis: Longitudinal Analysis from the Australian Idiopathic Pulmonary Fibrosis Registry

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6.1 Abstract

Introduction: Nintedanib and pirfenidone are antifibrotics recommended for the treatment of idiopathic pulmonary fibrosis (IPF). There are no current guidelines for ongoing management of patients who are started on antifibrotics. The study aimed to explore nuances in antifibrotic prescription patterns and to describe both patient and physician experiences in the first year of treatment of IPF.

Methods: Consecutive participants with IPF were recruited from multiple Australian interstitial lung disease centres into the Australian IPF registry (AIPFR). Participants without a recent multidisciplinary meeting case discussion and unable to consent were excluded. Participants were followed up at predetermined timepoints over a 12-month period. Both participants and their respective physicians completed proforma questionnaire at timepoints. Physicians were invited to participate in semi-structured telephone interviews.

Results: Between July 2017 and February 2022, 199 participants completed baseline questionnaires. Rates of antifibrotic use were high at the end of the study period (77.2%). Side effects of diarrhoea (68.0%) were commonly reported with nintedanib and photosensitive rash (32.7%) with pirfenidone, though they were mostly mild to moderate in severity. Rates of treatment pauses improved over the study period while treatment changes or cessation were rare. Referral rates to pulmonary rehabilitation, IPF support groups and clinical trials were average (<41%). Despite small divergence in perceptions between participants and physicians, most were satisfied with the overall care and were likely to continue on antifibrotics beyond the first year of treatment. Physicians placed importance on patient factors such as comorbidities, frailty and individual choices, when choosing to start on antifibrotics.

Conclusion: Our study showed that antifibrotics remained well tolerated and satisfaction level remained high despite reported side effects in Australia. However, referrals to pulmonary rehabilitation and other allied health services remained poor and further studies are needed to explore their impact on the management of patients with IPF and how best to improve service subscriptions.

6.2 Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial pneumonia and is usually characterised by relentless disease progression, leading to lung function decline, worsening quality of life and ultimately respiratory failure and death[1]. A definitive cure for IPF remains elusive, with only a few patients eligible for lung transplantation.

Current available antifibrotic therapies in the form of pirfenidone, a novel antifibrotic agent and nintedanib, a multiple tyrosine kinase inhibitor, have been widely prescribed for people living with IPF following the landmark studies in 2014 [2, 3]. While their tolerability and efficacy in slowing lung function decline is evident, both medications are associated with drug-related adverse events that may negatively impact patients' quality of life [4, 5, 6, 7]. While both medications are recommended for the treatment of IPF in current international guidelines [8], there are no guidelines or recommendations for ongoing management once patients are started on antifibrotic therapies. The literature is divided with regard to the benefits or pitfalls associated with switching between antifibrotic medications[9, 10], with evidence to support such a strategy and guidance as to when to do so, lacking.

The Australian IPF registry (AIPFR) is a multicentred, prospective and observational disease registry established in 2012, governed by the Lung Foundation Australia (LFA) aimed at fostering collaborative research and providing epidemiological insight on IPF in Australia [11]. With antifibrotic therapies being widely used to treat IPF in Australia, the AIPFR sought to explore the use of antifibrotic therapies for IPF at tertiary referral interstitial lung disease (ILD) centres in Australia. This study aims to identify nuances in decision-making process and

prescription patterns of antifibrotic therapies and to explore physician and patient experiences in the first year of treatment of IPF.

6.3 Methods

6.3.1 AIPFR Recruitment

In this study, phase 2 of AIPFR recruitment, AIPFR data were collected from participants recruited from 13 ILD centres, each equipped with an ILD multidisciplinary meeting (ILD MDM). Consecutive patients diagnosed with IPF at participating centres were recruited to the AIPFR between July 2017 and February 2022, providing written informed consent. Participants with a historic diagnosis of IPF without a MDM discussion or who were unable to provide written consent, were excluded from the study. Their respective treating physicians were also invited to take part in the study.

Data collection was performed by dedicated registry coordinators and has been previously described [12]. The study was approved by the human research ethics committee of Royal Prince Alfred Hospital, Sydney (HREC/11/RPAH/ X19-0476 &2019/ETH13556).

6.3.2 Study protocol

AIPFR co-ordinators in each state collected participant data including lung function data and patient reported outcome measures (PROMs) through standardized proforma questionnaires.
An additional questionnaire, designed with stakeholder input from health professionals, pharmaceutical industry and consumer representation was also administered with the goal of

capturing data on antifibrotic therapy prescription and management strategies for IPF (Figure S1). Separate physician-specific questionnaires were also administered to the participants' respective physicians (Figure S2). Baseline data and follow-up timepoints were three, six and 12 months from consent (+/- one month). Physicians directed the timing of subsequent follow-up reviews based on individual clinical need.

Physicians were invited by e-mail to participate in semi-structured telephone interviews. Using open-ended questions, the interview aimed to explore and describe physicians' opinions, experiences with antifibrotic therapies and decision-making process in the management of patients with IPF (Figure S3). Interviews were conducted by the primary study researcher, A.T. The interviews were audio-recorded and transcribed verbatim.

6.3.3 Analysis

Categorical data were analysed descriptively. Continuous data were recorded as mean and standard deviation (SD). Missing data were not estimated, and no imputations were conducted. Disease progression was defined as a sustained reduction in forced vital capacity (FVC) > 10% or diffusing capacity of the lungs for carbon monoxide (DLCO) >15% over two consecutive visits. Mortality events were defined by death or receipt of lung transplant. Interview response transcripts were analysed using a qualitative approach to content analysis, allowing for common themes to be extracted. STATA v15.1 (StataCorp, College Station, TX,USA) was used for all statistical analyses.

6.4 Results

6.4.1 Baseline characteristics

At baseline, 199 participants were included with a median age of 72.6 (68.1 – 77.4) years. 136/199 (68.3%) were male and only eight patients (4.3%) identified themselves as current smokers. At baseline, the mean forced vital capacity (FVC) was 87.5% predicted (SD 21.0) and mean diffusing capacity of the lungs for carbon monoxide (DLCO) was 52.2% predicted (SD 16.0). Lung function data and PROMs recorded during the pre-specified study follow-up timepoints are shown in Table 6.1. Overall, there were only small declines seen in FVC% predicted and DLCO% predicted. Similarly, there were no significant changes in participant PROMs recorded.

Table 6.1. AIPFR participant characteristics.

		Visit 2	Visit 3	Visit 4
Lung function				
	FVC	2.8 (0.8) *	2.95 (0.90) §	2.75 (0.88) ¶
	FVC% pred	89.3 (20.9) *	87.6 (19.6) §	83.8 (19.1) ¶
	DLCO% pred	52.0 (15.9) †	50.1 (14.5) ‡	48.3 (15.6) ¶
PROM				
	SGRQ	38.9 (19.8) (158)	38.7 (20.4) (84)	37.6 (16.3) (98)
	UCSD SOBQ	35.6 (24.7) (169)	37.4 (26.7) (89)	34.7 (22.1) (100)
	HADS-A	4.3 (3.3) (171)	3.9 (3.4) (90)	3.4 (2.9) (95)
	HADS-D	5.8 (3.0) (172)	6.2 (3.0) (90)	5.9 (2.6) (96)
GAP stage, n (%)				
	1	109 (61)	63 (64)	72 (64)
	2	64 (36)	34 (35)	37 (33)
	3	5 (3)	1 (1)	3 (3)

Data presented as mean (SD) or n (%). *90 participants, § 84 participants, ¶ 43 participants † 86 participants, ‡ 50 participants. FVC: Forced vital capacity; DLCO: diffusing apacity of the lung

for carbon monoxide; PROM: Patient reported outcome measures; SGRQ: St Georges Respiratory Questionnaire; UCSD SOBQ: University of California San Diego Shortness of Breath Questionnaire; HADS: Hospital Anxiety and Depression Scale; WHO: World Health Organisation; GAP: Gender-age-physiology index.

6.4.2 Patient Questionnaire: Antifibrotic Therapies

Following baseline, 99% of participants were commenced on antifibrotic therapies. At Visit 2, 107 of 166 (64.5%) participants who completed the questionnaire reported ongoing treatment with antifibrotic therapies. While the number of participants completing questionnaires had fallen by Visit 4, 88/114 (77.2%) participants reported continuing on antifibrotic therapies.

65/116 (56%) participants were taking nintedanib at Visit 2, 42/78 (53.9%) at Visit 3 and 52/89 (58.4%) at Visit 4. The most common side effects over 12 months were diarrhoea (68.0%), fatigue (54.8%), anorexia (52.4%), weight loss (50.5%) and nausea (42.3%). However, participants reported most of these side effects to be of mild to moderate severity. For example, 76.2% of patients with diarrhoea reported it to be of mild to moderate severity, and similarly 91.8% of those with fatigue, 89.0% anorexia, 90.4% weight loss, and 86.9% of those with nausea were mild to moderate severity.

51/116 (44%) participants were taking pirfenidone at Visit 2, 36/78 (46.2%) at Visit 3 and 37/89 (41.6%) at Visit 4. Over the 12 month follow up period, patients reported fatigue (53.4%), anorexia (47.9), nausea (47.5%), weight loss (37.7) and photosensitivity (32.7%) as the most common side effects. Similarly, most reported symptoms to be only mild to moderate in severity; fatigue (87.1%), anorexia (84.6%), nausea (90.9%), weight loss (91.8%) and photosensitivity (78.7%).

Participants taking nintedanib reported higher rates of diarrhoea compared to their counterparts on pirfenidone at all timepoints (Figure 6.1). Of those who reported moderate to severe diarrhoea, the use of anti-diarrhoeal medications was variable (range: 50-75% over 12 months). Rash or skin-related reactions were more frequently reported by participants on pirfenidone during the first two timepoints but reduced to similar rates reported by participants taking nintedanib by Visit 4. Weight loss was more frequently reported by participants on nintedanib within the first two timepoints but were similar to those taking pirfenidone at Visit 4 (Figure 6.1). However, few participants reported weight loss exceeding 5kg at Visit 2 (13.9%), Visit 3 (6.1%) and Visit 4 (4.9%) (Table 6.4). Few bleeding events (<2%) and liver function derangements (<11%) were seen with either nintedanib or pirfenidone.

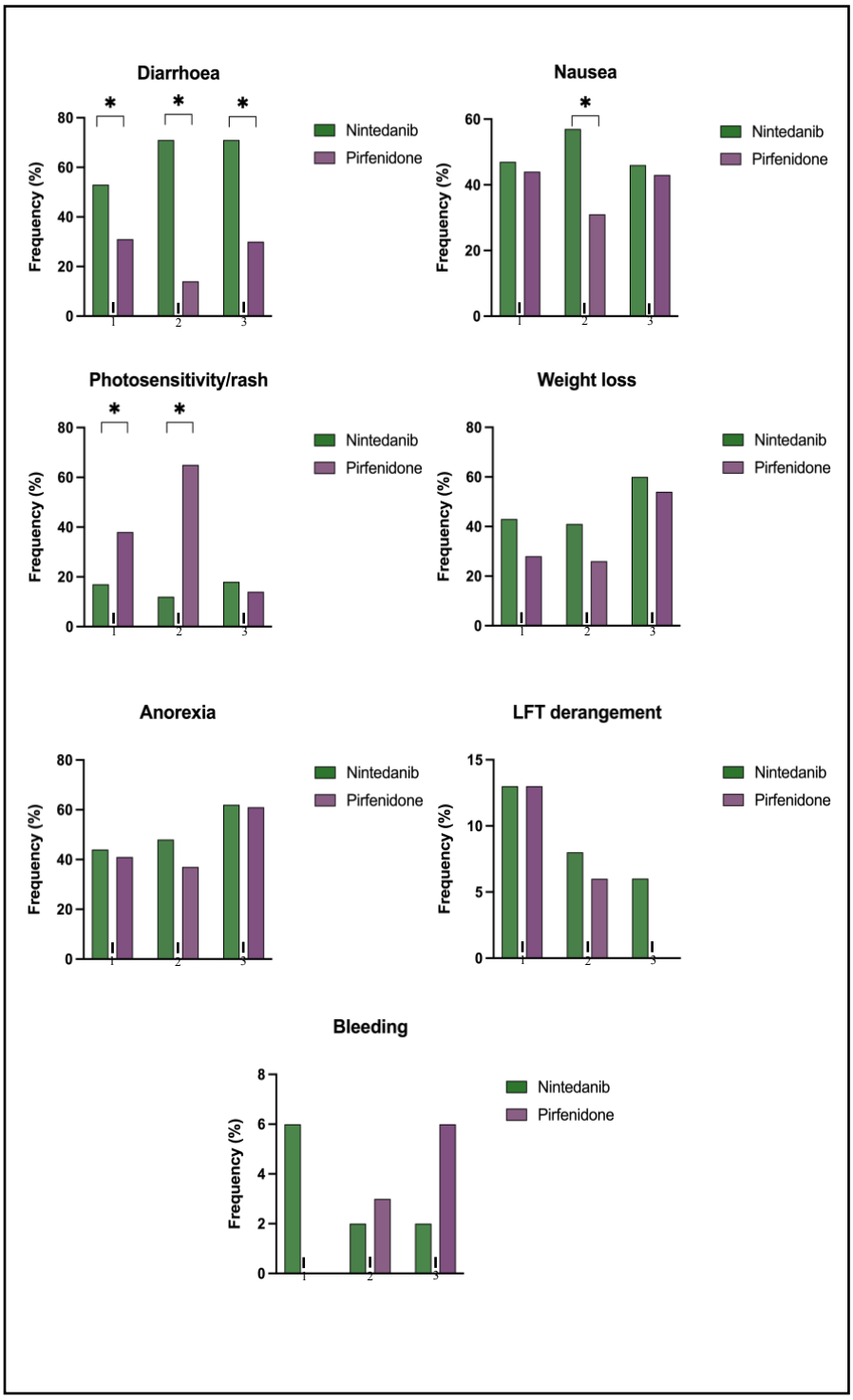

Figure 6.1. Frequency of medication-related side effects (%). Frequency is defined by the percentage (%) of participants who had side effects of those who were taking antifibrotic therapies at individual timepoints. * $p<0.05$. 1: Visit 2, 2: Visit 3, 3: Visit 4, LFT: Liver function test

6.4.3 Changes and Cessation of Therapy

Changes to therapy are shown in Table 6.2. Of participants taking nintedanib, 15/58 (25.9%) reported dose adjustments at Visit 2, 13/38 (34.2%) at Visit 3 and 14/50 (28%) at Visit 4. Participants taking pirfenidone reported dose adjustments in 11/48 (22.9%) at Visit 2, 3/30 (10.0%) at Visit 3 and 1/36 (2.8%) at Visit 4. Pauses in nintedanib therapy were more frequently reported at Visit 2 by 18/57 (31.6%) and reduced to 10/38 (26.3%) at Visit 3 and 9/52 (17.3%) by Visit 4. This trend was similar in pirfenidone; 12/46 (26.1%) at Visit 2, 5/33 (15.2%) at Visit 3 and reduced to 1/35 (2.9%) by Visit 4. Few participants required permanent cessation at any timepoint; Visit 2, 1/39 (2.6%) and 0/33 at Visit 3, and 0/50 and 2/37 (5.4%) at Visit 4. Similarly, few participants reported switching of antifibrotic agents. Switching from nintedanib to pirfenidone was seen in 7/55 (12.7%) at Visit 2, 4/29 (13.8%) at Visit 3 and 7/49 (14.3%) at Visit 4, whereas switching from pirfenidone to nintedanib was seen in 7/47 (14.9%) at Visit 2, 6/37 (16.2%) at Visit 3 and and 4/35 (11.4%) at Visit 4. Participants reported that changes to their treatment were mostly directed by their ILD physician (61.4%) while 22.5% were self-initiated. Side effects were the predominant reason for treatment changes at every timepoint (Table 6.5). Self-reported adherence was high with only few participants reporting below <80% compliance. Over 70% participants felt that they were likely or very likely to continue antifibrotic therapies (Figure 6.2). At all timepoints, majority of participants (>90%) were either satisfied or very satisfied with their overall care.

Table 6.2. Participants' perspective on antifibrotic therapies and management of IPF.

Taking antifibrotics		**Visit2**	**Visit 3**	**Visit 4**
Yes (%)		112/173 (64.7)	78/106 (73.6)	88/114 (77.2)
Nintedanib (%)		65 (56.0)	42 (53.9)	52 (58.4)
Pirfenidone (%)		51 (44.0)	36 (46.1)	37 (41.6)
Adherence, n (%)				
Never		1 (0.9)	6 (7.1)	2 (2.3)
Often (60-79%)		2 (1.7)	3 (3.5)	2 (2.3)
Always (80-100%)		115 (97.5)	76 (89.4)	85 (95.4)
Changes to therapy				
Paused (%)	Nintedanib	18/57 (31.6)	10/38 (26.3)	9/52 (17.3)
	Pirfenidone	12/46 (26.1)	5/33 (15.2)	1/35 (2.9)
Ceased (%)	Nintedanib	2/62 (3.2)	1/39 (2.6)	0/50 (0.0)
	Pirfenidone	2/48 (4.2)	0/33 (0.0)	2/37 (5.4)
Dose changed (%)	Nintedanib	15/58 (25.9)	13/38 (34.2)	14/50 (28)
	Pirfenidone	11/48 (22.9)	3/30 (10)	1/36 (2.8)
Agent changed (%)	Nintedanib	7/55 (12.7)	6/37 (16.2)	7/49 (14.3)
	Pirfenidone	7/47 (14.9)	4/29 (13.8)	4/35 (11.4)
Likelihood continuing treatment, n (%)				
Very unlikely		23 (16.1)	7 (8.1)	7 (7.4)
Unlikely		2 (1.4)	0 (0)	0 (0)
Not sure		15 10.5)	4 (4.7)	9 (9.5)
Likely		5 (3.5)	5 (5.8)	6 (6.3)
Very likely		98 (68.5)	70 (81.4)	73 (76.8)
Satisfaction with care received, n (%)				
Very dissatisfied		6 (3.6)	0 (0)	4 (3.6)
Dissatisfied		1 (0.6)	0 (0)	1 (1.0)
Neither		8 (4.8)	6 (5.8)	5 (4.5)
Satisfied		44 (26.3)	37 (35.6)	44 (39.6)
Very satisfied		108 (64.7)	61 (58.6)	57 (51.3)

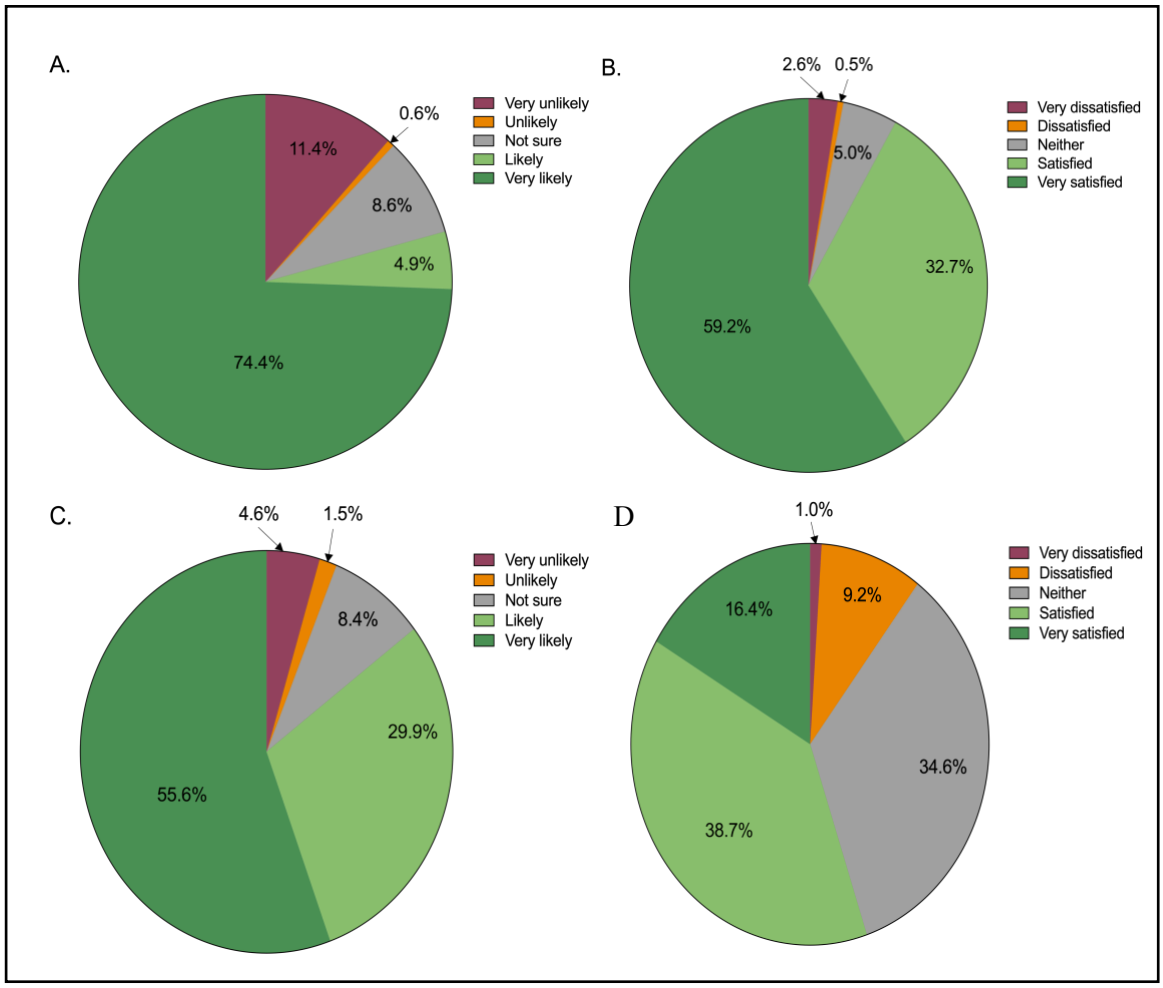

Figure 6.2. (A) Participants' likelihood of continuing antifibrotics, (B) Participants' satisfaction with overall care, (C) Physicians' likelihood of continuing antifibrotics, (D) Physicians' satisfaction with overall care.

6.4.4 Non-pharmacological Therapies

During the study period, participants reported 225/559 (40.3%) encounters in which they were offered a referral to a pulmonary rehabilitation program. Participants reported only 21/293 (7.2%) encounters in which they declined a pulmonary rehabilitation referral. Referrals to an IPF support group were consistent throughout the study period with a total of 152/552 (27.5%) encounters overall. While few participants declined this, uptake appeared to taper off by Visit 4 with 13/62 (21%) participants declining referrals. There were 221/549 (40.3%) encounters

where participants were offered referrals for clinical trials but only few reported declining (21/310, 6.8%). There were few encounters in which participants were offered referrals to a lung transplant clinic (29/557, 5.2%), palliative care (13/563, 2.3%), psychologists (19/564, 3.4%) or dieticians (35/562, 6.2%). Table 6.3 shows the referral patterns to additional services for each timepoint.

Table 6.3. Participants' perspective on extra support services.

Extra services offered, n/N (%)	**Visit 2**	**Visit 3**	**Visit 4**
Pulmonary rehabilitation			
Offered	71/170 (41.8)	20/95 (21.1)	43/108 (39.8)
Declined	3/88 (3.4)	3/43 (7.0)	11/61 (18.0)
IPF support group			
Offered	45/163 (27.6)	23/95 (24.2)	28/110 (25.5)
Declined	8/88 (9.1)	6/43 (14.0)	13/62 (21.0)
Clinical trials			
Offered	77/170 (45.3)	41/96 (42.7)	41/111 (36.9)
Declined	10/99 (10.1)	2/58 (3.5)	5/64 (7.8)
Transplant clinic referral (*offered*)	9/171 (5.3)	6/95 (6.3)	6/111 (5.4)
Palliative care clinic (*offered*)	3/173 (1.7)	0/96 (0)	3/110 (2.7)
Psychologist (*offered*)	6/171 (3.5)	4/97 (4.1)	3/111 (2.7)
Dietician (*offered*)	14/172 (8.1)	6/95 (6.3)	7/111 (6.3)

6.4.5 Physician Questionnaire: Antifibrotic Therapies

At Visit 2, 24/78 (30.8%) physicians reported cessation of antifibrotics. 8/72 (11.1%) physicians reported a temporary treatment pause while 16/66 (24.2%) elected to change the dose of antifibrotics. By Visit 4, physicians reported the number of patients requiring drug cessation had significantly reduced to 9/60 (15%), p=0.04. There were also significantly fewer

dose changes at Visit 4 (6/58, 10.3%, p=0.06). Physicians overwhelmingly reported medication side effects as the cause leading to changes to treatment (76.9%). Less than 5% of physicians stated progression of disease or lack of efficacy as a reason to change therapy. According to physicians, most changes to therapy across all visits (66.3%) were driven by ILD specialists. However, only 60.8% participants agreed with their physician that changes were made by an ILD specialist with 20.3% perceiving that the changes were made by themselves. Among physicians who perceived the changes were made by their patients, only 8/25 (32%) participants agreed with this perception. Instead, 13/25 (52%) participants felt it was the ILD specialist that made the change.

Similar to participants' reports, physicians also noted diarrhoea, nausea, anorexia and weight loss as the most common side effects from antifibrotics. However, physicians reported fewer side effects than their respective patients at all timepoints. Overall, the number of reported adverse events declined over the follow up period. Physicians reported a high adherence rate to therapy (>80%) by most of their patients at all timepoints. Of those that did not adhere to treatment, 42.9% physicians reported participants forgetting to take their medications while 44.4% had side effects limiting their adherence. Nonetheless, at least 80% physicians felt they were likely or very likely to recommend ongoing treatment with antifibrotics at all visits while only few reported being very unlikely to recommended ongoing use. Despite this, only approximately 59% physicians were satisfied or very satisfied with their patients' treatment across all timepoints (Table 6.6).

6.4.6 Physician Interviews

Six physicians were consented to participate in phone interview (four declined). Three identified themselves to have a subspecialty interest and experience in managing patients with ILD. All six work both in a hospital and in private practice. Five physicians work at tertiary referral hospitals with direct access to ILD MDMs while one physician worked in a non-metropolitan region and needed to remotely teleconference into an ILD MDM.

The common themes identified from the interviews are shown on Figure 6.3. Physicians commonly reported that while the prescription of antifibrotics in Australia required fulfilment of set criteria including lung function parameters and a multidisciplinary consensus diagnosis of IPF, patient factors such as age, frailty and pre-existing comorbidities carried weight when antifibrotics were being considered. For example, one physician quoted that they would not be considering antifibrotics in patients with severe disease limiting their quality of life while another highlighted the importance of striking a balance between maintaining quality of life versus years gained. For patients who are asymptomatic with mild disease, four physicians followed a close monitoring approach with another rationalising that commencing on antifibrotics may mask the natural disease trajectory in early disease and prevent future assessments on the efficacy of antifibrotics. However, all physicians suggested that at least a conversation with their patients regarding treatment options was needed, with the final decision being left to their patients. Physicians mostly agreed that the primary goal of antifibrotic therapy is to slow disease progression but a few were hopeful to see an improved survival and even an improvement in lung function and symptoms.

General advice by physicians predominantly revolved around the potential side effects of therapy and how to manage them, the rationale and goals of treatment. Physicians reported that these conversations often had to be repeated at follow-up consultations and that patients had to be reminded that changes to therapy can be considered if they failed to tolerate the initial treatment. One suggested the importance of their patients being comfortable or on-board with their treatment regime. While most physicians often left it to their respective patients to decide on which agent to use, some physicians may elect to make the choice on behalf of their patients due to concerns that patients may be limited by their understanding or may not have a strong enough preference. There was a mix of responses from physicians on when to make changes to treatment. Physicians commonly stopped or changed agents if there were intolerable side effects while some choose to do so if there was evidence of ongoing lung function or symptomatic decline. Physicians highlighted the need for community support services for patients and more access to ILD MDMs. Five physicians frequently referred their patients to pulmonary rehabilitation. When questioned on the impact of the COVID-19 pandemic on the care of IPF patients, physicians were receptive to the availability of telehealth appointments but highlighted limitations in monitoring lung function and potentially delaying access to ILD MDMs. All physicians were pleased regarding the availability of antifibrotic therapy for other ILD displaying a progressive pulmonary fibrosis (PPF) phenotype.

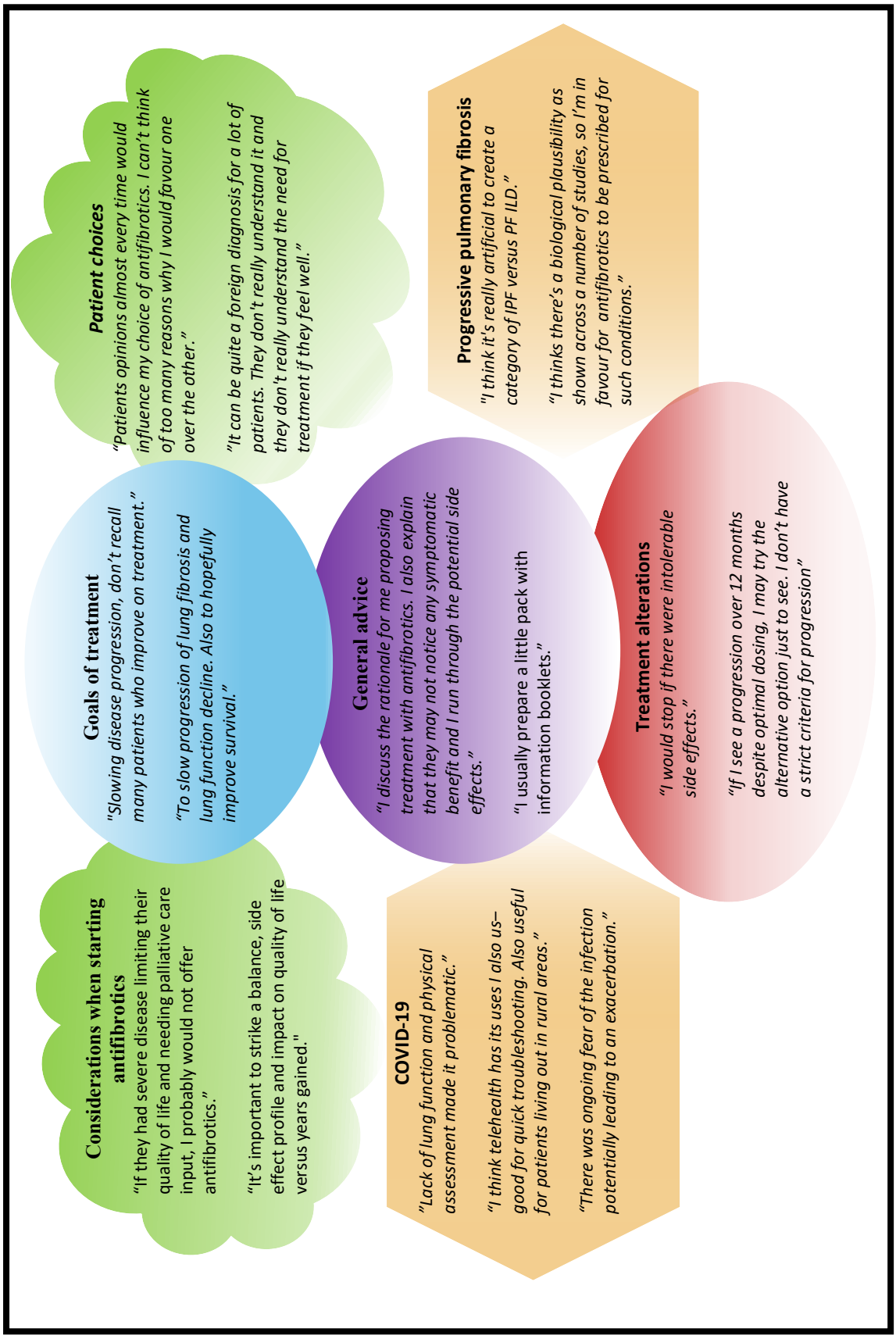

Figure 6.3. Main themes and responses from qualitative physician interviews.

6.4.7 Patient Outcomes

While there was no significant survival difference between participants who were taking antifibrotics and those who were not (HR 0.73, 95% CI 0.65 – 8.04), at 12 months, participants who were not taking antifibrotics had significantly higher risk of having disease progression (HR 2.19, 95% CI 1.04 – 4.60, p=0.04). Participants who permanently ceased antifibrotics had significantly poorer survival (HR 0.32, 95% CI 0.12 – 0.84, p=0.02). Changes to therapy did not significantly affect the risk of disease progression or mortality. Interestingly, participants with the nausea from antifibrotics had a higher risk of disease progression on univariate analysis (HR 1.60, 95% CI 1.16 – 2.21, p=0.004). This remained significant on multivariate analysis adjusted for age, gender and FVC % predicted (HR 1.61, 95% CI 1.08 – 2.31, p=0.02).

6.5 Discussion

In this study of AIPFR participants, we described the experiences of participants and their respective treating physicians within the first year of antifibrotic treatment for a diagnosis of IPF. At 12 months, there was still a high rate of more than 77% of participants that remained on antifibrotic therapies. While side effects of fatigue, anorexia, weight loss and nausea were commonly reported side effects from both pirfenidone and nintedanib (37.7 – 54.8%), most were only mild to moderate in severity. Diarrhoea was more frequently seen in those treated with nintedanib up to 12 months following treatment initiation. Photosensitive rash was more frequently reported at the start of treatment but appeared to reduce by 12 months. Our study showed a reduction in the frequency of treatment pauses over the course of the follow up period with few participants switching agents (17.3%) or permanently ceasing treatment (5.4%). The

overall satisfaction of care remained high among study participants with over 70% reporting a high likelihood of continuing treatment.

Our findings of the most frequent side effects of both nintedanib and pirfenidone are similar to that reported in the open-label extension studies and cumulative data from clinical trials [13, 14]. Side effect severity in our cohort was mild and in keeping with that reported in the literature. As side effects were the predominant factor driving changes to therapy, this may explain the small number of participants permanently stopping antifibrotic therapies. Of note, there were fewer participants in our cohort permanently ceasing antifibrotics compared to other studies. A Polish multicentre study reported 45.9% of their cohort discontinuing pirfenidone over a median follow up period of 17 months [15] while a Spanish multicentre prospective study reported a permanent withdrawal of nintedanib in 26.5% and pirfenidone in 19.7% of their study cohort over six years [16]. However, in these studies, there were fewer treatment pauses compared to our cohort. This reflects the variability in management strategies across countries, although other factors including disease severity and patient preferences play an important role in management choices. While patient age has been shown to impact the decision to initiate antifibrotics [17, 18], a recent study showed that elderly patients (>75 years) had higher incidences of adverse events but no difference in the rate of discontinuation [19]. Although our study numbers were small, more participants >75 years (6/33, 18.2%) permanently stopped treatment at 12 months compared to younger participants (2/71, 2.8%) (p=0.01).

In our study, just over 40% participants reported being referred to a pulmonary rehabilitation program. The referral uptake appears to be good with few participants (7%) declining the offer. A Cochrane meta-analysis has shown that pulmonary rehabilitation improves functional exercise capacity, dyspnoea levels and quality of life [20]. While further research is needed to

define the optimal exercise strategy for IPF, the role of pulmonary rehabilitation remains important in the management of IPF as detailed in international and national guidelines [1, 21]. Our findings of less than 50% of participants being offered a pulmonary rehabilitation referral was somewhat unexpected, considering that participants were recruited at large ILD centres. Furthermore, a previous study of Australian physicians found that most had access to pulmonary rehabilitation within their institutions, with only regional centres having to outsource referrals to external centres.

Approximately 28% participants were referred to IPF support groups. In Australia, peer-to-peer support programs and virtual peer support groups are available through the Lung Foundation Australia (https://lungfoundation.com.au) [22]. While well-received, the long-term impact on the quality of life and overall management of people with IPF remains unclear. Few participants in our cohort were offered referrals to a lung transplant clinic, palliative care service, psychologist or dietician as part of their management. This may be due to the milder disease severity of our cohort or inadequate access to such services. [23]. Further studies are clearly needed to understand barriers to such services and to investigate the long-term impacts on the overall care of people with IPF.

While there is substantial literature on the efficacy, safety, and tolerability of antifibrotics for the treatment of IPF, there is paucity in real world data to understand the rationale behind physicians' decisions with regard to antifibrotic therapy. Previous survey studies in Europe and USA have shown differing practices among respiratory physicians on the timing of treatment, the choice of medication and the titration scheme of treatment [24, 25]. Such variability in practice highlights individualised biases, perceptions and experiences among physicians on the use of antifibrotics despite compelling evidence that antifibrotics, regardless of disease severity or

baseline lung function, can delay irreversible lung function decline [26, 27, 28]. Using a qualitative approach, we interviewed physicians to tease out nuances that may account for differing management approaches to their patients with IPF in Australia. Physicians were like-minded on the efficacy of antifibrotics, provided there were no other confounding comorbidities and frailty limiting the quality of life of their patients. Similar to other studies, the decision to initiate treatment in asymptomatic patients with mild disease is variable with some choosing not to.

All physicians in our study placed importance on having an open conversation about antifibrotics with their patients and taking a shared-care approach, allowing patients the opportunity for self-management where the final decision is theirs to make. This concept is relatively new in the management of IPF and have previously been described in which physicians allow their patients to actively lead their management with an individualised approach and supported environment [29].

Physicians also noted that information on the rationale and goals of treatment as well as strategies on managing side effects required repetition during consultations. In addition, the divergence between physicians and participants on changes to therapy in our study could also reflect subtle differences in perceptions. Such misperceptions may provide a false sense of security to physicians that their patients fully understand their disease and management strategies, when in reality, the lack of understanding could fuel further anxiety and angst. This highlights the need for ongoing engagement and communication between physicians and their respective patients, particularly when managing an incurable and progressive lung disease.

Nonetheless, our study showed high levels of satisfaction among both participants and physician with regards to antifibrotics for the treatment of IPF. After 12 months of treatment, more than 76% of participants and 63% physicians were very likely to continue taking antifibrotics (Figure 2). Participant satisfaction with care received remained high at 12 months with close to 91% reported being satisfied or very satisfied. A previous study using a structured patient experiences and satisfaction with medication (PESaM) questionnaire, showed a good satisfaction mean score of 2.1 (on scale of -5 to 5) after 6 months of treatment and a moderate correlation between health-related quality of life and medication satisfaction [30, 31]. The study also showed that patients' experiences with effectiveness were significantly associated with satisfaction with treatment. While direct comparison is not possible, the overall satisfaction and high likelihood of treatment continuation up to 12 months in our study supports these findings. High adherence rates, low numbers of treatment cessation and mild adverse effect severity reported implies that our study participants may have placed more importance on medication effectiveness over side effects or ease of use, hence a higher satisfaction level.

Our study's strength was the multi-centred and prospective data collection of both participants and physicians involved in the care of patients with IPF. Using a unique, standardised questionnaire template, our study was able to capture longitudinal data on the safety and tolerability of antifibrotic therapies as well as both patient and physician experiences in the management of IPF. The use of a qualitative phone interview provided further individualised insight and perspective from physicians caring for people living with IPF in tertiary centres, private practice and rural locations. Our study has several limitations. Firstly, questionnaire responses were prone to missing data. This was further hampered by the COVID-19 pandemic in which recruitment were temporarily suspended and enrolled participants were requested to send in their responses by mail and not immediately following consultations, potentially

introducing recall bias. Data imputations were not used for missing data given the semi-quantitative nature of the questionnaire questions. Second, selection bias is likely given that participant recruitment occurred at major ILD centres and would not have captured those being treated in smaller rural centres or private practices. Lastly, a phenomenon in which participant responses to experience surveys can be dominated by positive response options could skew our findings and mask negative responses which one may argue to be more important. Phone interviews were used to overcome this but were limited by small number of physician participants.

In conclusion, 12-month follow up data from the AIPFR cohort show that antifibrotics continue to be well-tolerated with only mild to moderate adverse effect severity reported. Changes to therapy were rare and did not increase in frequency over the study period. Satisfaction level with the use of antifibrotics and general care received, remained high throughout the follow up period. However, referral to pulmonary rehabilitation and other allied health services remain low. Further research is needed to improve the subscription to such services and to understand the impact of a multidisciplinary approach to the management of IPF.

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6.7 Chapter Six Supplementary Data

Table 6.4. Participants' reported side effects and management strategies

Diarrhoea frequency		**Visit 2**	**Visit 3**	**Visit 4**
>7x/day		2 (%)	1	1
4-6x/day		3	5	15
Daily		12	12	6
slight, not daily		44	21	29
None		45	22	29
Weight loss				
>10kg		1 (1.0)	0	1 (1.2)
5-10 kg		13 (12.9)	4 (6.1)	3 (3.7)
2-5kg		30 (29.7)	18 (27.2)	22 (27.2)
<2kg		28 (27.7)	19 (28.8)	36 (44.4)
None		29 (28.7)	25 (37.9)	19 (23.5)
Anti-nausea use				
Multiple times daily		6	0	2
Daily		4	5	3
Few times a week		4	2	1
Few times a month		6	6	10
Never		112	58	72
Anti-diarrhoea use				
Multiple times daily		1	2	0
Daily		1	3	4
Few times a week		2	6	9
Few times a month		22	11	16
Never		106	50	59
Sunscreen use				
Multiple times daily		5	1	3
Daily		17	12	9
Few times a week		12	11	4
Few times a month		29	11	34
Never		69	37	37

Table 6.5. Participants' reported changes to therapy.

Changes to therapy								
Paused, n (%)	Nintedanib		18/57 (31.6)		10/38 (26.3)		9/52 (17.3)	
	Side effects (n)	*Abnormal bloods (n)*	14	4	10	1	8	2
	Pirfenidone		12/46 (26.1)		5/33 (15.2)		1/35 (2.9)	
	Side effects (n)	*Abnormal bloods (n)*	9	1	1	1	1	0
Ceased, n (%)	Nintedanib		2/62 (3.2)		1/39 (2.6)		0/50 (0.0)	
	Side effects (n)	*Abnormal bloods (n)*	2	0	1	0	0	0
	Pirfenidone		2/48 (4.2)		0/33 (0.0)		2/37 (5.4)	
	Side effects (n)	*Abnormal bloods (n)*	2	0	0	0	2	0
Dose changed, n (%)	Nintedanib		15/58 (25.9)		13/38 (34.2)		14/50 (28)	
	Side effects (n)	*Abnormal bloods (n)*	12	3	12	0	14	1
	Pirfenidone		11/48 (22.9)		3/30 (10)		1/36 (2.8)	
	Side effects (n)	*Abnormal bloods (n)*	9	0	1	1	1	0
Agent changed, n (%)	Nintedanib		7/55 (12.7)		6/37 (16.2)		7/49 (14.3)	
	Side effects (n)	*Abnormal bloods (n)*	5	1	6	0	6	0
	Pirfenidone		7/47 (14.9)		4/29 (13.8)		4/35 (11.4)	
	Side effects (n)	*Abnormal bloods (n)*	6	0	4	0	0	0

Table 6.6. Physician perspective on antifibrotic therapies.

Adherence	**Visit 2**	**Visit 3**	**Visit 4**

Never	2 (2.3)	1 (1.5)	1 (1.3)
Sometimes (40-59%)	2 (2.3)	0 (0)	1 (1.3)
Often (60-79%)	9 (10.0)	6 (8.8)	9 (11.7)
Always (80-100%)	76 (85.4)	61 (89.7)	66 (85.7)
Antinausea frequency			
Multiple times daily	2 (2.0)	2 (3.0)	1 (1.3)
Daily	1 (1.0)	2 (3.0)	5 (6.5)
Few times a week	2 (2.0)	1 (1.4)	2 (2.6)
Few times a month	4 (4.0)	4 (5.6)	1 (1.3)
Never	93 (91.0)	63 (87.0)	68 (88.3)
Antidiarrhoea frequency			
Multiple times daily	1 (1.0)	4 (5.6)	1 (1.3)
Daily	4 (4.0)	4 (5.6)	5 (6.5)
Few times a week	3 (2.9)	1 (1.4)	10 (13.0)
Few times a month	9 (8.8)	7 (9.7)	4 (5.2)
Never	85 (83.3)	56 (77.7)	57 (74.0)
Sunscreen frequency			
Multiple times daily	0 (0)	0 (0)	0 (0)
Daily	19 (18.8)	6 (8.6)	7 (9.1)
Few times a week	8 (7.9)	4 (5.7)	6 (7.8)
Few times a month	8 (7.9)	2 (2.9)	10 (13.0)
Never	66 (65.4)	58 (82.8)	54 (70.1)
Blood test frequency			
1-2x weekly	2 (2.0)	0 (0)	0 (0)
monthly	47 (47.5)	28 (41.8)	46 (56.1)
3-6 monthly	48 (48.5)	37 (55.2)	35 (42.7)
yearly	1 (1.0)	0 (0)	1 (1.2)
never	1 (1.0)	2 (3.0)	0 (0)

AIPFR
STAFF: IPF ID#: _____ Date Sent: _____ Date Received: _____Database Entry: _____

Follow up Treatment Questionnaire

IPF REGISTRY
AUSTRALIAN IDIOPATHIC PULMONARY FIBROSIS REGISTRY
LUNG FOUNDATION AUSTRALIA

1.Date when you completed this questionnaire:		
Date today, when you completed the questionnaire		Date: **_ _ / _ _ / 20_ _**
2. Therapy:		
A. Are you currently taking anti-fibrotic therapy?	Yes ☐ No ☐	*If no go to part 2D.*
B. What anti-fibrotic therapy are you currently taking?		*Please select **only one** answer for the following*

Nintedanib (OFEV)	Pirfenidone (Esbriet)	Pirfenidone (Pirfenex)	Clinical trial with Nintedanib	Clinical trial with Pirfenidone	Other Clinical trial
☐	☐	☐	☐	☐	☐

C. Approximately when did you first start this treatment?	**Date:**

D. Since your last questionnaire*, has there been any change to therapy?
If at your last questionnaire you were not taking anti-fibrotic therapy please answer "No" or "Not applicable

i. Permanently stopped taking anti-fibrotic therapy	Yes ☐ No ☐	
ii. Paused (temporarily stopped anti-fibrotic therapy)	Yes ☐ No ☐	iii. Length of time without any treatment Approx._____ days *or if no* Not applicable ☐
iv. Dose of anti-fibrotic therapy was changed	Yes ☐ No ☐	v. New dose _____mg *or if no* Not applicable ☐
vi. Changed to alternative anti-fibrotic therapy	Yes ☐ No ☐	vii. Name of new therapy _____ *or if no* Not applicable ☐

*If you answered **YES** to any questions in section 2D please complete **Q3 and Q4**.*
*If you answered **NO** to **ALL** questions and you are **STILL taking anti-fibrotic therapy** please go to **Q4**.*
*If you answered **NO** to **ALL** questions and are **NOT taking** anti-fibrotic therapy please go to **Q7**.*

3. Therapy changes:

A. Who made the change to your anti-fibrotic therapy? *Please select **ONLY one** answer (the main one)*

i. Pulmonary fibrosis specialist	☐	
Local respiratory specialist	☐	
Local doctor (GP)	☐	
The change was made by the hospital	☐	
I made the change yourself	☐	
Other	☐	
Not applicable	☐	

ii. If "other"please state who made the change:

B. Why was the change made? *Please select any number of relevant options*

Side effects	Abnormal blood test	It wasn't working	Other	Not applicable
☐	☐	☐	☐	☐

ii. If you selected "Side effects" please describe the side effect/s:

iii. If you selected "Other" give reason/s:

** If you can't remember the date of your last questionnaire please ask the Australian IPF Registry Coordinator in your State.*

AIPFR STAFF: IPF ID#: _____

4. Side effects:

In the last 3 months, how severe were your side effects

For each side effect please select only one option in each row.

	Very severe	Severe	Moderate	Mild	I did not have this side effect
A. Diarrhoea	☐	☐	☐	☐	☐
B. Nausea	☐	☐	☐	☐	☐
C. Vomiting	☐	☐	☐	☐	☐
D. Reduced appetite	☐	☐	☐	☐	☐
E. Abdominal pain	☐	☐	☐	☐	☐
F. Weight loss	☐	☐	☐	☐	☐
G. Liver function abnormality (blood test)	☐	☐	☐	☐	☐
H. Skin problems (e.g. rash, sunburn)	☐	☐	☐	☐	☐
I. Fatigue	☐	☐	☐	☐	☐
J. Bleeding	☐	☐	☐	☐	☐
K. Other side effect	☐	☐	☐	☐	☐
L. If "other" please describe					

	More than 7 stools/day compared to pre-treatment	4-6 stools/day compared to pre-treatment	Up to 4 stools/day compared to pre-treatment	Slight increase, but not daily	Not applicable (none)
M. Approximately, how frequently did you have diarrhoea?	☐	☐	☐	☐	☐

	More than 10 kg	5-10kg	2-5kg	Less than 2kg	Not applicable
N. How much weight have you lost in the last 3 months?	☐	☐	☐	☐	☐

5. Taking your therapy:

*This question should be answered by participants **still** taking anti-fibrotic therapy.*

A. How regularly do you take your anti-fibrotic therapy? *For the following please select **only one** from 5 options*

Never (0-19% of the time)	Infrequently (20-39% of the time)	Sometimes (40-59% of the time)	Often (60-79% of the time)	Always (80-100% of time)
☐	☐	☐	☐	☐

B. Why do you miss doses? *For the following please select **only one** from 5 options*

i. I Forget to take the therapy	I have side effects	I ran out of tablets	Other	Not applicable (I don't forget)
☐	☐	☐	☐	☐

ii. If you selected "Other" please describe the reason/s you miss your dose.

AIPFR STAFF: IPF ID#: _____

6. Monitoring and Additional Therapy:

*This question should be answered by participants **still** taking anti-fibrotic therapy.*

For the following please select only one answer for each question.

	1-2 times a week	Monthly	Every 3-6 months	Yearly or less often	Never
A. How frequently are you having blood tests to monitor your anti-fibrotic therapy?	☐	☐	☐	☐	☐

	Multiple times per day	Daily	A few times a week	A few times a month or less often	Never
B. Approximately how often are you taking anti-nausea medications?	☐	☐	☐	☐	☐
C. Approximately how often are you taking anti-diarrhoeal medications?	☐	☐	☐	☐	☐
D. Approximately how often are you using sunscreen?	☐	☐	☐	☐	☐

	Very unlikely	Somewhat unlikely	Not sure	Somewhat likely	Very likely
E. Overall, how likely are you to continue to take your anti-fibrotic therapy?	☐	☐	☐	☐	☐

7. Other therapies: ALL participants to answer

A. Since you last completed this questionnaire, have you been offered any of the following?

For the following questions please select an answer in each column, up to four responses in each row.

If you are unsure of what the question is referring to please select "No".

If in the first column you answer "No" please continue to answer all 4 sections of this question (row).

For example, you may be attending pulmonary rehabilitation that you were offered/referred to when you last completed a questionnaire.

	Have you been offered/referred to this service	**Are you currently attending this service**	**Have completed this service**	**Have you decided not to attend this service**
i. Pulmonary rehabilitation	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
ii. Lung transplant clinic	Yes ☐ No ☐	Yes ☐ No ☐	NA	Yes ☐ No ☐
iii. Palliative care specialist	Yes ☐ No ☐	Yes ☐ No ☐	NA	Yes ☐ No ☐
iv. PF support group	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
v. Dietician	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
vi. Psychologist	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
vii. Advance care planning	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
viii. Smoking cessation	Yes ☐ No ☐ Not applicable ☐	Yes ☐ No ☐ Not applicable ☐	Yes ☐ No ☐ Not applicable ☐	Yes ☐ No ☐ Not applicable ☐
ix. Clinical trial participation	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

AIPFR STAFF: IPF ID#: _____

B. Are you currently on any of the following therapies? *Please answer each question either yes or no*	**Yes**	**No**
i. Anticoagulation (blood thinners including warfarin)	☐	☐
ii. Reflux medications (e.g. Somac, Nexium, Losec, Zantac)	☐	☐
iii. Anti-depressants	☐	☐
iv. Anti-anxiety medications	☐	☐
v. Inhalers	☐	☐
vi. Prednisone (steroids)	☐	☐
vii. Other immune suppressants (e.g. methotrexate, azathioprine, cyclophosphamide, mycophenolate)	☐	☐
viii. Oxygen (Continuous or most of the day, e.g. a stationary concentrator)	☐	☐
ix. Oxygen (Ambulatory, for use only during physical activity e.g. cylinders for walking or a portable concentrator)	☐	☐
x. CPAP therapy	☐	☐
xi. Medication to help relieve or prevent severe breathlessness or coughing (e.g. morphine syrup, tablets or patches)	☐	☐

8. Hospital admission history:	
A. Have you been admitted to hospital since your last questionnaire?	Yes ☐ No ☐ *if no go to Q9*
B. If yes, what was the date or dates you were admitted to hospital? *(Please list a date for every hospital admission since you completed your last questionnaire, do not include clinic appointments or visits)*	**Date (s):**
C. If yes, was this for your pulmonary fibrosis?	Yes ☐ No ☐

9. How satisfied are you with your overall care? *For the following question please select only one answer*	Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
How satisfied are you with your overall care?	☐	☐	☐	☐	☐

Thank you for taking the time to complete this questionnaire. We appreciate your time and effort

All information provided to the Australian IPF Registry is bound by Commonwealth and State privacy legislation and guidelines, including the Health Records and Information Privacy Act and the NSW Health Privacy Manual. The Australian IPF Registry is committed to providing a high standard in handling personal information. Your information will only ever be used for health research. The researchers conducting any study will not have access to your identifying information unless you give your consent to participate.

CHECKLIST Please take a moment to check you have completed all the relevant sections on this Questionnaire.

	Participant		
Question number	**Taking anti-fibrotic therapy**	**STOPPING or CHANGING anti-fibrotic therapy**	**NOT taking anti-fibrotic therapy**
1. Date - **ALL Participants**	☒	☒	☒
2. Therapy (anti-fibrotic)	A, B, C, D	A and D	A and D
3. Therapy changes (anti-fibrotic)		☒	
4. Side effects (anti-fibrotic)	☒	☒	
5. Taking your therapy (anti-fibrotic)	☒	If you are still taking anti-fibrotic therapy	
6. Monitoring and additional therapy	☒	If you are still taking anti-fibrotic therapy	
7. Other therapies - **ALL Participants**	☒	☒	☒
8. Hospital admissions - **ALL Participants**	☒	☒	☒
9. Care – satisfaction - **ALL Participants**	☒	☒	☒

Figure 6.4. Patient-Specific Follow-Up Questionnaire.

AIPFR STAFF: IPF ID#: _____ Date Sent: _____Date Received: _____Database Entry: _____

Patient name:_____ Patient DOB: _ _ / _ _/ _ _ _ _

Follow-up Treatment Physician Form*

IPF REGISTRY AUSTRALIAN IDIOPATHIC PULMONARY FIBROSIS REGISTRY | LUNG FOUNDATION AUSTRALIA

Name of Respiratory physician:

Date this patient attended clinic

1.Date of Clinic Visit: _ _ / _ _/ 20_ _

2. Anti-fibrotic medication that your patient currently taking

A. Is your patient currently taking anti-fibrotic medication?	Yes ☐	
	No ☐ *If no go to Q2C.*	
B. What anti-fibrotic medication is your patient currently taking?		
Nintedanib (OFEV) 150mg BD ☐	Pirfenidone (Esbriet) 2403mg/day ☐	Pirfenidone (Pirfenex) ☐
Nintedanib (OFEV) 100mg BD ☐	Pirfenidone (Esbriet) 534-2402mg mg/day ☐	Pirfenidone clinical trial ☐
Nintedanib clinical trial ☐	Pirfenidone (Esbriet) <534mg /day ☐	Other clinical trial ☐
C. When did you first prescribe treatment?	**Date:**	
D. Changes to anti-fibrotic therapy		
i. In the last 3 months have there been any changes to therapy?	Yes ☐ No ☐	*If no go to Q4.*
ii. Stopped	Yes ☐ No ☐	
iii. Paused	Yes ☐ No ☐	iv. Length of time without any treatment Approx._____ days *or if no* Not applicable ☐
v. Changed	Yes ☐ No ☐	vi. New dose *or if no* Not applicable ☐ _____mg
vii. Changed to alterative anti-fibrotic therapy	Yes ☐ No ☐	viii. Name of new therapy *or if no* Not applicable ☐ _____

3. Anti-fibrotic medication changes

A. Who made the change	*Please select **ONLY one** answer (the main one)*	
i. ILD specialist	☐	
Local respiratory specialist	☐	
Local doctor (GP)	☐	
Hospital	☐	
Patient	☐	
Other	☐	
Not applicable	☐	
ii. If "other" please state who made the change:		

B. Why was the change made? *Please select one answer for the following question*

i. Side effects ☐	Abnormal blood test ☐	Patient choice ☐	Perceived loss of efficacy/progression ☐	Other ☐	Not applicable ☐

ii. If you selected "Other" give reason:

AIPFR STAFF: IPF ID#: _____

4. Anti-fibrotic medication compliance

A. How often do you think your patient takes their dose? *For the following please select **only one** from 5 options*

Never (0-19% of the time)	Infrequently (20-39% of the time)	Sometimes (40-59% of the time)	Often (60-79% of the time)	Always (80-100% of time)
☐	☐	☐	☐	☐

B. Why do you think that your patient misses their dose?

i.Forget	Side effects	Ran out of tablets	Other	Not applicable (They don't forget)
☐	☐	☐	☐	☐

ii.If you selected "Other" please describe the reason/s you think they miss the dose.

5. Side effects

How severe do you think the patient's side effects were <u>in the last 3 months</u>? *Select only one option*

	Very severe	Severe	Moderate	Mild	Pt did not have this side effect
A. Diarrhoea	☐	☐	☐	☐	☐
B. Nausea	☐	☐	☐	☐	☐
C. Reduced appetite	☐	☐	☐	☐	☐
D. Vomiting	☐	☐	☐	☐	☐
E. Abdominal pain	☐	☐	☐	☐	☐
F. Weight loss since starting medication	☐	☐	☐	☐	☐
G. Liver function abnormality	☐	☐	☐	☐	☐
H. Skin problems	☐	☐	☐	☐	☐
I. Fatigue	☐	☐	☐	☐	☐
J. Bleeding	☐	☐	☐	☐	☐
K. Other side effect	☐	☐	☐	☐	☐

L. If "other" please describe

6. Monitoring

For the following please select only one answer for each question

	1-2 times a week	Monthly	Every 3-6 months	Yearly or less often	Never
A. Approximately how frequently is your patient having blood tests for IPF medication?	☐	☐	☐	☐	☐

7. Additional therapy

For the following please select only one answer for each question.

	Multiple times per day	Daily	A few times a week	A few times a month or less often	Never
A. Approximately how often is your patient needing anti-nausea medications?	☐	☐	☐	☐	☐
B. Approximately how often is your patient needing anti-diarrhoeal medications?	☐	☐	☐	☐	☐
C. Approximately how often is your patient using sunscreen?	☐	☐	☐	☐	☐

AIPFR STAFF: IPF ID#: _____

	Very unlikely	Somewhat unlikely	Not sure	Somewhat likely	Very likely
D. Overall, how likely are you to continue to recommend ongoing treatment with anti-fibrotic therapy?	☐	☐	☐	☐	☐

8. Co-morbidities:

A. Since the last questionnaire has the patient had any of the following co-morbidities NEWLY diagnosed?

If yes, please give the date of diagnosis, if no select not applicable

	Yes	No	Date of diagnosis	Not applicable
i. COPD	☐	☐		☐
ii. GORD	☐	☐		☐
iii. Pulmonary Hypertension	☐	☐		☐
iv. Sleep apnoea	☐	☐		☐
v. Lung Cancer	☐	☐		☐
vi. Diabetes Mellitus	☐	☐		☐
vii. Chronic heart failure	☐	☐		☐
viii. Depression and/or anxiety	☐	☐		☐
ix. Coronary heart disease (or atherosclerotic heart disease) including a history of MI	☐	☐		☐
x. Arterial hypertension	☐	☐		☐

B. Have you offered/referred any of the following TODAY?	**Yes**	**No**
i. Pulmonary rehabilitation	☐	☐
ii. Lung transplant clinic	☐	☐
iii. Palliative care specialist	☐	☐
iv. Pulmonary Fibrosis support group	☐	☐
v. Dietician	☐	☐
vi. Psychologist	☐	☐
vii. Advance care planning	☐	☐
viii. Smoking cessation	☐	☐
ix. Pulmonary hypertension clinic	☐	☐

C. Have you INITIATED any of the following medications TODAY?	**Yes**	**No**
i. Anticoagulation	☐	☐
ii. Reflux (PPI or H2)	☐	☐
iii. Anti-depressants	☐	☐
iv. Anti-anxiolytics	☐	☐
v. Inhalers	☐	☐
vi. Pulmonary vasodilators	☐	☐
vii. Prednisone	☐	☐
viii. Other immunosuppression	☐	☐
ix. Oxygen: LTOT	☐	☐
x. Ambulatory oxygen	☐	☐
xi. Overnight oxygen	☐	☐

9. Exacerbation History:

	Yes	No	B. Date/s of Exacerbation	Not applicable
A. Since the last questionnaire, has the patient had an acute exacerbation?	☐	☐		☐

AIPFR STAFF: IPF ID#: _____

C. Aetiology of exacerbation? *Select only one*				
i.Unknown ☐	Infective ☐	PE ☐	Cardiac ☐	Other ☐
ii. If "Other" selected please describe.				

D. Treatment of Acute exacerbation *(Select all relevant options)*	
i. Hospitalisation	☐
ii. Antibiotics	☐
iii. Prednisone	☐
iv. ICU	☐
v. Supportive ventilation (NIV, CPAP etc)	☐
vi. Other	☐
vii. If "Other" selected please describe.	

10. Physical Findings:

	Room air	Oxygen		
A. SpO2	☐	☐	ii. Resting O_2 saturation	___%
If Oxygen selected			iii. O_2 flow rate	___L/min
B. WHO FC (I-IV)	___			
	Yes	**No**		
C. Crackles	☐	☐		
D. RHF	☐	☐		
E. Clubbing	☐	☐		
F. CTD features	☐	☐		

11. Overall Satisfaction

How satisfied are you with your patient's treatment?

Very dissatisfied ☐	Dissatisfied ☐	Neither satisfied nor dissatisfied ☐	Satisfied ☐	Very satisfied ☐

Overall, how likely are you to continue to recommend ongoing treatment with anti-fibrotic therapy

Very unlikely ☐	Somewhat unlikely ☐	Not sure ☐	Somewhat likely ☐	Very likely ☐

12. Additional information & vitality status

Please complete the following questions if relevant.

A. Lung transplant	Yes	Date	Day unknown*	Month unknown*
i. This patient has had a lung transplant	☐	ii._ _ / _ _/ 20	iii. ☐	iv. ☐
B. Patient deceased	Yes	Date	Day unknown*	Month unknown*
i. This patient is deceased	☐	ii._ _ / _ _/ 20	iii. ☐	iv. ☐

*If actual date is not known please provide as much information as available and indicate unknown information using the fields (iii) and (iv).

Figure 6.5. Physician-Specific Follow-Up Questionnaire.

Chapter Seven: Conclusion

7.1 General conclusions

Idiopathic pulmonary fibrosis (IPF) is a chronic, fibrosing interstitial lung disease (ILD) with an unknown aetiology characterised by relentless disease progression and worsening pulmonary fibrosis, leading to respiratory failure, poor quality of life and death. The diagnostic criteria for IPF have been refined over the last few years and requires the exclusion of other known causes for an ILD and the presence of a usual interstitial pneumonia (UIP) pattern on high resolution computer tomograph (HRCT). The diagnosis hinges on a multidisciplinary discussion at an ILD multidisciplinary meeting (MDM) as the current 'gold standard' diagnostic tool for ILD.

Despite evidence highlighting its importance in the diagnostic pathway of IPF, there is a lack of standardisation of the ILD MDM, and little is known of its best practice. Furthermore, there is ongoing interest in identifying an ideal diagnostic and prognostic biomarker of IPF, though this remains elusive. Accurate and early diagnosis of IPF is important given the availability of treatment in the form of antifibrotics. While landmarks studies have shown their efficacy in slowing disease progression, much remains unknown about the real-world impact of antifibrotics and how they will impact and reshape the overall management landscape of IPF.

Chapter two was designed to identify the essential and highly desirable features of an ideal, well-functioning ILD MDM. Chapter three explored the impact of antifibrotic therapies on extracellular matrix proteins that could be studied further as diagnostic biomarkers. We also explored the role of serum monocytosis as a potential prognostic biomarker in IPF. Chapter four reviewed and summarised the efficacy and safety of antifibrotics in IPF and other ILD with a progressive pulmonary fibrosis (PPF) phenotype. Lastly, chapter five and six focused

on exploring the diagnostic and management strategies of IPF, the use of antifibrotic therapies and describing patient and physician experiences in an Australian prospective cohort of IPF patients.

7. 2 Research findings and future directions

7.2.1 Chapter two: Essential Features of an Interstitial Lung Disease Multidisciplinary Meeting: An International Delphi Study

In this chapter, using a modified Delphi model, we conducted semi-structured interviews and administered online survey questionnaires to a large international panel of ILD experts and clinicians, aiming to seek consensus on essential features of an ideal ILD MDM. The study identified five essential items of an ILD MDM; (i) the attendance of at least one radiologist, (ii) access to visual projection system for viewing of radiology images, (iii) the use of a high-quality HRCT scan, (iv) a quiet setting conducive for easy interaction and high-quality discussions and (v) a standardised summary template to collate patient information and discussion points. In addition to these, the study identified other desirable features and highlighted potential role for a benchmarking and validation process in the future.

While questions remain on how best to validate or benchmark an ILD MDM, our study has laid the foundation on which future studies on the standardisation of ILD MDMs can be run. Currently, our group is undertaking a study aiming to standardise ILD MDMs and improve diagnostic agreement.

7.2.2 Chapter Three

7.2.2.1 Part A: Effect of Antifibrotic Therapies on the Extracellular Matrix in Idiopathic Pulmonary Fibrosis

In Part A of this chapter, we explored the effects of pirfenidone and nintedanib on extracellular matrix (ECM) proteins in IPF. Using pulmonary fibroblasts harvested from ex-planted IPF lungs or lung resections from healthy normal, we conducted an ECM enzyme-linked immunosorbent assay (ELISA) to study the effect of both antifibrotic agents on the expression of a panel of ECM proteins. Our study showed that both pirfenidone and nintedanib reduced the expression of periostin. We also found that nintedanib reduced tenascin-C expression, while the same was not seen following pirfenidone treatment, suggesting a different mechanistic pathway.

Our study provides further insights into the potential mechanism of action of nintedanib and its effect on the lung ECM while also highlighting variable effect of both agents on the ECM. Our findings suggests that there are likely multiple pathogenic pathways in IPF involving the ECM, and also highlights the need for further studies to better define the pathogenesis of IPF and hopefully, inform the discovery of future therapeutic agents.

7.2.2.2 Part B: Blood Monocyte Counts as a Potential Prognostic Marker for IPF: Analysis from the Australian IPF Registry

In Part B, we focused on the role of monocytosis as a prognostic marker, in which higher peripheral monocyte counts were associated with poorer survival in several international cohorts. Using data from the Australian IPF Registry, we performed a Cox proportional hazards

analysis and showed that elevated peripheral monocyte counts was an independent predictor for poorer survival which remained significant following multivariate analysis accounting for age, gender and baseline percent predicted forced vital capacity (ppFVC)

Our study findings added further validity to findings from internationally diverse cohorts of patients with IPF. We also showed that neutrophilia was a significant predictor of mortality, highlighting the need for future studies to provide better mechanistic insight into the role of monocytes and neutrophils in IPF, particularly those with more severe disease.

7.2.3 Chapter Four: Antifibrotic Therapy for Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis: A Systematic Review and Meta-Analysis

In Chapter four, we conducted a systematic review and meta-analysis to evaluate and summarise the efficacy and safety of antifibrotic therapies for the treatment of IPF and PPF with the primary endpoints of interest being change in FVC, progression-free survival (PFS) and health-related quality of life (HrQOL). Our study showed that both nintedanib slowed the rate of decline in ppFVC in IPF and while pooled analysis on pirfenidone could not be done, individual studies included showed treatment efficacy in slowing ppFVC decline. Both agents were also shown to be more favourable than placebo in slow ppFVC decline in the PPF cohort. Meta-analysis on PFS could not be performed due to various terminologies while nintedanib was shown to improve HrQOL scores in IPF and pirfenidone, in PPF. We also showed that both agents significantly reduced all-cause and respiratory-cause mortality in IPF studies, but there were no significant differences seen in the PPF studies.

Our study highlights the efficacy in both nintedanib and pirfenidone in slowing lung function decline in IPF and more recently in PPF. It also shows that both medications are safe for the treatment of IPF and PPF. However, it also raises several issues with regards to the design of current clinical trials. Firstly, there is a need for standardised endpoint measures in patient reported outcomes and definitions of PFS. Secondly, while FVC decline is widely accepted as a clinically meaningful endpoint, there is a pressing need to seek better endpoints that do not rely on trends of irrecoverable lung function loss. Lastly, more studies are needed on therapies that focus on alleviation of symptoms in addition to slowing lung function decline.

7.2.4 Chapter Five: Diagnosis and Antifibrotic Choice for Idiopathic Pulmonary Fibrosis: Analysis from the Australian Idiopathic Pulmonary Fibrosis Registry

Chapter Five described the characteristics and management pathways of newly diagnosed IPF patients in Australia. The study prospectively recruited patients and their respective physicians onto the Australian IPF Registry and semi-quantitative questionnaires administered to both patient participants and physicians, aimed to capture data on diagnostic pathways, antifibrotic prescription practices and management strategies. Additional semi-structured phone interviews with patients were also conducted to explore opinions and experiences regarding their diagnostic and management journey.

Our study showed that many participants were satisfied with the diagnostic process with participants identifying medication side effects as the biggest factor impacting the choice of antifibrotic agents. Our study identified significant diagnostic delays and the need for better patient education. Hence, this reinforces findings of the first two chapters in which better and high-quality diagnostic tools are needed to address delay and improve access to appropriate treatment. We introduced the concept of shared decision-making processes in antifibrotic

therapies and showed a collective desire of self-management but highlighted discrepancies in perception and understanding between participants and their respective physicians. The study was conducted across multiple ILD centres and provided insight to the use of antifibrotic therapies for the treatment of IPF in Australia from leading centres during a time where such therapies were newly approved by the Therapeutics Good Administration (TGA) and real-world experience in Australia was lacking.

7.2.5 Chapter Six: Antifibrotic Therapies and the Management of idiopathic Pulmonary Fibrosis: Longitudinal Analysis from the Australian Idiopathic Pulmonary Fibrosis Registry

In Chapter Six, our study aimed to explore nuances in antifibrotic prescription patterns in the first 12 months of diagnosis while describing the experiences of both participants and physicians during the same period. Longitudinal data from the Australian IPF Registry semi-quantitative questionnaire was used along with semi-structured phone interviews of physicians to further describe experiences with antifibrotics and the decision-making process in the management of IPF. In this study, there was a high rate of participants remaining on antifibrotic therapies despite experiencing side effects, which were mostly mild to moderate in severity. Over the 12-month follow up period, there was a reduction in treatment pauses and treatment cessation remained low. Despite side effects reported, satisfaction and likelihood of treatment continuation remained high. Our study highlighted a low referral rate to non-pharmacological adjunct therapies such as pulmonary rehabilitation, support groups and clinical trials. Physicians interviewed in the study, placed importance on open conversation and discussion with their patients on the use of antifibrotic therapies and the general management of IPF, once again highlighting the concept of shared decision-making.

Over the 12-month follow up period, this study showed that antifibrotic therapies continue to be well-tolerated and well-received by patients with IPF and their respective physicians. Further studies are needed to explore the lower-than-expected referrals to other services like pulmonary rehabilitation and to further evaluate the role of a multidisciplinary management approach in IPF.

7.3 Final Conclusion

While there have been major advances in the field and understanding of idiopathic pulmonary fibrosis, much remains unknown and many questions, unanswered. In this thesis, it is shown that there is a need to further improve and standardise the ILD MDM as the primary 'gold standard' diagnostic tool for IPF. There is also much needed work in identifying an ideal diagnostic and prognostic biomarker and our studies suggest that the ECM and peripheral monocytosis may be potential starting points.

In this thesis, the efficacy and safety of nintedanib and pirfenidone as novel antifibrotic therapies have been summarised. Finally, this thesis provides an Australian experience and rea-world perspective on the use of antifibrotic therapies in the management of IPF. While these therapies have truly changed the landscape of IPF management, there is much to improve. Future therapeutic studies will likely need standardisation with newer outcomes of interest and more focus should be poured into patient-reported outcomes.

Appendix

Nonspecific Interstitial Pneumonia

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Abstract

Nonspecific interstitial pneumonia (NSIP) is a complex disorder commonly associated with other conditions such as connective tissue diseases (CTDs) and environmental exposures. Although idiopathic NSIP has been recognized as a separate clinical entity, recent studies have suggested that a proportion of these cases have autoimmune features suggestive of underlying CTDs. The diagnosis of NSIP usually carries a better prognosis compared with idiopathic pulmonary fibrosis but has an unpredictable natural history. Its pathogenesis is thought to be an inflammatory-driven process involving multiple pathways, including a genetic predisposition. The lack of specific clinical features often makes the diagnosis of NSIP difficult. The huge variability of radiological and histological features seen in NSIP adds to the complexity of achieving an accurate diagnosis of NSIP and a multidisciplinary approach is often required. There is a lack of consensus on the optimal management strategy of NSIP. Early clarification of the goals of therapy and close monitoring for the progression of disease is important across the spectrum of NSIP irrespective of its etiology. Although immunosuppressive and immunomodulatory agents are commonly used for severe and progressive disease, the therapeutic landscape of NSIP is constantly evolving as the role of newer agents such as antifibrotic therapies is being explored.

Keywords
- interstitial lung disease
- nonspecific interstitial pneumonia
- diagnosis
- management
- disease behavior

"Nonspecific interstitial pneumonia" (NSIP) was first described as a histopathological pattern seen in patients infected with human immunodeficiency virus (HIV). The initial description of the histologic features included mild to moderate lymphoid infiltration mainly distributed in a peribronchiolar and perivascular fashion.[1] NSIP was seen to occur in patients without evidence of *Pneumocystis jiroveci* pneumonia infection, and was found to account for 32% of all episodes of clinical pneumonitis in one HIV cohort study.[2–4]

In 1994, Katzenstein and Fiorelli[5] described the histological features of NSIP in their seminal paper of 101 open lung biopsies. They reported 64 cases with varying degrees of inflammatory or fibrotic processes that did not meet the histological criteria of other specific interstitial pneumonia, namely, usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), or lymphoid interstitial pneumonia (LIP). The key distinguishing histologic feature was temporal uniformity, in contrast to the temporal heterogeneity seen in UIP. Although initially NSIP was considered as an ambiguous conglomeration of patients that could not be classified as one of the more well-defined histopathological patterns of interstitial lung diseases (ILDs), Katzenstein and Fiorelli highlighted the prognostic and treatment implications for patients with an NSIP, compared with those with a UIP pattern on histology. Following this, several case series retrospectively re-evaluated cases that were previously classified as idiopathic pulmonary fibrosis (IPF), previously known as cryptogenic fibrosing alveolitis. These studies showed similar findings in which patients with an NSIP pattern had a better prognosis when compared with their counterparts who were found to have a UIP pattern.[6–9] In a small case series by Cottin et al, an NSIP pattern on lung

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histology was associated with a variety of etiologies, including connective tissue disease-related ILD (CTD-ILD) and hypersensitivity pneumonitis (HP), but no etiology was identifiable in half of their patient cohort, suggesting the presence of an idiopathic form of the condition.[10]

NSIP was first given a provisional clinical entity of its own in the American Thoracic Society (ATS) and European Respiratory Society (ERS) 2002 classification of idiopathic interstitial pneumonias (IIP), but concerns were raised that its definition were often regarded as a "wastebasket" category, prompting further research. In 2008, an ATS NSIP workshop was undertaken to achieve a consensus on the diagnosis of the idiopathic form of NSIP.[11] Although idiopathic NSIP was officially included as a separate IIP in 2013, NSIP as a whole has numerous overlapping features with other ILDs and is known to be associated with a wide array of conditions, particularly in CTD-ILD.

Epidemiology

Idiopathic NSIP was first described as its own clinical entity in 2008,[11] with the acknowledgment that there was a need for further research into determining its true prevalence and incidence. Based on extrapolated data from previous retrospective series, the prevalence of idiopathic NSIP was suggested to range from 1 to 9/100,000.[12] A more recent Danish cohort study estimated the incidence of idiopathic NSIP to be 3 per million/year.[13] Studies have also reported NSIP to have a slight female predominance, affecting a younger population compared with IPF.[5,14–16] However, NSIP is commonly associated with other conditions, such as connective tissue diseases (CTDs), HP, and drug-related ILD, making it difficult to determine the true prevalence and incidence of NSIP overall.

Pathogenesis

Over the course of the past few decades, our understanding of the pathogenesis of NSIP has continued to evolve. An early hypothesis that provoked debate was that a UIP pattern was the end-stage form of an NSIP pattern. This concept arose from the description of both NSIP and UIP patterns in multiple lobes that were biopsied from the same patient. Based on earlier radiological studies that suggested that ground glass opacity (GGO) in NSIP represented areas of inflammation and fine fibrosis, the proposed narrative was that the changes seen in cellular NSIP, fibrotic NSIP, and UIP represented a continuum in which the fibrotic processes progress from mild inflammation to a more "burnt-out" stage as seen in UIP.[17] Other recent studies have demonstrated a small subgroup of NSIP patients progressing to a UIP pattern over time both histologically and radiologically.[18,19] Katzenstein et al reported similar findings in 12 out of 15 biopsy specimens of patients who were thought to clinically and radiographically have a UIP process, although majority of the NSIP-like areas were relatively minor in comparison to the heterogeneous "patchwork" features of UIP. However, the finding of NSIP-like areas on explant specimens that were absent on earlier biopsies is more suggestive of two different fibrotic processes occurring.[20]

However, the pathogenesis of NSIP is currently understood as an autoimmune and inflammatory-driven process, a rationale explained by the fact that NSIP is the most common radiological and histopathological patterns seen in CTD-ILD.[21] One study reported significantly increased levels of autoantibodies to heat shock protein-47, an autoantigen reported in sera of patients with rheumatoid arthritis, when compared with patients with an idiopathic UIP pattern.[22] Another study reported more than half of their cohort of IIP with biopsy-proven NSIP displayed symptomatic or serological criteria that would meet the definition of an undifferentiated CTD (UCTD).[23] Similar findings were also noted in a retrospective case series, further suggesting that even cases with idiopathic NSIP could have an autoimmune-predominant pathogenic process compared with IPF.[15]

The focus on NSIP being an immunological-driven process is supported by studies looking at the role of lymphocytes. It is well known from early histological studies examining lung biopsy samples that a mononuclear lymphocytic infiltrate occurs in NSIP.[5,24] One study analyzed the lymphocyte population of 10 patients with NSIP and found a largely lymphocytic infiltrate expressing the B cell–specific antigen but also a high CD4/CD8 ratio, exhibiting a Th1-type response with was substantially richer in cytokines, particularly interferon gamma (IFN-y), when compared with UIP tissue.[25] The finding of a high CD4/CD8 ratio contrasts to other studies that both reported a lower ratio in bronchoalveolar lavage (BAL).[26,27] The authors postulated that their cohort had a more cellular-predominant NSIP pattern and the perifollicular locations of these cells making them less likely to be sampled during a BAL could explain this difference. These findings draw attention to the potential role that the host's immune response have on the pathogenesis of NSIP. Yoshinouchi et al explored this further and found a significantly higher expression of the chemokine receptor CXCR3 rather than CXCR4 in lung tissue of patients with NSIP compared with those with IPF.[28] Their findings support that NSIP appears to be a Th-1-driven process, which impairs fibroblast activation and proliferation, thereby potentially explaining the paucity of fibroblastic foci seen in NSIP. However, this observation appears to be more complex in HP, where an NSIP pattern appears to be more common in acute or subacute forms of the disease, while the chronic form is characterized by fibrotic features that often overlap with a fibrotic NSIP or UIP pattern.[29] One study reported that T cells from BAL sampled from patients with HP had significantly increased production of IFN-y, indicating a Th-1 response.[30] Another study described similar findings when studying the T cell profile in subacute HP patients but found that patients with chronic HP (CHP) had a different functional T cell subset that had a reduced production of IFN-y and an increased CXCR4 expression, in keeping with a Th-2 response phenotype.[31]

While fibroblasts and myofibroblasts and their interaction with an abnormal extracellular matrix (ECM) have been extensively studied in IPF, research on their role in NSIP is

lacking.[32,33] However, several studies provide some evidence suggesting NSIP as a different pathogenic entity. Fibroblasts cultured from lung biopsy specimens with UIP were found to be more contractile than those with NSIP.[34] Vimentin, a structural protein found on mesenchymal cells and fibroblasts, was reported in a proteomic study to be exist as different subtypes when compared between UIP and NSIP.[35] Periostin, an ECM protein reported to be associated in the pathogenesis of IPF, was reported to be elevated in the sera of fibrotic NSIP patients but was only weakly expressed in those with a cellular NSIP.[36] Several other ECM-modulating enzymes and proteins have also been found to be able to significantly distinguish IPF patients from non-IPF patients, including those with NSIP.[37] Another study investigated the role of vascular endothelial growth factor-A and matrix metalloproteinase-2, in the pathogenesis of neovascularization of early alveolar fibrotic lesions and found their expression to be increased in fibrotic NSIP compared with UIP.[38] Other pathogenic pathways have also been explored with one study interestingly reporting a procoagulant state in IPF patients compared with NSIP patients and controls, suggesting endothelial activation and microvascular injury.[39] Another comparative proteomic analysis of lung tissue reported that although fibrotic NSIP and UIP were histologically different, they carried similar proteomic profiles and hence suggesting similar pathogenic principles. However, intracellular clearance of reactive oxygen species and misfolded protein carbonyls appear to be enhanced in fibrotic NSIP due to enhanced expression of antioxidant acting proteins.[40] Drawing from these findings, abnormal oxidative stress might have a role to play in the pathogenic mechanism of NSIP. Suffice to say, the true pathogenesis of NSIP is still unknown and further research is needed. Much of the challenges in establishing its pathogenesis could potentially stem from both its histological and radiological heterogeneity as well as its various possible etiologies.

Risk Factors

While cigarette smoke has been linked to several IIPs such as respiratory bronchiolitis-ILD and DIP, and its role in the pathogenesis of IPF has also been explored, the link is less clear with NSIP.[41,42] When the syndrome of combined pulmonary fibrosis and emphysema was first described in 2005 in current or ex-smokers, high-resolution computed tomography (HRCT) demonstrated upper zone emphysema and lower zone features of honeycombing, reticular intralobular opacities, and traction bronchiectasis. Although prominent GGO was an exclusion criteria, approximately two-thirds of the patients had focal GGO detected with 34% being consistent with a pattern of fibrosing NSIP.[43] Another retrospective study compared the prevalence of emphysema in "healthy" smokers with a normal forced expiratory volume in 1 second, chronic obstructive pulmonary disease (COPD) patients, and patients with an NSIP pattern.[44] It showed a high prevalence of emphysema in the NSIP and COPD patients compared with "healthy" smokers, hence indirectly suggesting a common pathogenic role of cigarette smoke in both NSIP and emphysema. Further research is certainly required to explore the role of cigarette smoke in NSIP specifically.

As not every smoker develops NSIP, a "two-hit" mechanism with an environmental insult in a genetically predisposed population has been suggested. One study identified that a smoking history was significantly associated with the presence of familial interstitial pneumonias when families with a history IIPs were assessed.[45] Phenotypic presentation was heterogenous with some patients demonstrating NSIP either radiologically or histologically, highlighting a possible genetic link in some cases of NSIP. Since then, several genetic mutations have been identified and associated with IPF and other familial forms of IIPs.[46,47] Recently, a study documented a comprehensive gene expression profile analysis of IPF and NSIP patients compared with normal controls.[48] Using explanted lungs, the study described genes that were significantly expressed in NSIP were involved in regulatory mechanisms of immune reaction. These genes differed from those expressed in IPF which were involved in epithelial-to-mesenchymal transition, myofibroblast proliferation, matrix remodeling, and collagen deposition.

These findings support the hypothesis of genetic predisposition as a possible risk factor in the development of NSIP and also suggest NSIP as a stand-alone, transcriptionally homogenous condition. Therefore, it is recommended that all patients presenting with NSIP should be questioned about any relevant family history of ILD. It is also important to note that familial cases of IIP do not always present with HRCT features that conform with classical patterns of NSIP and may potentially require further investigations such as a lung biopsy.[49] Finally, smoking cessation should be strongly advocated despite the paucity of data on its association.

Prognosis

Katzenstein and Fiorelli reported a low mortality rate of 11% in their cohort of patients with NSIP. It was also noted that 83% of patients being followed up remained alive with their disease or recovered, even in those with most severe fibrosis.[5] These findings were also echoed in the ATS NSIP report which noted a 5-year and 10-year survival rates of 80 and 73%, respectively.[11] These studies along with several other early case series describe a good prognosis among NSIP patients, a stark contrast to that of IPF patients.[6,10] Previous studies have also described better outcomes in NSIP cases associated with an autoimmune etiology compared with truly idiopathic NSIP.[50,51] The degree of fibrosis seen in NSIP has been proposed to impact on the overall prognosis of patients, with studies demonstrating a significant difference in survival rate between those with fibrotic and cellular NSIP.[52,53] The pattern of fibrosis have also been implicated as an important prognostic factor with studies showing that an NSIP pattern in patients with UCTD had better outcomes than their counterparts with a UIP pattern.[54,55]

However, interval changes in pulmonary function have been proposed to carry significant prognostic implications in NSIP. Latsi et al examined several prognostic variables including histopathological diagnoses and serial trends in

pulmonary function testing in a cohort of UIP and NSIP. First, they reported significantly higher mortality in UIP patients after 3 years of follow-up, with no significant mortality difference from NSIP during the preceding years. Second, at the 6-month follow-up, the histopathological diagnosis remained as an independent predictor of mortality using several different proportional hazards model. However, at the 12-month follow-up, histopathological pattern was no longer predictive of mortality with pulmonary function trends remaining as a significant predictor for mortality.[56] A subsequent study of 48 fibrotic NSIP and 131 IPF patients found that only the 6-month change in forced vital capacity (FVC), initial diffusing capacity of lung for carbon monoxide (DLCO), and sex to be significant predictors of survival on multivariate analysis.[57] When taken together, it is suggested that baseline histopathological pattern can be used as an initial predictor for mortality, but over time, this is replaced by serial trends in lung physiology, supporting the need for regular monitoring for progression in these patients. It is important to note, however, that the natural history of NSIP can be unpredictable and variable, with some patients remaining stable or showing improvement, while others follow a more progressive decline or develop acute exacerbations.[41,58,59]

Clinical Features

The characteristic clinical symptoms of patients with NSIP are nonspecific and are insufficient for clinicians to use to distinguish it from other ILD. In general, patients with NSIP are reported to have a cough (33–83%) and dyspnea (70–-100%) as the most common presenting symptom, regardless of the underlying disease etiology.[6,10,11,14,15,60] However, other symptoms including fevers and constitutional symptoms such as fatigue and weight loss may occur.[7,10,14,27,60,61] Physical examination findings such as digital clubbing (0–40%) and fine inspiratory crepitations can be present but do not discriminate NSIP from other forms of ILD.[8,10,62] A thorough clinical examination remains important, as findings such as a skin rash or Raynaud's phenomena can add impetus for the clinician to further investigate for an underlying etiology, such as an occult CTD.[11,63]

Diagnostic Testing

Pulmonary function testing classically demonstrates a restrictive ventilatory defect with a reduction in gas transfer capacity, but likewise, these findings are not specific to NSIP.[11,52,64] Resting hypoxemia may be present in some patients and often worsens during exercise.[10,27]

BAL can be performed in patients with suspected NSIP to exclude concomitant infection and to also obtain a differential cellular analysis.[65] Lymphocytosis, defined by guidelines as a lymphocytic cellular pattern with more than 15% lymphocytes, has been found to be present in NSIP patients compared with those with a UIP pattern in some but not all studies.[7,14,66] A study by Ohshimo et al[67] suggested a threshold level of 30% for lymphocytosis in BAL to demonstrate a favorable discriminative power for the diagnosis of NSIP compared with IPF. However, subsequent studies have[68] found no difference in the BAL cellular profile between fibrotic NSIP and IPF patients. As such, there is little diagnostic role for BAL lymphocytosis to differentiate IPF from fibrotic NSIP. More importantly, lymphocytosis is not specific to NSIP and can be seen in other forms of ILD.[69,70]

Autoantibodies have been widely used by rheumatologists as a clinical tool in the diagnosis of underlying CTDs.[71] The detection of these autoantibodies often plays a crucial role in the diagnostic workflow of NSIP, as it is the most common form seen in CTD-ILD. Its presence may assist the diagnosis of a previously unrecognized occult CTD and would have major implications for the subsequent management and prognosis of such patients.[21] However, there is no universal consensus on which autoantibody carries the most significance during the initial assessment of NSIP patients. In the 2011, ATS/ERS/Japanese Respiratory Society/Latin American Thoracic Association guidelines, testing for antinuclear antibody, anticyclic citrullinated peptide, and rheumatoid factor was recommended in all patients with an ILD. More specific testing for extractable nuclear antigen antibodies and myositis antibodies was recommended only in selected cases, based on clinical suspicion.[72] However, a small retrospective study showed that an extended autoantibody panel provided additional information that allowed clinicians to reclassify several cases of ILD.[73] In addition, repeat serological testing was also recommended in the guidelines as subsequent reviews may yield a positive result, as demonstrated by a recent study in which 25% of a large patient cohort demonstrated a positive seroconversion in autoantibodies that were originally negative during their initial assessment.[74] Taken together, we recommend that serial autoantibody testing be used as a diagnostic adjunct to the clinicians' assessment with a complete medical history and clinical examination in cases of NSIP. The paucity of data and lack of consensus on what constitutes an initial autoantibody panel test are an identifiable research need, and currently, are driven by individual centers' experiences.

Radiology

Chest X-rays of patients with NSIP have been described to demonstrate patchy parenchymal opacities and infiltrates, usually affecting the lower lobes of the lungs bilaterally.[5,60] Chronicity of these findings may prompt clinicians to suspect an underlying interstitial process, leading to further diagnostic studies, namely, a HRCT scan.[75]

Early studies of HRCT in NSIP report the presence of patchy GGOs as the salient feature of NSIP (►**Fig. 1**) which may also be accompanied by reticular pattern of fibrosis, volume loss, and traction bronchiectasis (►**Fig. 2**).[7,76–80] Honeycombing is rarely seen and its presence would usually steer clinicians away from the diagnosis of NSIP.[53,81,82] An ATS project working group was tasked in 2008 to define the characteristics on idiopathic NSIP.[11] They were able to characterize HRCT features from 61 idiopathic NSIP patients and these findings are very often extrapolated to also describe

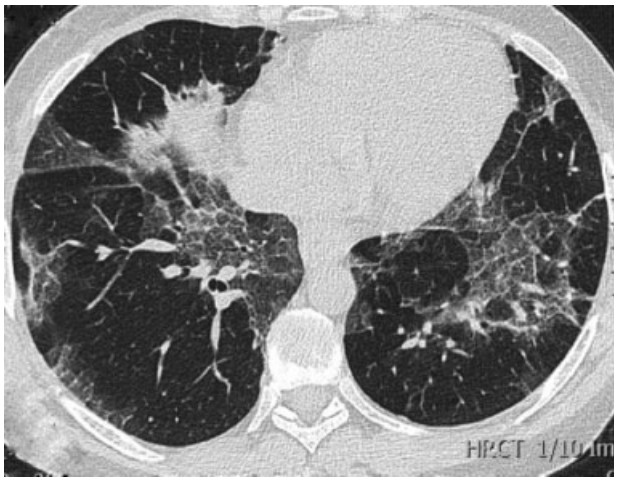

Fig. 1 HRCT findings of nonspecific interstitial pneumonia. Patchy areas of ground glass opacities with interlobular septal thickening and reticulation involving bilateral lower lobes. HRCT, high-resolution computed tomography.

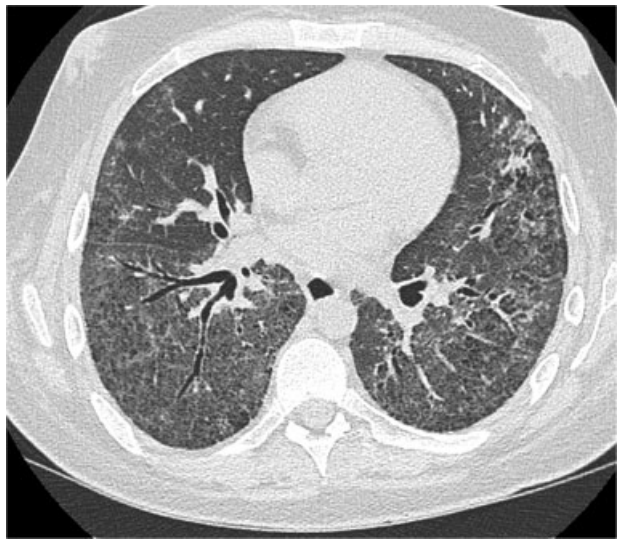

Fig. 2 Widespread increased reticulation and mild areas of ground glass opacities bilaterally, accompanied by traction bronchiectasis and relative subpleural sparing suggestive of fibrotic nonspecific interstitial pneumonia.

features of NSIP from other etiologies. Parenchymal abnormalities predominantly involve the lower lobes (92%) with the remainder having equal severity and distribution in the upper lobes. The most common HRCT features were a reticular pattern (87%) rather than GGO (44%). Similar to other series, traction bronchiectasis (82%) and lobar volume loss (77%) were also seen with just more than half of the patients having a diffuse distribution. Subpleural sparing is considered as a feature of an NSIP pattern but is not always present.[19,83] ►**Table 1** shows a list of characteristic radiological findings of NSIP.

Overlap Patterns

Unlike the diagnosis of IPF, which, based on recent clinical guidelines,[84] can be heavily influenced by HRCT findings, the clinical utility of HRCT for the diagnosis of NSIP may still be inadequate in a proportion of NSIP cases. In fact, three overlap patterns have been identified in NSIP: NSIP/UIP, NSIP/organizing pneumonia (OP), and NSIP/HP.[77,78,85] Features such as honeycombing can be present in NSIP, highlighting the overlap which can be seen in UIP and NSIP. One study of idiopathic NSIP suggested that the presence of honeycombing was predictive of poorer survival.[86] In another series, the ability of HRCT to delineate cases of histologically confirmed NSIP from UIP was modest at best with a sensitivity of 78% and a specificity of 64%.[82]

In some NSIP patients, there is also a coexisting OP pattern (NSIP/OP overlap). This pattern has been reported in CTD related and inflammatory myopathic ILD.[41,87] Huo et al found features of OP in up to 79% of their cohort of 33 NSIP patients.[88] The presence of an OP/NSIP overlap pattern on surgical lung biopsies was associated with unfavorable disease progression in a study, but only 27% of these patients had radiological features of consolidation.[89] Several studies have reported GGO as an overlapping feature found in both NSIP and cases of HP.[77,90] A retrospective study attempted to assess the accuracy of thin section CT in helping to distinguish CHP from NSIP using histologic findings as a reference standard.[85] Unsurprisingly, both CHP and NSIP cases displayed a spectrum of features with varying extent, in particular however, was the presence of GGO. Although up to 34% of NSIP cases demonstrated lobular areas of decreased attenuation, this feature appears to be more specific for

Table 1 Characteristic radiological and histological features of NSIP

Radiology	Histopathology
Homogeneous distribution with lower zone predominance Ground glass opacities Subpleural sparing[a] Traction bronchiectasis[b] Organizing pneumonia[a]	Temporal and spatial homogeneity Interstitial inflammatory cell infiltrate (lymphocytes and plasma cells) Collagen bundles intertwined with cellular infiltrate and rare fibroblastic foci[b] Organizing pneumonia[a]

Abbreviation: NSIP, nonspecific interstitial pneumonia.
[a]Features are not always present in every case.
[b]Features are more commonly seen in fibrotic compared to cellular phenotypes.

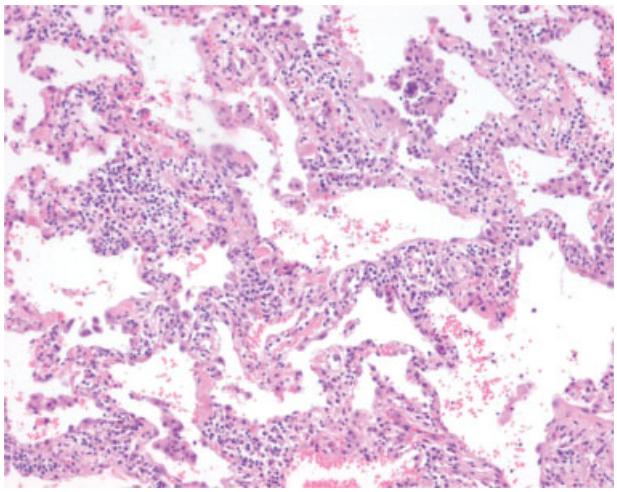

Fig. 3 Diffuse and homogeneous expansion of interstitium by chronic inflammatory cells seen in cellular nonspecific interstitial pneumonia.

CHP, while subpleural sparing would be more suggestive of NSIP. Other distinguishing features of HP such as the centrilobular distribution of GGO and an upper zone-predominant pattern of reticulation have been proposed but is not standardized across all cases.[91,92] In summary, the predominant presence of GGO, subpleural sparing with or without traction bronchiectasis, and OP is suggestive of an NSIP pattern.

Histopathology

When Katzenstein and Fiorelli first published their seminal paper on the histopathological features of NSIP, they described interstitial pneumonias that did not fulfill pathological criteria that were already well described.[5] They divided cases into three different groups based on the relative amount of inflammation and fibrosis. Group 1 was characterized by cellular interstitial pneumonia with relatively little fibrosis, Group 2 contained a mixed pattern involving both cellular infiltration with areas of fibrosis, while Group 3 was predominantly fibrotic in nature with parenchymal architectural distortion and collagen deposition. However, all three groups displayed temporal and spatial homogeneity, a feature that is now well described in NSIP which contrasts sharply to the temporal heterogeneity of histopathological features of UIP. The pathologic infiltrate in NSIP usually comprises a mixture of lymphocytes and plasma cells, often seen within the alveolar septa (►**Fig. 3**). The process is also frequently accentuated in the peribronchiolar interstitium, and there may also be prominent alveolar pneumocytes present. In cases of NSIP where fibrosis is present, collagen bundles are intertwined with cellular infiltration with few fibroblasts, again contrasting to that of UIP where fibroblastic foci are seen abundantly[24] (►**Fig. 4**). Studies have also attempted to simplify the original proposed histopathological criteria and divided NSIP to a cellular and fibrotic patterns.[27] Similar to radiological studies, histopathological findings of an OP/NSIP overlap pattern are common and have been reported in up to 79% of NSIP cases, but its extent is usually overshadowed by other interstitial changes[88,93] (►**Fig. 5**). Its presence, however, may suggest the presence of an underlying CTD-ILD.[94] Overlapping histological features of NSIP with HP have also been reported.[95] Subacute HP cases often demonstrate a lymphoplasmacytic infiltrate histologically making it difficult to distinguish from NSIP and only the presence of loosely arranged granulomas can help differentiate them.[96,97] A list of characteristic histological features of NSIP is shown in ►**Table 1**.

Histopathology plays a pivotal role in discriminating cases with a radiological pattern of UIP from NSIP. Its importance was demonstrated in a retrospective study evaluating the correlation of CT patterns with pathological diagnoses. In this study, 38% of patients with a reported radiological pattern of NSIP were found to have a UIP pattern histologically.[98] Similar to radiological findings, the histopathological

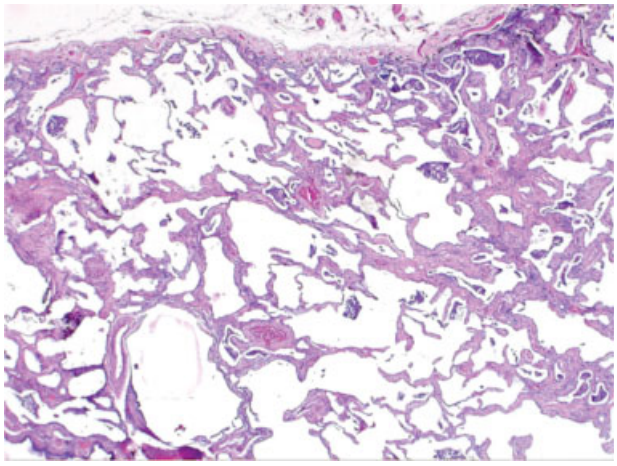

Fig. 4 Mild expansion of interstitium and thickening of alveolar septa by fibrosis in keeping with fibrotic pattern of nonspecific interstitial pneumonia.

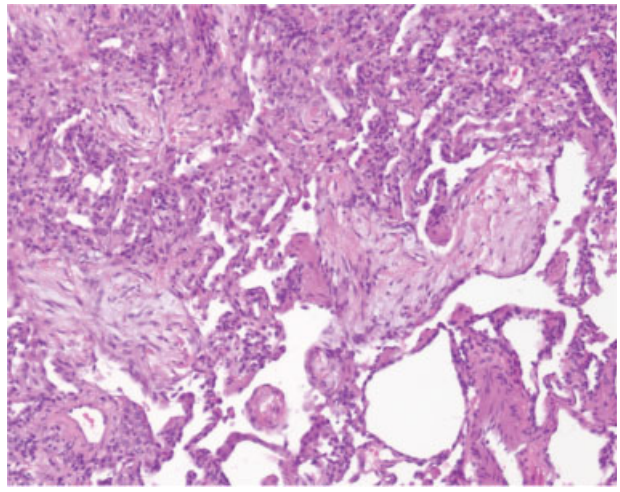

Fig. 5 Patchy expansion of interstitium by chronic inflammatory cells in association with polypoid intra-alveolar fibroblastic proliferation (organizing pneumonia pattern).

patterns seen in NSIP carry relevant prognostic implications. Fibrotic NSIP has been implicated in multiple studies to predict a poorer prognosis compared with cellular NSIP.[17,27,99] However, the narrative on the prognostic impact of OP/NSIP pattern is less certain. Todd et al reported an unfavorable disease progression following a multivariate analysis within their cohort of patients with an OP/NSIP overlap, irrespective of their underlying etiology.[89] However, Huo et al did not find the presence of OP to have a significant impact on prognosis, despite it being a common finding in their cohort.[88]

The histological diagnosis of NSIP is often not straightforward. One study showed that a small proportion of their cohort (12.5%) had discordant UIP and NSIP features when multiple lung biopsy samples were performed.[100] This highlights the potential for overlapping patterns to be present within the same patient and proposes a rationale for lung biopsies to be sampled from multiple areas. Another major factor that needs to be considered is the interobserver variability among pathologists. Following the inclusion of NSIP as an IIP in the ATS/ERS update, Nicholson et al evaluated the real-life level of agreement among 10 expert pathologist and found only fair agreement with a kappa value of 0.32, with more than half of the observer noise related to NSIP.[101] Another more recent study suggested that this has improved over the course of the last decade with a kappa value of 0.73.[98] However, Walsh et al assessed seven international multidisciplinary meetings and found a poor level of agreement for the diagnosis of NSIP from pathologists (weighted kappa 0.30) as well as clinicians and radiologists (weighted kappa 0.31 and 0.32, respectively).[102] Although this is in stark contrast to the good agreement level for IPF, there was an improvement in the degree of agreement among pathologists (weighted kappa 0.42) for NSIP following discussion in a multidisciplinary meeting. Importantly, in this study, the poor concordance among the pathologists (weighted kappa 0.21) is in direct contrast to the high concordance among clinicians for CTD-ILD (weighted kappa 0.76).[102] This suggests that a lung biopsy may not be warranted in CTD-ILD. Taken together, careful consideration should be given to select patients requiring a biopsy to confirm the presence of NSIP. The presence of an underlying CTD may preclude the need for histopathological evaluation and a discussion in a multidisciplinary setting would be highly recommended. That being said, the presence of an NSIP pattern on a lung biopsy should immediately prompt clinicians to re-evaluate the case with renewed vigilance, in particular, focusing on obtaining a complete occupational and environmental exposure history as well as a careful physical examination, before labeling the disease as idiopathic.[62]

Multidisciplinary Evaluation

Multidisciplinary collaboration among pulmonologists, radiologists, and pathologists plays a critical role in the diagnostic process of NSIP. As previously described, multiple overlapping radiological patterns pose a challenge for clinicians to be confident on the diagnosis. A multidisciplinary approach allows the integration of clinical, radiological, and particularly in non-IPF cases such as NSIP, histological information available to allow for a consensus diagnosis to be made.[11,41,103] A study showed that a multidisciplinary team's agreement for a diagnosis of CTD-ILD was good (weighted kappa 0.73).[102] However, the agreement for cases of idiopathic NSIP was only moderate at best (weighted kappa 0.42), suggesting that limitations are still present in diagnosing all NSIP cases even when discussed in a multidisciplinary setting. Nonetheless, a multidisciplinary meeting is the current gold standard for the diagnosis of an ILD, and therefore, should be used in NSIP cases. As NSIP is commonly seen in CTD-ILD, collaboration with rheumatologists in these forums would be desirable, but may not be logistically possible.[104] A proposed diagnostic algorithm for NSIP is illustrated in ►**Fig. 6**.

CTD-ILD

CTDs are a heterogeneous group of autoimmune disorders and are often associated with an underlying ILD. CTD-ILD carries a considerable burden of morbidity and mortality for these patients, hence early recognition and detection is paramount.[105] The overall most common histological and radiological patterns seen in these conditions is NSIP.[106,107] NSIP can be seen in Sjogren's syndrome,[108] systemic sclerosis,[109] and particularly in polymyositis and dermatomyositis, where NSIP has been reported to be present in up to 82% of patients with an associated ILD.[110–112] ILD is less common in systemic lupus erythematosus (SLE), and its presence should prompt clinicians to exclude other conditions such as pulmonary edema or infections. However, cellular and/or fibrotic NSIP have been described as the most common pattern on lung biopsy in few cases.[113] When compared with the other CTD, rheumatoid arthritis-associated ILD (RA-ILD) is more commonly associated with a UIP pattern, but NSIP can also be seen.[114–116] Irrespective of which CTD is involved, clinicians should note that an ILD can present as the first clinical feature of an underlying CTD. A previous retrospective study has reported almost one-third of consecutive ILD patient satisfied published criteria for an underlying CTD that was unrecognized during the initial assessment.[117] Kono et al reported 17% of their patients who were previously diagnosed with idiopathic NSIP, were diagnosed with CTD within a mean follow-up period of 2 years.[118] Sato et al described a similar trend where patients with histologically proven NSIP developed stigmata of a CTD more than 6 months after their initial presentation.[119] Thus, a patient presenting with NSIP should be thoroughly investigated and clinicians are recommended to monitor vigilantly for any extrapulmonary signs of an underlying CTD.[120]

Idiopathic NSIP

In the late 20th century, early case series floated the concept of a group of patients who had "idiopathic" NSIP in the absence of an underlying CTD or identifiable environmental and drug exposures.[7,8,27] Following provisional recognition

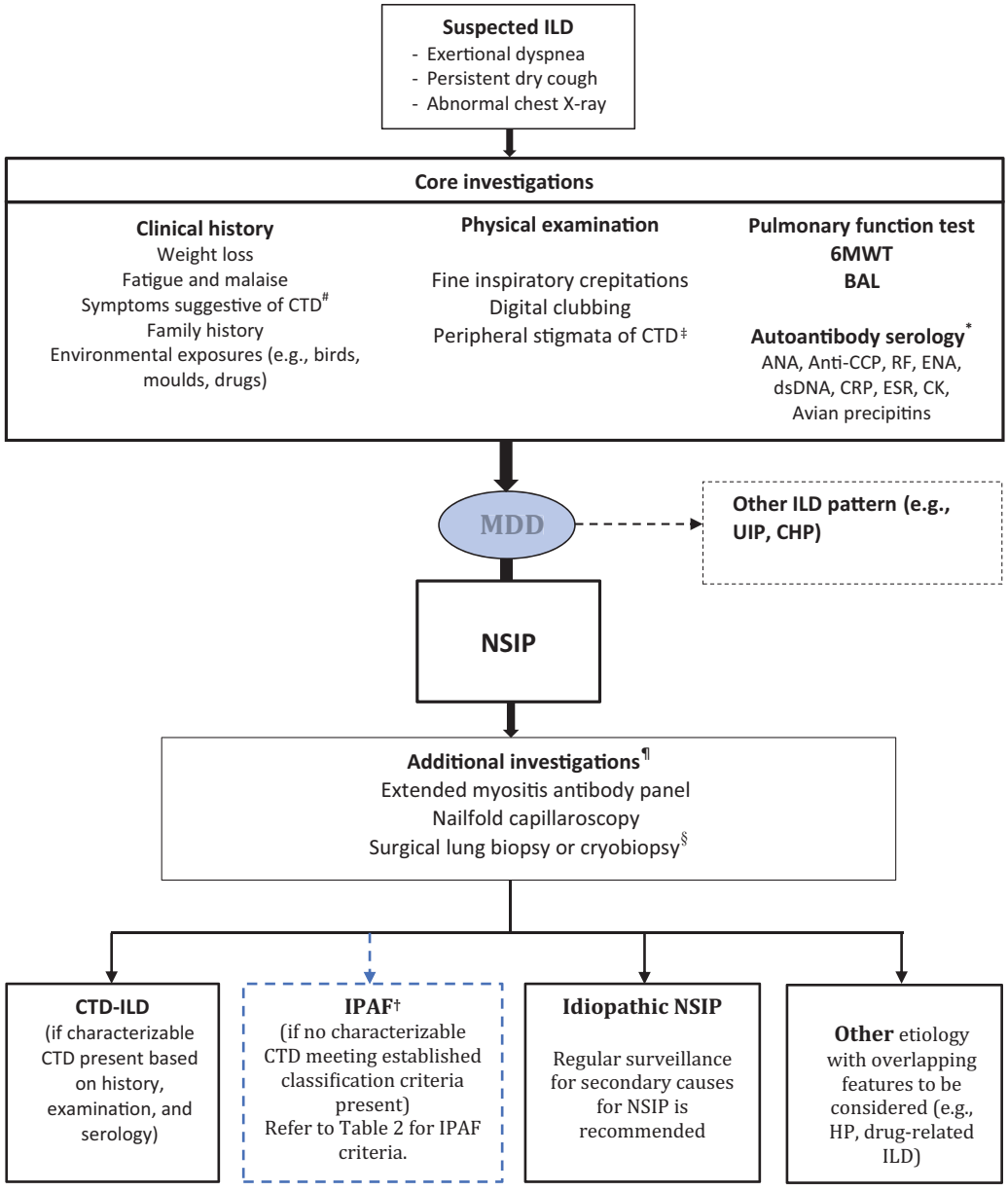

Fig. 6 Diagnostic algorithm for NSIP. ANA, antinuclear antibody; anti-CCP, anticyclic citrullinated peptide; BAL, bronchoalveolar lavage; CHP, chronic hypersensitivity pneumonitis; CK, creatinine kinase; CRP, C-reactive protein; CTD, connective tissue disease; DIP, desquamative interstitial pneumonia; dsDNA, double-stranded DNA; ENA, extractable nuclear antibody; ESR, erythrocyte sedimentation rate; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune feature; NSIP, nonspecific interstitial pneumonia; RF, rheumatoid factor; 6MWT, 6-minute walk test; UIP, usual interstitial pneumonia. #Symptoms include but are not limited to arthralgias, morning stiffness, sicca symptoms, Raynaud's phenomena, photosensitivity, myalgias, and weakness. ‡Peripheral stigmata of CTD include but are not limited to sclerodactyly, telangiectasia, digital ulceration, nail fissuring, mechanic's hands, Gottron's papules, and small joint synovitis. *Although autoantibody testing is suggested for patients suspected with NSIP, there is no consensus guideline indicating which antibody requires initial testing. ¶Additional investigations can be performed to assist in achieving a diagnosis but as there are no consensus guidelines, these are not performed at every center. §A surgical lung biopsy or cryobiopsy is not indicated in patients who are high risk for peri- and postoperative complications. In cases with a clear history of underlying CTD, lung biopsy is often not required. However, lung biopsy is required for the diagnosis of idiopathic NSIP by excluding other alternative diagnoses. †IPAF currently remains as a research terminology and should not be used in the clinical setting.

of idiopathic NSIP as a separate entity in the ATS/ERS 2002 statement on the classification of IIP, Travis et al studied this population further and reported its good prognosis compared with IPF, with a 5-year mortality rate of less than 18%, which was comparable to other studies. Interestingly, however, a proportion of the study cases had clinical stigmata suggestive of an underlying CTD or a positive serology and two patients were later diagnosed with a CTD.[11] Fujita et al examined cases of idiopathic and CTD-related NSIP and found it difficult to radiologically and histologically differentiate both groups. Furthermore, 27% of patients classified as idiopathic NSIP had autoantibodies present but did not develop a CTD despite a 5-year follow-up, leading the authors to propose the concept of idiopathic NSIP being an

"autoimmune interstitial pneumonia."[121] Findings from another study appeared to support this concept, having showed no significant difference in survival rates between cases of idiopathic NSIP and NSIP associated with a CTD.[122]

Interstitial Pneumonia with Autoimmune Feature

It is now recognized that there is a cohort of patients with some clinical and serological manifestations of a CTD who do not fulfill criteria for a defined rheumatological disorder. These conditions were collectively named UCTDs, lung dominant CTD, or autoimmune-featured ILD.[23,123,124] Kinder et al reviewed IIP cases from their institution and proposed the use of a modified criteria to identify patients with UCTD. The criteria they used included symptoms commonly described in CTD, a list of autoimmune serologies, and markers of disease activity, namely, erythrocyte sedimentation rate and C-reactive protein levels.[23] Corte et al retrospectively studied IIP patients who underwent surgical lung biopsy and re-evaluated them for UCTD based on Mosca et al's criteria.[123,125] They demonstrated that UCTD was present more frequently in NSIP (31%) than in IPF (13%) and a diagnosis of UCTD had a specificity of 88% for NSIP histology. The association between the presence of UCTD and NSIP histology was weaker than what was reported by Kinder et al and appeared to be dependent on the choice of criteria for UCTD being used, highlighting the lack of consensus on this topic. Furthermore, the term UCTD is usually considered by rheumatologist to be a condition that is mild in severity, with cohort studies reporting very low rates of pulmonary fibrosis in these patients.[126–128] The uptake and acceptance of these proposed criteria has been limited by their overlapping nature and there is a need for standardization to allow for further research in this area.[122,129,130] Recently, an ATS/ERS research taskforce was tasked to generate consensus regarding the classification of these patients, and proposed the term "interstitial pneumonia with autoimmune features (IPAFs)."[131] The proposed classification uses a list of features that are organized into three central domains: (1) a clinical domain consisting of specific extrathoracic features suggestive of an underlying CTD, (2) a serological domain with specific autoantibodies, and (3) a morphologic domain comprising specific radiological, histological, and pulmonary physiological features (full criteria shown in ►**Table 2**). Patients need to have at least one feature from at least two domains to be classified as having IPAF. Radiological patterns included in the criteria are NSIP, NSIP with OP, and LIP. However, the presence of a radiological pattern of UIP does not exclude patients from being classified as IPAF if they had at least one feature from the other domains. Although the introduction of the term IPAF served as a standardized set of criteria, early studies using the proposed criteria highlighted the need for further research and evaluation. Oldham et al reported that a high proportion of patients fulfilling the IPAF criteria had a UIP pattern rather than an NSIP pattern, and this was significantly associated with a worse outcome.[132] Meanwhile, a study by Chartrand et al reported no deaths within a mean follow-up period of 5.5 years with only 9% of their cohort having a UIP pattern.[133] Currently, the classification of patients with IPAF has yet to be validated in large prospective cohorts and thus, remain as a research statement. As such, idiopathic NSIP remains as a recognized distinct clinical entity, but there is a growing body of evidence suggesting it as an occult manifestation of an autoimmune disorder.

Management

There is a paucity of randomized-controlled studies for the management of NSIP. In light of this, a "disease behavior" classification was proposed in the 2013 ATS/ERS guidelines which can be incorporated into a management strategy for NSIP.[41] These classifications were broadly divided into five categories based on disease severity and the degree of reversibility of the condition, allowing clinicians to make informed management decisions. In general, a conservative approach with close monitoring for disease progression while addressing other potential contributing comorbid conditions can be taken for those with limited disease or have demonstrated a period of stability.[134] However, early intervention with immunosuppressive or immunomodulatory agents for those with progressive and/or severe disease is recommended with the goals of treatment focused on achieving disease regression or stabilization. FVC, DLCO, and a 6-minute walk test are broadly accepted as variables that clinicians can use to monitor the progression of disease and assess for response to initiated therapy.[135,136] ►**Fig. 7** illustrates a proposed algorithm for the management of NSIP.

Corticosteroids

Early cohort studies often described corticosteroid use in their population with a subgroup of more severe disease often requiring the addition of other immunomodulatory agents.[5–7,10,76] However, not all NSIP patients respond equally well to corticosteroid therapy and iatrogenic side effects are common.[137,138] One study reported a maximal increase in vital capacity (VC) percentage in patients with an NSIP pattern by up to 50% following treatment with corticosteroids. They also described that the percentage increase in VC was significantly higher in cellular NSIP compared with those with a more fibrotic form.[139] Another study reported that a majority of their patients with cellular or fibrotic NSIP were treated with either corticosteroid therapy alone or in combination with a cytotoxic agent and most of them maintained a stable pulmonary function following the initial treatment.[86] Recently, Lee et al retrospectively analyzed the use of corticosteroid therapy as initial treatment in a small cohort of NSIP patients at their center. Their data showed a response rate of 86% and a significantly higher initial dose was seen among patients who did not relapse within the mean follow-up period of 55 months.[140] However, a small proportion of their patients were unable to be weaned off therapy with some requiring the addition of other cytotoxic agents to maintain disease stability.

Table 2 Proposed classification criteria for interstitial pneumonia with autoimmune features

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) 2. Exclusion of alternative etiologies 3. Does not meet criteria of a defined connective tissue disease 4. At least one feature from at least two of these domains: A. Clinical domain B. Serologic domain C. Morphologic domain
A. Clinical domain
1. Distal digital fissuring (i.e., "mechanic hands") 2. Distal digital tip ulceration 3. Inflammatory arthritis or polyarticular morning joint stiffness $\geq$60 min 4. Palmar telangiectasia 5. Raynaud's phenomenon 6. Unexplained digital edema 7. Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)
B. Serologic domain
1. ANA $\geq$1:320 titer, diffuse, speckled, homogeneous patterns or a. ANA nucleolar pattern (any titer) or b. ANA centromere pattern (any titer) 2. Rheumatoid factor $\geq 2 \times$ upper limit of normal 3. Anti-CCP 4. Anti-dsDNA 5. Anti-Ro (SS-A) 6. Anti-La (SS-B) 7. Anti-ribonucleoprotein 8. Anti-Smith 9. Anti-topoisomerase (Scl-70) 10. Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS) 11. Anti-PM-Scl 12. Anti-MDA-5
C. Morphologic domain
1. Suggestive radiology patterns by HRCT (see text for descriptions): a. NSIP b. OP c. NSIP with OP overlap d. LIP
2. Histopathology patterns or features by surgical lung biopsy: a. NSIP b. OP c. NSIP with OP overlap d. LIP e. Interstitial lymphoid aggregates with germinal centers f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
3. Multicompartment involvement (in addition to interstitial pneumonia): a. Unexplained pleural effusion or thickening b. Unexplained pericardial effusion or thickening c. Unexplained intrinsic airways disease[a] (by PFT, imaging, or pathology) d. Unexplained pulmonary vasculopathy

Abbreviations: ANA, antinuclear antibody; Anti-CCP, anticyclic citrullinated peptide; dsDNA, double-stranded DNA; HRCT, high-resolution computed tomography; LIP, lymphoid interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PFT, pulmonary function test.
Source: Reproduced from Fischer et al.[131]
[a]Includes airflow obstruction, bronchiolitis or bronchiectasis.

Currently, the optimal dose and duration of corticosteroid therapy for NSIP are unknown and not standardized. Hence, it is important for clinicians to take an individualized approach by assessing the severity of disease and historical rate of disease progression. In rapidly progressive disease, initial high-dose corticosteroid therapy (0.75–1 mg/kg/d) is suggested. In fulminant disease, pulse intravenous (IV) methylprednisolone at 750 to 1,000 mg/d for 3 days may be required to achieve initial control of disease. Following this, a tapering oral corticosteroid regimen with close monitoring for response to therapy in 4 to 6 weeks is often used, often to a lower dose (5–10 mg/d) maintenance therapy.[134] Due to inconsistent data on corticosteroid monotherapy, other immunosuppressive agents are commonly

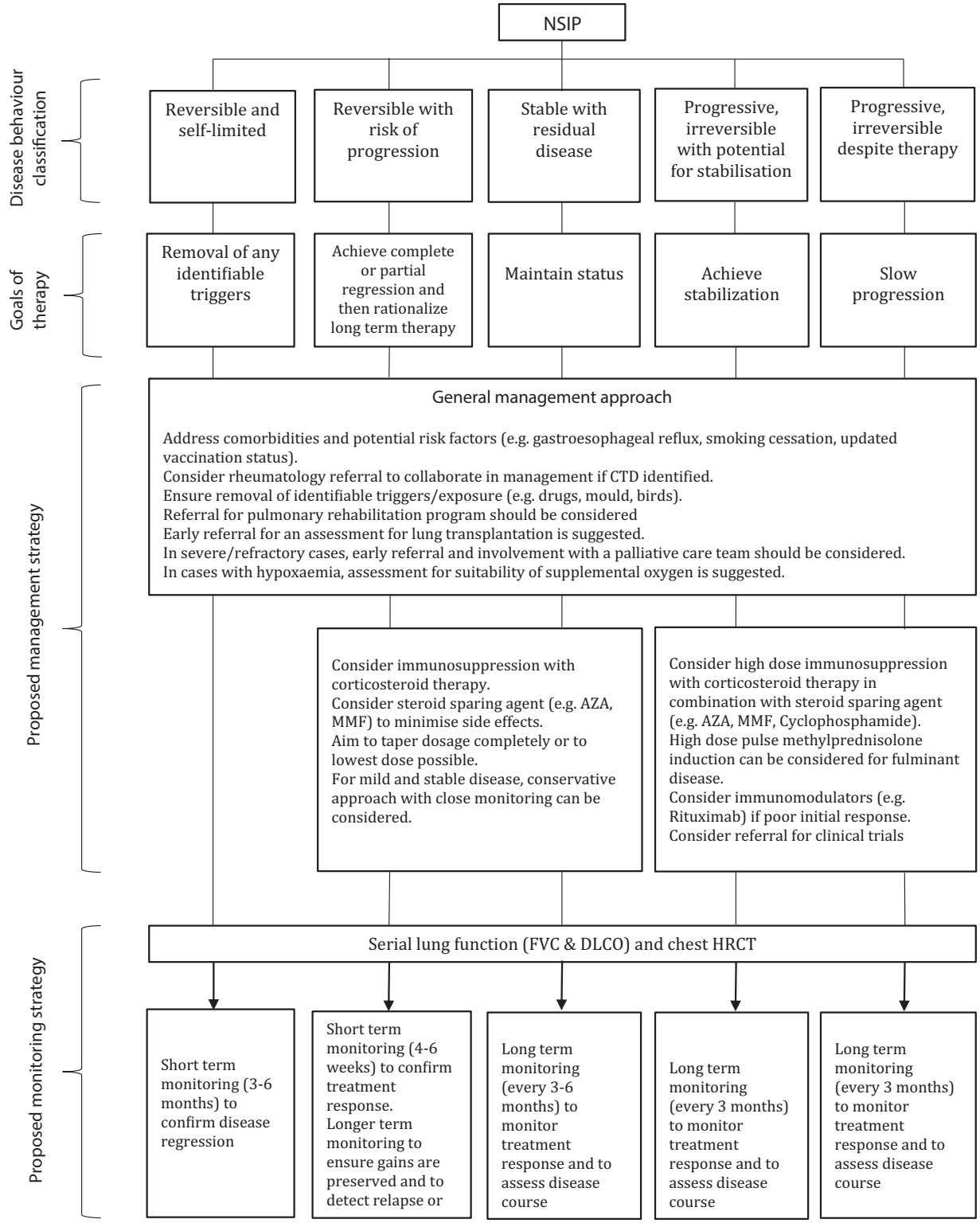

Fig. 7 Proposed management algorithm for NSIP. AZA, azathioprine; DLCO, diffusing capacity of lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; MMF, mycophenolate mofetil; NSIP, nonspecific interstitial pneumonia. Adapted from Travis et al.[41]

used. Commencement of these drugs has been shown to stabilize lung function when combined with steroids and also reduces the unwanted adverse effects of corticosteroid therapy.[141]

Cyclophosphamide

Multiple other immunosuppressive agents have been trialed and are often used in combination with corticosteroids for

refractory or relapsing NSIP. The rationale that these agents be used in NSIP cases is heavily influenced by clinical studies documenting the experience on CTD treatment. The Scleroderma Lung Study was a 1-year, multicenter, double-blinded, placebo-controlled trial evaluating the efficacy and safety profile of oral cyclophosphamide in scleroderma-related ILD.[142] Cyclophosphamide is an alkylating agent and immunosuppressant that causes lymphocyte cell death. Although the study demonstrated treatment efficacy in FVC, dyspnea, skin, and quality of life scores, high attrition rate and incidences of severe side effects were concerning. A subsequent study trialing monthly IV cyclophosphamide for 6 months followed by oral azathioprine showed similar trends that did not achieve statistical significance, likely due to the small number of patients recruited.[143] It is important to note, however, that active treatment was associated with stabilization of lung disease, rather than regression. This may be a pragmatic goal for those with more severe, fibrotic lung disease but falls short on being ideal for those with milder and potentially reversible disease. Nonetheless, cyclophosphamide was acknowledged by a European League Against Rheumatism statement as a potential treatment option of ILD associated with systemic sclerosis.[144] Extrapolation of these findings to other forms of NSIP is limited to small nonrandomized studies. Kondoh et al described 33% of patients with biopsy-proven fibrotic NSIP improving, while the rest remained stable, following an initial intermittent 3-day pulse methylprednisolone for 4 weeks, followed by cyclophosphamide and low-dose prednisone. Although this was seen as a more favorable response when compared with IPF patients, 21% of patients reported nontrivial side effects such as hemorrhagic cystitis, leukopenia, myelodysplastic syndrome, herpes zoster, and aspergilloma.[145] Corte et al retrospectively analyzed 54 (non-systemic sclerosis) patients with either biopsy-proven or suspected NSIP receiving IV cyclophosphamide. They found that despite having severe and progressive disease, patients treated with IV cyclophosphamide demonstrated disease stability in 46% of patients and improvement in 41% at 6 months, with significantly better outcomes reported in those with overlapping radiological features of NSIP and OP. In addition, only 30% of their cohort developed side effects, the most common of which were infections.[146]

Azathioprine

Azathioprine is purine analog that exerts its immunosuppressive effects by nonselectively inhibiting purine synthesis particularly in lymphocytes.[147] An early retrospective study showed a small improvement in dyspnea scores and FVC percentage predicted in systemic sclerosis-associated ILD.[148] A small open-label study showed that patients with systemic sclerosis-associated ILD who were randomized to 18 months of azathioprine had worsening FVC and DLCO compared with those randomized to receive cyclophosphamide.[149] However, evidence is still conflicting with another study showing that azathioprine was comparable to cyclophosphamide in stabilizing lung function.[150] While its efficacy and safety profile in CTD-ILD is comparable to newer agents such as mycophenolate, one study showed poorer tolerability due to nonrespiratory side effects.[151] Other retrospective studies support the use of azathioprine as maintenance therapy following induction therapy with cyclophosphamide.[152,153]

Mycophenolate Mofetil

Mycophenolate mofetil (MMF), an agent with cytostatic effect on lymphocytic function was studied in the Scleroderma Lung Study II, where systemic sclerosis patients were randomized either to oral MMF for 24 months or cyclophosphamide for 12 months followed by 12 months of placebo. Both arms demonstrated improvement in FVC at 24 months, but MMF was better tolerated with less side effects and fewer treatment withdrawals.[154] Fischer et al also previously reported an improvement in FVC and DLCO predicted percentages following treatment in a diverse group of CTD-ILD with low rate of side effects and discontinuation.[155] A recent small, retrospective cohort study also suggested that MMF may have a role in the management of patients fulfilling the IPAF criteria.[156]

Rituximab

Rituximab is chimeric anti-CD20 B cell depleting monoclonal antibody that has been increasingly used in CTD such as RA, SLE, dermatomyositis–polymyositis, and vasculitides.[157] It was not long before several studies evaluated the efficacy of rituximab in CTD-ILD, particularly those associated with systemic sclerosis and dermatomyositis–polymyositis.[158–161] Although study results were mostly positive with either stabilization or improvement in lung physiology parameters, they were retrospective or open-label cohort studies with small subject numbers. Several other small studies assessed the use of rituximab in a more diverse population of CTD-ILD. Fitzgerald et al retrospectively studied 10 patients from their center who were received rituximab therapy. They reported an improvement in FVC and DLCO predicted percentage as well as CT severity scores in 8 out of the 10 patients who had a CTD-ILD.[162] Another study also showed stabilization of FVC and DLCO predicted percentage in a mixed group of 24 patients with CTD-ILD. Nine out of the 11 patients with biopsy samples available showed an NSIP pattern.[163] However, Chartrand et al did not report any meaningful improvement in FVC predicted percentage in their retrospective study on CTD-ILD patients.[164] Keir et al retrospectively assessed 50 patients with severe, progressive ILD with varying etiologies (CTD = 33, HP = 6, and other ILD = 11), who were unresponsive to conventional immunosuppressive therapies and reported a median improvement in FVC predicted percentage and stabilization of DLCO predicted percentage.[165] Currently, rituximab is generally reserved as a rescue therapy for patients with severe and progressive ILD despite conventional therapy. More prospective randomized controlled studies are needed to guide patient selection and develop appropriate protocols for the use of such agents in not only CTD-ILD but also to evaluate its effect on other causes of NSIP.

Antifibrotic Agents

Pirfenidone and nintedanib are two antifibrotic agents recommended in the treatment of IPF, having shown to slow disease progression over 12 months of therapy.[166,167] There is a growing interest in studying these agents as potential treatment options for NSIP, once again predominantly driven in the CTD-ILD population. Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is a pyridine compound that has anti-inflammatory, antioxidant, and antifibrotic properties. A small open-label study showed an acceptable tolerability profile when pirfenidone was used concomitantly with mycophenolate therapy.[168] Another study studied the use of pirfenidone in rapidly progressive ILD related to clinically amyopathic dermatomyositis.[169] When compared with retrospectively selected matched controls, there was an overall trend toward lower mortality, but no difference was seen in those with a subacute disease duration of less than 3 months. Larger prospective and randomized trials are underway to validate these early findings. The TRAIL1 study (NCT02808871) is a current phase II study assessing the safety, tolerability an efficacy of Pirfenidone in patients with RA-ILD. Although not specific for NSIP, a recent phase II trial studied the efficacy and safety of Pirfenidone in fibrotic unclassifiable disease, some of which may include cases of NSIP. This study reported a significantly lower mean decline in FVC at 24 weeks from baseline with Pirfenidone treatment compared with placebo (−17.8 vs. −113 mL). Fewer patients in the Pirfenidone group had an absolute decline in FVC% predicted of more than 5 and 10%.[170]

Nintedanib (previously known as substrate BIBF 1120) is a 6-methoxycarbonyl-substituted indoline derivative acting as a multiple-receptor tyrosine kinase inhibitor. Results from a recent randomized, placebo-controlled phase III trial investigating the efficacy and safety of nintedanib in systemic sclerosis-associated ILD (SENSCIS) was recently published.[171] It demonstrated a smaller decline in FVC over 52 weeks in the nintedanib group compared with placebo (−52.4 and −93.3 mL, respectively) irrespective of concomitant use of MMF. Although the population of interest was specific to systemic sclerosis-associated ILD, supplementary data reported that GGO was found in more than 80% of participants, suggesting a radiological pattern of NSIP in some cases. Another multicenter randomized, placebo-controlled phase III trial of nintedanib in patients with progressive, fibrotic ILD (INBUILD, NCT 02999178) has recently been completed.[172] The study recruited ILD cases of various etiologies including CTD-ILD, CHP, and idiopathic NSIP. It showed a significant overall reduction in the annual rate of absolute FVC decline in patients receiving nintedanib compared with those who received placebo (−80.8 vs. −187.8 mL/y). Subgroup analysis of patients with UIP-like pattern of fibrosis on HRCT also showed a significant reduction in FVC decline (−82.9 mL/y with nintedanib vs. −211.1 mL/y with placebo). However, patients with other fibrotic patterns (non-UIP patterns) had a nonstatistically significant reduction in FVC decline when treated with nintedanib (−79 mL/y with nintedanib vs. −154 mL/y with placebo).[173] Taken together, these results highlight the potential role that antifibrotic agents have in progressive fibrotic diseases. However, these results cannot be applied to the entire spectrum of NSIP and more studies are required to explore their specific role in the different subsets of NSIP.

Nonpharmacological Approaches

A holistic approach with the inclusion of nonpharmacological approaches should be undertaken in the management of these patients. Although pulmonary rehabilitation remains a weak positive recommendation for ILD in the current guidelines, a recent Cochrane review reported on the safety of pulmonary rehabilitation for ILD patients in addition to reducing dyspnea, increasing walk distance, and improving quality of life. Supplemental oxygen has long been proposed to be beneficial in improving maximal exercise performance and reducing the risk of hypoxia-induced pulmonary hypertension in ILD patients.[174,175] However, the provision of supplementary oxygen is often wrought with problems ranging from equipment malfunction, the lack of manageable portable systems to the lack of patients' confidence in using machines provided.[176] Hence, it is important that the prescription of supplementary oxygen needs to be accompanied with clear communication among patients, clinicians, and caregivers, addressing the patients' expectations, any potential psychological stigma, or practical issues of using oxygen supplementation.[177] In appropriate cases, concurrent involvement of a palliative care team should be considered to provide a symptom-centered approach aiming to improve or maintain quality of life.[178] Lung transplantation remains as the only effective therapy in patients with progressive disease but is unfortunately, universally limited by the number of available donor organs. Hence, early discussion and referral to a lung transplant center for an assessment coupled with close monitoring for serial progression in lung function and radiology are paramount.[179]

Conclusion

NSIP is a complex disorder, likely encompassing several phenotypes. Although idiopathic NSIP has been recognized as a separate clinical entity, recent studies have suggested that a proportion of cases also meet the criteria for IPAF suggesting the presence of an underlying CTD. Ongoing research is still very much needed to determine its prognostic significance and appropriate treatment. The management of NSIP remains uncertain and not standardized. It is paramount for goals of therapy to be established early and in stable cases, vigilant monitoring. Immunosuppressive therapy can be used in more severe and progressive disease, but larger trials are needed and the role of newer agents such as antifibrotics needs further exploration.

Conflict of Interest
None declared.

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CONTEMPORARY CONCISE REVIEW

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Contemporary Concise Review 2020: Interstitial lung disease

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Abstract

The year 2020 was one like no other, as we witnessed the far-reaching impact of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) global pandemic. Yet despite an unprecedented and challenging year, global research in interstitial lung disease (ILD) continued to break new grounds. Research progress has led to an improved understanding in new diagnostic tools and potential biomarkers for ILD. Studies on the role of antifibrotic therapies, newer therapeutic agents, supportive care strategies and the impact of coronavirus disease 2019 (COVID-19) continue to reshape the management landscape of ILD. In this concise review, we aim to summarize the key studies published in 2020, highlighting their impact on the various aspects of ILD.

KEYWORDS

idiopathic pulmonary fibrosis, interstitial lung disease, progressive fibrotic interstitial lung disease

INTRODUCTION

The year 2020 was truly unprecedented, as we saw the severity of the global impact of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Despite the significant changes to daily life, researchers across the globe have continued to make great strides into the understanding of interstitial lung disease (ILD) at an unrelenting pace. Australian ILD patients and their carers have identified their top 10 research priorities in a formal priority setting study.[1] Pleasingly, a number of these priorities have been targeted during 2020. New strides have been made to improve not only the diagnostic process, but also the management strategies and therapeutic options for ILDs. Along with these, ILD patients' quality of life remain a research focus in 2020. In this concise review of ILD, we aim to summarize the key and important studies in 2020.

DIAGNOSIS OF ILD

Key Points

- The international clinical practice guideline for hypersensitivity pneumonitis (HP) presents an updated algorithm and recommendations for diagnostic tools while also highlighting the need for further research.
- Transbronchial lung cryobiopsy (TBLC) has a high histopathological and diagnostic agreement compared to surgical lung biopsy (SLB). TBLC also increases the diagnostic confidence of ILD when incorporated into the ILD multidisciplinary discussion (MDD).
- Higher high-attenuation areas (HAAs) *z*-scores are associated with the development of interstitial lung abnormalities (ILA), poorer lung function and exertional dyspnoea.

The year 2020 has led to some crucial changes to the understanding and approaches to ILD diagnosis. HP, an immune-mediated ILD in susceptible individuals exposed to environmental agents, remains a diagnostic challenge due to the lack of consensus diagnostic criteria.[2–4] An official American Thoracic Society/Japan Respiratory Society/Latin American Thoracic Association (ATS/JRS/ALAT) clinical practice guideline for the diagnosis of HP was published to guide clinicians in early and accurate recognition of HP, allowing timely interventions.[5] Classification of HP as fibrotic or non-fibrotic was proposed as a more objective and consistent parameter that may reflect disease presentation.

Within this guideline, radiographic and pathological criteria were defined. Although a diagnostic algorithm with various tools were recommended, these were proposed with low confidence given the paucity of data in the literature. A subsequent ATS workshop report proposed the need for validated antigen exposure questionnaires to be locally adapted. While several antigen identification tools exist, their interpretation and role in the diagnosis of HP remain unstandardized. While highlighting the need for further research into these tools, the workshop report proposed a framework whereby results from antigen identification tools are considered along a spectrum of probability for each individual case.[6]

Several studies have investigated the potential role of quantitative computed tomography (CT) in ILD diagnosis. One study evaluated HAAs, a measure of subclinical ILD, in 696 healthy subjects[7] from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort.[8] The authors reported that higher HAA *z*-scores were associated with the development of ILAs, lower forced vital capacity (FVC) and exertional dyspnoea. ILA are now more commonly identified, primarily due to lung cancer screening programmes, and are associated with functional impairment, risk of progression and increased all-cause mortality.[9–11] This year, the Fleischner Society published a multidisciplinary position paper addressing ILA on CT,[12] standardizing terminology of ILA, along with potential risk factors and clinical outcomes, with a focus on subpleural predominant fibrotic ILAs which are most likely to progress.

Another study analysed a primary care clinical cohort ($n = 2223$) for trends in respiratory symptoms and lower respiratory healthcare resource utilization (HRU) in the 10 years prior to diagnosis of pulmonary fibrosis (PF).[13] HRU progressively increased with 79% of patients having lower respiratory complaints the year preceding their diagnosis (38% with ≥5 healthcare contacts). The study highlights the potential opportunity for clinicians to diagnose PF earlier, with further research into case-finding algorithms and education strategies for primary care physicians being required.

The landmark COLDICE study, a prospective multicentred study, aimed to establish the diagnostic accuracy of TBLC compared to SLB.[14] This study reported a high histopathological agreement at 70.8% (weighted κ 0.70, 95% CI 0.55–0.86) and diagnostic agreement at MDD of 76.9% (κ 0.62, 95% CI 0.47–0.78). While not designed to assess safety, no new safety signals were identified in this study. These findings support the clinical utility of incorporating TBLC in the diagnostic algorithm of ILD. In a post hoc analysis, the authors went on to show that histological findings of 'patchy fibrosis, fibroblastic foci and absence of features to suggest an alternative diagnosis' allowed for a confident interpretation of usual interstitial pneumonia (UIP) from TBLC, without the need for 'subpleural or paraseptal fibrosis'. Diagnostic accuracy of TBLC increased when more samples were taken (with an optimum of five samples).[15] The authors suggested incorporation of modified TBLC criteria to the idiopathic PF (IPF) diagnostic guidelines[16] to be considered. In another prospective study, TBLC significantly increased the diagnostic confidence of specific ILD when incorporated as a diagnostic tool in an ILD MDD setting.[17]

While these studies provide compelling data to support the utility of TBLC integration into ILD diagnostic algorithms, the utility of lung biopsies in the diagnosis of IPF is less clear. A retrospective multicentre analysis between 2011 and 2017 showed that more than half of the patients with a possible UIP pattern on HRCT were labelled and treated as IPF with antifibrotic agents, suggesting a general tendency of clinicians avoiding invasive procedures.[18] More importantly, the study showed that patients with a possible UIP pattern on HRCT without histopathological confirmation had similar mortality and disease progression compared to those with a definite diagnosis of IPF.

THE PROGRESSIVE FIBROTIC PHENOTYPE

Key Points

- In a study of patients with unclassifiable, progressive fibrotic ILD (PF-ILD), pirfenidone was shown to lower mean change in FVC percentage (FVC %) predicted compared to placebo. The study results further support the utility of antifibrotic agents in PF-ILD following the INBUILD trial the year prior.
- With the ongoing recognition of the PF-ILD phenotype, more research continues to study prediction models and factors that can reliably identify patients with progressive disease.

Over 2020, much has changed with regard to the approach of ILD, particularly with the global recognition of a PF-ILD phenotype. This has largely followed the publication of the landmark INBUILD trial where progression was defined using relative decline in FVC percent predicted, worsening symptoms or increased fibrosis on HRCT.[19,20] This study demonstrated that nintedanib, an antifibrotic agent first studied in IPF, effectively slowed the rate of lung function decline in a range of PF-ILD, independent of the radiological fibrotic pattern. A subsequent analysis studied that the effects of nintedanib were present across five prespecified subgroups (HP, autoimmune ILDs, idiopathic non-specific interstitial pneumonia, unclassifiable idiopathic interstitial pneumonia and other ILDs).[21] These findings suggest that patients with PF-ILD who have progressed despite appropriate clinical management may benefit from nintedanib treatment.

This application of antifibrotics to the broader ILD cohort was also supported in a multicentre, double-blind, randomized, placebo-controlled phase 2 trial assessing the efficacy and safety of pirfenidone in patients with unclassifiable PF-ILD.[22] Although the primary endpoint of mean predicted change in FVC using home spirometry could not be assessed due to intra-individual variability, the

study showed a lower mean change in FVC% predicted measured by site spirometry in patients receiving pirfenidone with a treatment difference similar to that seen in IPF patients of 95.3 mL (95% CI 35.9–154.6, $p = 0.002$). Patients treated with pirfenidone were less likely to have a FVC decline of either ≥5% (OR 0.42, 95% CI 0.25–0.69, $p = 0.001$) or ≥10% (OR 0.44, 95% CI 0.23–0.84, $p = 0.011$).

The search for a reliable method to identify those patients who will have progressive disease remains an important research focus. In one retrospective study of 153 patients with rheumatoid arthritis-associated ILD, old age (≥60 years), high fibrosis score (≥20% total lung extent), UIP pattern and emphysema on HRCT were identified as poor prognostic factors on multivariate Cox analysis.[23] The proposed prediction model showed a good performance in predicting the 5-year mortality, with similar findings seen in a separate validation cohort. In another study of 445 patients with IPF,[24] the presence of pleuroparenchymal fibroelastosis (PPFE) (6.3%) was associated with more frequent pneumothoraces and pneumomediastinum, more progressive decline in lung function decline and poorer prognosis. It is clear, however, that further studies are needed to identify potential biomarkers to assess for disease progression.

BIOMARKERS

Key Point

- Several candidate biomarkers have been identified with potential to improve the diagnosis and prognostication of ILD patients.

The search for effective biomarkers to refine the diagnosis, prognostication and monitoring of ILD has continued to make progress in 2020. Endoplasmic reticulum (ER) stress plays a role in the pathogenesis of IPF, in which the adaptive response by activating the unfolded protein response fails in IPF.[25,26] One study explored the role of mesenchymal stem cells (MSCs) in the modulation of (ER) stress.[27] In a bleomycin murine model, administration of MSC at the peak of ER stress resulted in a significant decrease on BiP expression and attenuated ER stress via the protein kinase RNA-like ER kinase (PERK)-Nrf2 pathway. Although protein expression from other PERK pathways were not affected by MSC, the study findings suggest the PERK-Nrf2 pathway as a main functioning pathway for fibrosis in a bleomycin model and MSC as a potential therapeutic option, albeit the need for further studies.[27]

Adult stem cells undergo dynamic changes in response to tissue damage, with type-2 alveolar epithelial cells (AEC) as the primary cell in the alveolar epithelium involved in homeostasis and regeneration after injury.[28–30] One study proposed a novel pre-alveolar type-1 transitional cell state (PATS) with a specific gene expression signature that traverses between AEC2 and AEC1.[31] Using alveolar organoid and in vivo injury–repair models, PATS-like cells were identified in fibrotic regions of IPF lungs that are enriched for genes associated with cellular senescence and fibrosis. While critical for stabilization, they are vulnerable to DNA damage from the extensive stretching during AEC2 differentiation. These new findings on PATS redefine senescence as a state that can occur as a normal phenomenon of tissue maintenance and the accumulation of PATS-like cells in human fibrotic lungs suggests this transitional state is not immune to homeostatic derailment and its persistence can lead to fibrosis.

Serum S100 calcium-binding protein A4 (S100A4), a fibroblast marker,[32,33] was studied as a potential biomarker that may help predict disease progression in IPF.[34] In this study of 95 IPF patients and 50 healthy controls, serum S100A4 levels were detectable in 26 (27.3%) IPF patients ($p < 0.01$) with S100A4-expressing cells seen around fibroblastic foci on immunostaining. Patients with higher serum S100A4 levels were found to have a significantly worse prognosis with a 2-year cumulative survival rate of 41.7% versus 77% ($p < 0.01$). Baseline serum S100A4 levels were independently associated with higher disease progression rate and mortality on multivariate analysis. Another study studied serum levels of Krebs von den Lungen-6 (KL-6) and cytokeratin 19 fragment (CYFRA21-1) as potential prognostic biomarkers in systemic sclerosis-associated ILD (SSc-ILD).[35] Using both retrospective ($n = 189$) and prospective ($n = 118$) cohorts, measured serum levels of both biomarkers were highest in patients with lung involvement and in those with extensive ILD. However, KL-6 was significantly associated with diffusing capacity of the lung for carbon monoxide (DLCO) decline in both cohorts and with FVC decline in the retrospective cohort. On multivariate analysis correcting for age, gender, ethnicity, smoking history and mucin-like glycoprotein (MUC1) allele carriage, KL-6 also remained predictive of decline in DLCO irrespective of disease severity, suggesting its potential risk stratification role for progressive SSc-ILD.

MANAGEMENT OF ILD

Key Points

- Observational and long-term data continue to show the efficacy of antifibrotic agents in slowing the annual rate of FVC decline in IPF patients.
- Corticosteroid therapy was shown to be associated with poorer survival when used in acute exacerbations of IPF (AE-IPF), highlighting the ongoing need for more research in this area.
- The management landscape of various ILDs continue to improve, as demonstrated by a multitude of clinical trials of novel pharmacological agents.

Despite the SARS-CoV-2 pandemic, and its universal disruption of many clinical trials across the globe, the management landscape of ILD has continued to evolve with long-term and real-world data on the effect of antifibrotic therapies for the treatment of IPF and other fibrotic ILDs. A subgroup analysis of the efficacy and safety of nintedanib in Asian patients from the INPULSIS-ON study[36] showed that the efficacy of nintedanib is maintained over the long term with consistent annual rate of decline in FVC compared to the overall trial population. Safety and tolerability profile were also consistent with the overall trial population.[37] Observational data from the INSIGHTS-IPF registry also showed a significant better survival in patients receiving antifibrotic therapy with a 1- and 2-year survival rate of 87% and 62%, respectively, versus 46% and 21% in patients who were not treated. The risk of death was 37% lower in patients receiving antifibrotic therapy (hazard ratio [HR] 0.63, 95% CI 0.45–0.87, $p = 0.005$), despite similar rates of lung function decline.[38] A subgroup analysis of elderly patients (≥75 years) from the same cohort showed similar improved survival benefit and FVC decline reduction, despite higher number of comorbidities.[39] A comprehensive systematic review of cohort and randomized controlled studies in IPF showed an overall survival rate of only 31% at 5 years and a mean survival, derived from a meta-analysis of two studies with 10-year follow-up duration, of only 4 years.[40]

AE-IPF carry significant morbidity and mortality risk in IPF patients.[41,42] When the 2016 criteria for AE-IPF[43] were applied to a retrospective cohort of patients with fibrotic ILD, AE was reported in 69 patients.[44] The time to first AE was significantly longer in fibrotic ILD than IPF. In a multivariate Cox proportional analysis, baseline disease severity was closely associated with the incidence of AE and even after adjustment for other clinical variables, AE had a negative impact on overall survival with similar poor short-term outcomes to AE-IPF. Another study investigated the predictive value of circulatory high-mobility group box 1 (HMGB1) for disease progression and prognosis of IPF in stable and AE phases.[45] Serum HMGB1 levels were significantly higher in IPF patients, with higher levels seen in patients with AE-IPF. High HMGB1 levels were significantly associated with earlier onset of AE in stable IPF patients and with shorter survival in AE-IPF, suggesting its potential as a useful prognostic biomarker. The evidence for treatment of AE-IPF remains limited. A retrospective study assessed 82 AE-IPF patients of whom 37 (45%) received corticosteroid therapy.[46] There was no statistically significant association between corticosteroid treatment and in-hospital mortality. Overall survival was reduced in AE-IPF subjects receiving corticosteroids (HR 6.17, 95% CI 1.35–28.14, $p = 0.019$), highlighting the need for further therapeutic studies in AE-IPF.

Through 2020, several new potential therapeutic agents for ILD at various stages of testing have been reported. Based on previous studies on αvβ6 monocloncal antibodies,[47] a preclinical study of an inhaled αvβ6 arginylglycinyl-aspartic acid-mimetic showed rapid internalization and high affinity binding to αvβ6 in human IPF lung epithelial cells, reducing downstream pro-fibrotic transforming growth factor (TGF) to normal levels.[48] In murine models, the molecule inhibited TGF signalling, reduced collagen deposition and slowed IPF disease progression. These early findings suggest nebulized formulation of this molecule to be a potential future antifibrotic agent in IPF. While early studies on tocilizumab, an anti-IL-6 receptor antibody, focused on skin fibrosis improvement in SSc,[49,50] a prespecified exploratory analysis in a phase 2 trial showed promise by reducing lung function decline in patients receiving tocilizumab.[51] A subsequent multicentre, randomized, placebo-controlled phase 3 trial assessed the safety and efficacy of subcutaneous tocilizumab 162 mg weekly in the treatment of SSc.[52] Although the study did not meet its primary endpoint of skin score change, secondary analysis of FVC and exploratory analysis of radiographically determined lung fibrosis suggests that tocilizumab treatment might preserve lung function in those with early SSc-ILD and elevated acute phase reactants (least squares mean difference in change from baseline in FVC% predicted of 4.2, 95% CI 2–6.4, $p = 0.0002$).

Exercise-induced hypoxaemia can occur in IPF patients without resting hypoxaemia and is associated with poorer prognosis[53] but previous studies on the benefit of supplemental oxygen during exercise have yielded conflicting results.[54,55] A randomized, crossover trial evaluated the efficacy of supplemental oxygen versus air during exercise in IPF patients without resting hypoxaemia. Supplemental oxygen was found to significantly increase endurance, maintain transcutaneous oxygen saturation and improve symptoms in patients with mild–moderate IPF.[56] Taken together, coupled with concerns of high costs offsetting any potential benefit, high quality evidence with further larger trials is needed.[57–59]

WHAT MATTERS TO PATIENTS

Key Points

- Supportive care needs for patients with PF remain unmet despite the introduction of antifibrotic therapy.
- Peer support and home monitoring programmes have been shown to have a huge potential in improving the care of patients living with ILD.

Irrespective of the ILD phenotype, disease progression is commonly associated with high symptom burden, reduced quality of life and higher HRU, and negatively impacts mental health.[60–63] A systematic review and meta-analysis of 134 studies aimed to assess health-related quality of life (HRQoL) of people living with IPF and patient-reported outcome measures used in IPF studies.[64] Analysis of

standardized means for both St George's Respiratory Questionnaire and Short Form 36 demonstrated worse score in physical health domains compared to mental health domains. However, other aspects of life including physical, social and emotional health were also impacted. Supportive care needs, originally described in the field of oncology covering informational, emotional spiritual, social or physical needs experienced at any stage of the healthcare journey, have been studied in PF.[65–67] A systematic review aimed to identify the supportive needs reported by people with PF and their caregivers.[68] The most frequently reported needs were in the domain of education, psychosocial needs and access to peer support for families and carers. The study highlights that the supportive care needs for patients with PF remain unchanged in the antifibrotic era with many yet to be met.

While peer support programmes have been studied in cancer patients, evidence of their role in ILD is limited.[69,70] The Lung Foundation Australia (LFA) developed the Peer Connect Service that matches eligible PF patients to others going through a similar experience in order to provide mutual support.[67] Using semi-structured interviews with participants of the service to document their experiences and the resources required to support the service,[71] major themes were identified such as the value of shared experiences and the importance of shared personal characteristics in allowing information and emotional support needs to be met. Meanwhile, home monitoring programmes providing physicians with real-time clinical spirometric data have been shown to be feasible and viewed favourably by patients.[72–74] A multicentre, randomized controlled trial investigated whether a home monitoring programme could improve HRQoL and medication adherence in newly diagnosed IPF patients.[75] Although the study showed no statistically significant difference in the King's Brief Interstitial Lung Disease health status questionnaire scores between the home monitoring group versus standard care, psychological and general well-being were higher. Home monitoring was also greatly appreciated by patients and allowed for individualized treatment adjustment, perhaps suggesting a future avenue in personalized treatment for IPF.

ILD AND COVID-19

Key Points

- ILD patients infected with SARS-CoV-2 have a poorer survival compared to those without ILD.
- IPF patients share some clinical features with patients with severe SARS-CoV-2, raising the possibility of the role of antifibrotic therapy in the management of this disease.

The devastating impact of coronavirus disease 2019 (COVID-19) is prevalent in all aspects of life across the globe. A multicentre international audit compared patients with prior ILD diagnoses admitted to the hospital with COVID-19 to those without ILD.[76] In 349 ILD patients, 161 of whom were hospitalized with COVID-19 matched with propensity scoring, the overall mortality was 49%. ILD patients with COVID-19 had poorer survival (HR 1.6, CI 1.17–2.18, $p = 0.003$) compared to age-, sex- and comorbidity-matched patients without ILD. ILD patients with poorer lung function (FVC < 80%) and obesity had an increased risk of death (HR 1.72, 95% CI 1.05–2.83 and HR 2.27, 95% CI 1.39–3.71, respectively). Initial reports of patients with severe COVID-19 infections were seen in elderly males with a smoking history and multiple comorbidities, strikingly similar to those with IPF.[77] With early data and the scale of the pandemic suggesting a future tsunami of post-COVID-19 fibrosis, the current and novel antifibrotic therapies may have a potential role in mitigating the severity of COVID-19 sequalae.[78–80] For now, as the long-term impacts of the pandemic on ILD patients remain unknown, it is critical that collaborative research continues, especially during these unprecedented times.

CONCLUSION

Despite such a difficult year in the setting of the SARS-CoV-2 pandemic, global research in ILD has continued without missing a beat. This year, in particular, has been a testament to the resilience of ILD researchers. As we bravely venture into the new year, so must the research work in ILD continue to move forward for the sake of those living with ILD.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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Reply to Mehmood

From the Author:

I thank Dr. Mehmood for his comments. I agree that the pathological importance of vascular leakage extends far beyond sepsis and acute lung injury (acute respiratory distress syndrome) to include diverse syndromes such as heart failure (1, 2), renal failure (3), and connective tissue diseases (4). In my opinion, this reflects the fact that increased endothelial permeability is usually maladaptive, given the detrimental effects of tissue edema. Furthermore, severe vascular leakage may be difficult for the body to remediate, given the limited ability of the mature endothelium to proliferate (5).

As we enter the era of clinical trials for agents that stabilize the vascular barrier (6), it is important to remember that multiple cellular and molecular mechanisms exist for vascular leakage. These include endothelial apoptosis (7), pyroptosis (8), and remodelling of endothelial cell–cell junctions and the cellular cytoskeleton (9). The success of drugs aimed at reducing vascular leakage in clinical trials may therefore depend on the cause of the leakage and the mechanism of action of the drug. Nonetheless, given its ubiquity in clinical medicine, the prospect of either harnessing (10) or counteracting vascular leakage without impairing the immune response (11) is an intriguing prospect for clinicians. ■

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Importance of Occupational Exposure Data: A National Idiopathic Pulmonary Fibrosis Registry Perspective

To the Editor:

We read with interest the insightful opinion provided by Nett and colleagues regarding the importance of gathering

occupational and environmental exposure data within registries of patients with idiopathic pulmonary fibrosis (IPF) (1). We agree with the authors that the collection of relevant exposure history data is crucial for understanding the pathophysiology of IPF and enriches patient registry data, as summarized by Culver and colleagues (2). Furthermore, capturing detailed exposure data aligns with a recent American Thoracic Society and European Respiratory Society statement, which noted that up to 26% of IPF cases are potentially attributable to occupational and environmental exposures, including vapors, silica, and agricultural and metal dusts (3). In recognition of this, participants in the Australian IPF Registry (AIPFR) complete a comprehensive occupation and exposure questionnaire at baseline, giving investigators the opportunity to explore the potential contribution of these factors to the development of IPF.

The AIPFR was established in 2011 as a platform for national and international collaborative research, and to provide multifaceted insights into IPF in Australia (4). Participants are followed prospectively and data are collected at baseline and every 6 months. Similar to other registries, clinical data, including smoking history, family history, medication history, and relevant associated comorbidities (e.g., gastroesophageal reflux disease), are collated within the registry. In addition, as suggested by Nett and colleagues, the AIPFR collects detailed demographic, environmental, and occupational exposure data in the form of a questionnaire completed upon enrollment in the registry. Such data have provided researchers with a number of opportunities, such as an ongoing study that is exploring ambient air quality in various geographical locations across Australia with regard to its impact on patients with IPF. In addition, the AIPFR has collaborations with relevant government bodies studying the health economic impact of IPF with and without antifibrotic treatment, within which the impact of environmental exposures will also be considered. Finally, the AIPFR is linked to a national blood biobank, allowing interactions among genetic, demographic, and environmental influences to be explored.

We agree with Nett and colleagues' suggestion that a collaborative effort across registries in capturing and pooling occupational and environmental exposure data together is critical. The AIPFR's comprehensive approach provides a ready platform for international collaborations to occur. Although registries are useful for providing "real-world" data regarding a heterogeneous population, their limitations need to be acknowledged. Incomplete data entry is a recurring issue and tight quality control is required to minimize errors. However, other challenges, such as patient recall bias in establishing the time latency between multiple occupational or environmental exposures, development of symptoms, and time of diagnosis, are more difficult to address (5). Although validated job exposure matrices are available (6), their uptake remains variable from one country to another, and further efforts to standardize their usage are very much needed. We encourage continued discussions and collaboration among relevant parties in developing a standardized method and format that can be used globally to collect exposure data, which may contribute to future novel research in IPF. ■

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