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FinnishIPF

A national real-world study on disease characteristics, pharmacotherapy, and prognosis in idiopathic pulmonary fibrosis

Jaana Kaunisto

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Knowledge has a beginning but no end.

Geeta Iyengar

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a rare disease characterized by the progressive scarring of lung tissue. Common symptoms are dyspnea and a prolonged cough. The majority of IPF patients die in respiratory failure. The cause of the disease is still unclear; consequently, there is no cure for IPF. Two antifibrotic medications are currently available: pirfenidone and nintedanib, both of which may slow down disease progression. As better treatment options have become available, an accurate diagnosis of IPF has become more important than ever.

The FinnishIPF project was initiated to gain real-world data on the prevalence, diagnosis, treatment, and prognosis of IPF patients in Finland.

In this thesis, we aimed to identify reliable methodologies used in studies related to the epidemiology of IPF. The FinnishIPF project began by describing the clinical characteristics and the diagnostic accuracy of IPF in the university hospital cohort. The prognosis and clinical predictors of survival were then analyzed and the use of antifibrotic medications and comedications was evaluated.

Only a limited number of epidemiological studies on IPF have been published. Various epidemiological methodologies have been used but none are without limitations. The exact prevalence of IPF is not known. The ICD-10 coding system is an inaccurate tool for IPF. The use of hospital registries in epidemiological studies may give an unreliable prevalence of this rare disease if the diagnoses are not validated.

According to the FinnishIPF study, lung function is usually quite well preserved at diagnosis. After the multidisciplinary re-evaluation of prior diagnoses, nearly 10% of the cases did not fulfill the current criteria of IPF. Antifibrotic treatment is initiated for every second IPF patient. Younger age at diagnosis predicts initiation of the treatment. Lower lung function at diagnosis predicts earlier ($\leq$ 1 year) initiation. Polypharmacy is common, as nearly 60% of IPF patients have $\geq$ 5 simultaneous medications at diagnosis. The median overall survival of IPF is 4.5 years. High age and low pulmonary function at diagnosis are predictors of mortality.

KEYWORDS: antifibrotic treatment, idiopathic pulmonary fibrosis, incidence, mortality, nintedanib, pirfenidone, prevalence, prognosis, real-world study

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TIIVISTELMÄ

Idiopaattinen keuhkofibroosi (idiopathic pulmonary fibrosis, IPF) on harvinainen ja etenevä keuhkokudosta arpeuttava sairaus. Taudin oireita ovat hengenahdistus ja pitkittynyt yskä. Suuri osa IPF-potilaista kuolee hengitysvajaukseen. Taudin perimmäinen syy on edelleen epäselvä, eikä näin ollen ole pystytty kehittämään parantavaa lääkehoitoa. Hoito on kuitenkin kehittynyt antifibroottisten lääkkeiden tultua markkinoille. Antifibroottiset lääkkeet: pirfenidoni ja nintedanibi voivat hidastaa taudin etenemistä. Parempien hoitomahdollisuuksien myötä, IPF:n täsmällinen diagnostiikka on tullut entistä tärkeämmäksi.

FinnishIPF-projektin tarkoituksena on ollut kerätä tietoa IPF:n esiintyvyydestä, diagnostiikasta, hoidosta ja ennusteesta Suomessa.

Väitöskirjatutkimuksen ensimmäisenä tavoitteena oli etsiä luotettava epidemiologinen menetelmä taudin esiintyvyyden arvioimiseksi analysoimalla kirjallisuutta. FinnishIPF-tutkimus aloitettiin kuvaamalla yliopistosairaaloissa hoidettujen IPF-potilaiden kliinisiä piirteitä. Diagnostiikan osuvuutta arvioitiin moniammatillisesti. IPF-potilaiden ennustetta ja ennusteeseen vaikuttavia tekijöitä analysoitiin. Lisäksi selvitettiin antifibroottisten hoitojen toteutumista.

IPF:stä on julkaistu niukasti epidemiologisia tutkimuksia. Tutkimuksissa on käytetty vaihtelevia menetelmiä, joissa kaikissa on puutteita. IPF:n tarkkaa esiintyvyyttä ei tiedetä. ICD-10-tautiluokitus ei ole riittävän täsmällinen epidemiologinen työkalu IPF:n osalta. Sairaalarekisterit tuottavat epäluotettavia epidemiologisia lukuja, jos IPF-diagnooseja ei varmisteta.

FinnishIPF-tutkimuksen mukaan IPF-potilaiden keuhkotilavuudet ovat hyvätasoisia diagnoosivaiheessa. Yliopistosairaalakohortissa 10 % vanhoista IPF-diagnooseista ei täyttänyt taudin nykykriteerejä moniammatillisen arvioinnin perusteella. Antifibroottinen lääke on aloitettu noin joka toiselle IPF-potilaalle. Nuorempi ikä ennustaa lääkkeen aloitusta. Diagnoosivaiheen alentunut keuhkofunktio ennustaa aikaisempaa (≤ 1 v. diagnoosista) lääkkeen aloitusta. Polyfarmasia on yleistä. Lähes 60 %:lla IPF-potilaista on ≥ 5 lääkettä käytössä diagnoosivaiheessa. IPF:n elinajanennusteen mediaani on 4.5 vuotta. Diagnoosivaiheen korkea ikä ja matala keuhkojen toimintakokeiden taso ennustavat kuolleisuutta.

AVAINSANAT: antifibroottinen lääke, idiopaattinen keuhkofibroosi, insidenssi, mortaliteetti, nintedanibi, pirfenidoni, prevalenssi, prognoosi, tosielämän tutkimus

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Abbreviations

AE-IPF	Acute exacerbation of idiopathic pulmonary fibrosis
AIP	Acute interstitial pneumonia
ALAT	Latin American Thoracic Association
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
BMI	Body mass index
CAD	Coronary artery disease
CI	Confidence interval
COP	Cryptogenic organizing pneumonia
CT	Computed tomography
CTD	Connective tissue disease
DIP	Desquamative interstitial pneumonia
DLCO	Diffusing capacity of the lungs for carbon monoxide
DLCO/VA	Diffusing capacity of the lungs for carbon monoxide divided by alveolar volume
DX	Diagnosis
ERS	European Respiratory Society
FEV1	Forced expiratory volume in 1 second
FIP	Familial interstitial pneumonia
FVC	Forced vital capacity
GAP	Gender, age physiology
GERD	Gastroesophageal reflux disease
HFNC	High-flow nasal cannula
HP	Hypersensitivity pneumonitis
HPS	Hermansky-Pudlak syndrome
HRCT	High-resolution computed tomography
H	International Classification of Diseases
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease

IPF	Idiopathic pulmonary fibrosis
JRS	Japanese Respiratory Society
LIP	Lymphocytic interstitial pneumonia
MDD	Multidisciplinary discussion
MDT	Multidisciplinary team
MV	Mechanical ventilation
6MWT	6-minute walk test
NIV	Non-invasive ventilation
NSIP	Nonspecific interstitial pneumonia
OR	Odds ratio
OSA	Obstructive sleep apnea
PF-ILD	Progressive fibrosing interstitial lung disease
PH	Pulmonary hypertension
PPFE	Pleuroparenchymal fibroelastosis
RB-ILD	Respiratory bronchiolitis-associated interstitial lung disease
RCT	Randomized controlled trial
RWD	Real-world data
SD	Standard deviation
SGRG	St. George's Respiratory Questionnaire
SII	Social Insurance Institution
SLB	Surgical lung biopsy
TBLC	Transbronchial lung cryobiopsy
UIP	Usual interstitial pneumonia
VC	Vital capacity
VDGF	Vapor, dust, gas, and fume
WHO	World Health Organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Kaunisto J, Salomaa ER, Hodgson U, Kaarteenaho R, Myllärniemi M. Idiopathic pulmonary fibrosis - a systematic review on the methodology for the collection of epidemiological data. *BMC Pulm Med,* 2013;20:13–53.

II Kaunisto J, Kelloniemi K, Sutinen E, Hodgson U, Piilonen A, Kaarteenaho R, Mäkitaro R, Purokivi M, Lappi-Blanco E, Saarelainen S, Kankaanranta H, Mursu A, Kanervisto M, Salomaa ER, Myllärniemi M. Re-evaluation of diagnostic parameters is crucial for obtaining accurate data on idiopathic pulmonary fibrosis. *BMC Pulm Med,* 2015;19:15–92.

III Kaunisto J, Salomaa ER, Hodgson U, Kaarteenaho R, Kankaanranta H, Koli K, Vahlberg T, Myllärniemi M. Demographics and survival of patients, with idiopathic pulmonary fibrosis in the FinnishIPF registry. ERJ Open Res., 2019; 5(3):00170-2018.

IV Manuscript: Kaunisto J, Salomaa ER, Koivisto M, Myllärniemi M. Overall drug treatment of idiopathic pulmonary fibrosis patients from national registries – a real-world study.

1 Introduction

The beginning of the 21st century has been full of changes for the diagnosis and treatment of idiopathic pulmonary fibrosis (IPF). Awareness of this rare disease has increased a lot following the publication of revised guidelines for its diagnosis and management in 2011 (G. Raghu et al. 2011). The launch of new treatment options has given new hope for patients suffering from the disease. National and multinational IPF registries have been built mainly to gather data on the epidemiology and natural history of the disease. In Finland, the FinnishIPF project has been ongoing since 2012.

IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP) (G. Raghu et al. 2011). The definition and nomenclature of pulmonary fibrosis have evolved markedly since it was described by doctors Hamman and Rich in the 1930. Hamman and Rich (1935) are usually attributed as being the first ones to report the clinical entity of IPF. They reported a small series of patients dying from a fulminant respiratory illness. Before death, patients were suffering from extreme dyspnea, cough, and cyanosis. The pathologic features of the lungs were considered new and unfamiliar and were characterized by a remarkable proliferation of interstitial connective tissue. Today, nearly a hundred years later, Hamman-Rich´s syndrome refers to acute interstitial pneumonia (AIP) – an important entity in the differential diagnosis of IPF. Although the definition of IPF has become more accurate, its diagnosis is occasionally very challenging, and it requires a multidisciplinary approach in specialist centers.

Currently, there is no cure for IPF. The progressive scarring of the lung parenchyma leads to the decline of lung function and finally to death. Before the 2010s patients with pulmonary fibrosis were treated with corticosteroids and other immunomodulatory medications (Ganesh Raghu 2017) but then pivotal data were published. In October 2011, the Panther-IPF trial (testing therapies used for IPF) was discontinued because the triple-therapy arm, a combination of prednisone, azathioprine, and N-acetylcysteine, showed increased hospitalization, rate of death, and severe adverse events compared to placebo (Ganesh Raghu et al. 2012).

Following this, the treatment guidelines have changed entirely as two new antifibrotic medications –pirfenidone and nintedanib– have been approved for the treatment of IPF (G. Raghu, Rochwerg, et al. 2015). According to clinical trials (Noble et al. 2011; T. E. King et al. 2014; Luca Richeldi et al. 2014), both products can slow disease progression. To complement the results of randomized controlled trials (RCT), the use and long-term effect of antifibrotics need to be studied in a real-world setting.

The overall purpose of the FinnishIPF project has been to increase our knowledge and understanding of IPF and to develop the management of patients suffering from this severe disease. This thesis aims to identify reliable methodologies used in epidemiological research on IPF. It describes the demographics and distribution of IPF cases in Finland according to FinnishIPF registry data. The accuracy of the IPF diagnoses is evaluated retrospectively in the university hospital cohort. The prognosis is estimated, and the clinical predictors of survival are analyzed. Finally, the use of antifibrotic medications and comedications is evaluated in a real-world setting.

2 Review of the Literature

2.1 Epidemiological real-world data on idiopathic pulmonary fibrosis

The true prevalence and incidence of idiopathic pulmonary fibrosis are unknown. Prior published data have suggested a varying prevalence of 2–29/100 000 globally (G. Raghu et al. 2011). The European Union defines a disease to be rare when it affects a maximum of 5 per 10 000 (50/100 000) persons thus IPF is classified as a rare disease. Patient registries have a particularly crucial role in understanding rare diseases.

Over the past 10–15 years, several national and multinational IPF registries have been established to gain real-world data (RWD) on IPF. In contrast to RCTs with strictly selected patients, registries offer data on unselected patient populations with more severe and complex cases. The limitations of registry data are discussed later in this thesis.

Based on the results of a survey of ERS members in 2017 (Vincent Cottin et al. 2019), there were 93 individual registries and biobanks for interstitial lung diseases (ILD) within Europe, of which many were specifically for IPF. In a recent publication, Culver and colleagues (2019) described the data of 21 IPF/ILD registries across the world. The registries are very heterogeneous in goals, size, extent, quality control, scientific analysis, publication, and funding.

In Finland, the national IPF project, FinnishIPF, was initiated in 2012. The FinnishIPF project is a national, longitudinal, research project of strictly selected IPF patients in a real-life setting. Originally, the project was designed to investigate the incidence of IPF in Finland, follow disease behaviour and to estimate the prognosis. The registry now holds the diagnostic and follow-up information of over 900 IPF patients from all pulmonary units across Finland.

2.1.1 Demographics

Several IPF/ILD registries across the world have published demographical data, summarized in **Table 1**. It can be concluded that IPF occurs primarily in elderly people and the prevalence increases with age. IPF is strongly associated with exposure to cigarette smoke. The disease is more common in males, with a typical male-female ratio of 3:1.

Table 1. Summary of baseline characteristics from different national/multinational IPF/ILD projects which have published publications in English. Based on the reference Culver et al. 2019.

COUNTRY OR COUNTRIES/ NAME OF THE REGISTRY	**REFERENCE**	**COHORT SIZE (N)**	**AGE, YEARS ± SD (mean)** OR **Q1-Q3 (median)**	**MALE %**	**CURRENT AND FORMER SMOKER %**	**FVC% OF PREDICTED ± SD (mean) OR Q1-Q3** (median)	**DLCO% OF PREDICTED**
AUSTRALIA/ AIPFR	Jo et al. (2017)	647	70.9±8.5	67.7	71.7	81.0±21.7	48.4±16.7
AUSTRALIA AND NEW ZEALAND/ AILDR (ILD REGISTRY)	Moore et al. (2020)	1061	68.3±12.5	54.7	-	79.1±20.4	58.5±17.9
BELGIUM AND LUXEMBOURG/ PROOF AND PROOF-NEXT	Wuyts et al. (2018)	277	69.6±8.6	76.9	73.3	80.6±19.9	46.9±13.8
CANADA/ CARE-PF (IPF COHORT)	Fisher et al. (2019)	1287	70.9±8.5	72.2	78.2	72.8±19.5	49.9±16.7
FINLAND/ FINNISHIPF REGISTRY	Kaunisto et al. (2015)	111	73.5	60.4	54	80.4	57.3
GERMANY/ INSIGHTS-IPF-REGISTRY	Behr et al. (2015)	502	68.7±9.4	78	61	72.2±20.6	35.5±15.5
GERMANY/ EXCITING REGISTRY	Kreuter et al. (2016) (abstract)	201	68	62	57	72	51
INDIA/ ILD-INDIA REGISTRY (IPF COHORT)	Singh et al. (2017)	1084	64.7±8	73.6	43.9	57.5±22.3	-
ITALY/ FIBRONET REGISTRY	Poletti et al.(2021)	209	69.54 ±7.43	82.8	70.3	80.01±20.41	51.68 ±13.52
JAPAN/ JIPS REGISTRY	Bando et al. (2015)	436	-	78.8	72.6	-	-

COUNTRY OR COUNTRIES/ NAME OF THE REGISTRY	REFERENCE	COHORT SIZE (N)	AGE, YEARS ± SD (mean) OR Q1-Q3 (median)	MALE %	CURRENT AND FORMER SMOKER %	FVC% OF PREDICTED ± SD (mean) OR Q1-Q3 (median)	DLCO% OF PREDICTED
SPAIN/ SEPAR REGISTRY	Fernández-Fabrellas et al. (2019)	608	70.2±9.2	80.8	72.7	77.6 ± 19.4	48.5 ± 17.7
SWEDEN/ SWEDISH IPF REGISTRY (MEDIAN)	Gao et al. (2021)	662	72.0 (67.0–77.0)	74.0	64.8	71.0 (61.0–85.0)	47.0 (37.0–56.0)
TURKEY/ TURK-UIP (ILD)	Benan et al. (2021)	150	65.6±8.3	88.7	84.7	-	44.9±17.0
UNITED KINGDOM, BTS/UK IPF REGISTRY	Spencer et al. (2021)	2474	74±8.3	79	66	78.2± 18.3	48.4±16.0
UNITED STATES/ IPF-PRO/ILD-PRO REGISTRY	Snyder et al. (2020)	498	70 (65–75)	75.5	63.9	70.6 (58.9, 80.8)	42.1 (33.0–51.6)
UNITED STATES/ PFF-PATIENT REGISTRY	Wang et al. (2020)	1230	71±8	76	64	69±17	42±17
CROATIA, CZECH REPUBLIC, HUNGARY, ISRAEL, POLAND, SERBIA, SLOVAKIA, AND TURKEY/ EMPIRE	Doubková et al. (2018)	514	67.0 (50.0–82.0)	69.8	52.8	80.0(48.7;116.3)	45.6 (21.3–72.3)
AUSTRIA, CZECH REPUBLIC, FRANCE, GERMANY, HUNGARY, ITALY, SPAIN, AND UNITED KINGDOM/ EURIPFREG	Guenther et al.(2018)	525	65.2± 11.6	73.7	69.4	68.4± 22.6	42.1±17.8

DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; max, maximum; min, minimum; SD, standard deviation; Q1, first quartile; Q3, third quartile

In addition, there are several projects which have not yet published data in English to our knowledge. These projects are the PORTRAY registry (Xie et al. 2020), DANILDA (Bendstrup et al. 2019), INDULGE IPF (Greece), REGIS (Romania), and Pulmonary Fibrosis Contact Registry (USA).

2.1.2 Prevalence, incidence, and mortality

There are few studies containing data on the prevalence, incidence, and mortality of IPF. As we state in our systematic review (presented later in this thesis) only 13 epidemiological English language articles were published from 1/2001–9/2012. Within a wider timeframe, 1990–2011, Nalysnyk and colleagues (2012) identified 15 articles providing prevalence and incidence data in their epidemiological review. Nalysnyk et al. (2012) concluded that IPF prevalence in Europe ranged from 1.25 to 23.4 cases per 100 000 population. In the USA the estimated prevalence varied between 14–27.9/100 000 using narrow case definitions, and between 42.7–63/ 100 000 population using broad case definitions.

In this thesis (Study I), we present the results of our epidemiological review with global prevalence and incidence numbers. Moreover, we note that published epidemiological studies on IPF have varying study methodologies, datasets, and case definitions, which make the summary and comparison of statistics difficult (Kaunisto et al. 2013). Caminati and colleagues (2015) investigated the epidemiological heterogeneity further by expanding the results of our systematic review of the literature (Study I) and adding studies published before 1/2001 and between 9/2012 and 4/2015. They identified 22 publications, 13 of which corresponded to those included in our systematic review. As was done in our study, Caminati divided studies into three categories: national registries of interstitial lung diseases (ILDs), questionnaires send to pulmonologists, and the most common method used in IPF epidemiological studies, the use of pre-existing databases.

Recently Maher and colleagues (2021) published an epidemiological literature review with adjusted global prevalence and incidence data. The adjustment was done to obtain more comparable data from the heterogeneous epidemiological studies (differences in study design, methodologies, etc). They identified 22 epidemiological studies from 12 countries published from 1/2009-4/2020. Statistical modelling was applied to adjust for between-study differences where possible. The adjusted incidence estimates ranged from 0.35 to 1.30/10 000 in Asia–Pacific countries, 0.09 to 0.49 in Europe, and 0.75 to 0.93 in North America. The adjusted prevalence estimates ranged from 0.57 to 4.51 in Asia–Pacific countries, 0.33 to 2.51 in Europe, and 2.40 to 2.98 in North America. There were evident geographic gaps in IPF epidemiological data.

Hutchinson et al. (J. Hutchinson et al. 2015) reviewed global incidence and mortality data from 1968–2012. In studies from 2000 onwards, they estimated a

conservative incidence range of 3–9/100000/year for Europe and North America. In East Asia and South America, the incidence was lower. In most studies, the incidence seemed to be increasing, but studies from Denmark (Kornum et al. 2008) and the USA (Fernández Pérez et al. 2010) showed a decrease.

Literature on ILD is mostly published in Europe and North America with little data from South America, Africa, and Asia (Hutchinson et al. 2015; Kaul et al. 2021). Publications from developing countries are sparse but one large Brazilian study (Rufino et al. 2013) estimated the incidence of IPF at 0.26 cases per 100 000 persons per year in 1996, rising to 0.48 per 100 000 persons per year in 2010.

Epidemiological studies conducted in primary health care showed that over the study period of 2002–2017, prevalence had statistically significantly increasing trend while the incidence rate started to increase only in the last 3 years. The authors speculated that the increase in incidence rate is probably a result of growing awareness of IPF among general practitioners, while the increase in prevalence rates may be due to an increase in survival, a result of recent advances in the diagnosis, management, and therapy of the disease (Harari et al. 2020).

A newly published study by Kaul et al. (2022) examined extensive data on U.S veterans by using a Veterans Health Administration (VHA) electronic health record system (N= 10.7 million veterans). They found that between 2010 and 2019, 139 116 (1.26%) people were diagnosed with IPF. The prevalence increased from 276 cases per 100 000 in 2010 to 725 cases per 100 000 in 2019. The geographic distribution of the disease was heterogeneous across the U.S. with rural residences associated with higher odds of IPF.

IPF is associated with a high mortality rate, though there is substantial variation in rates between studies. A review article by Hutchinson et al. (2015) reported global mortality rates ranging from 1 to 14/100 000 populations per year during the study period of 1979–2012. A more recent review by Zheng et al (2022) identified six studies reporting on the mortality of IPF between 2000 and 2019. Age-standardized mortality for IPF varied from 0.5–12/100 000 populations per year after the year 2000. There were rising mortality trends for IPF in Australia, Brazil, Belgium, Canada, the Czech Republic, Finland, France, Germany, Hungary, Italy, Lithuania, the Netherlands, Poland, Portugal, Spain, Sweden, and the UK. Austria, Croatia, Denmark, Romania, and the USA showed decreased mortality trends (Zheng et al. 2022). An extensive mortality study of World Health Organization (WHO) from 17 European countries reported sex differences in mortality; rates were higher in males (Marshall et al. 2018).

The main cause of death in patients with IPF is the disease itself. This was confirmed in a Finnish study by Kärkkäinen and colleagues (2018), where the most common underlying cause of death among Finnish IPF patients was IPF, followed by ischemic heart disease.

2.2 Pathophysiology and risk factors

The precise underlying pathophysiological mechanisms of IPF remain unknown. The current generally accepted hypothesis is that IPF results from sustained or repetitive lung epithelial injury to genetically predisposed alveolar epithelium and subsequent failure of re-epithelialization and repair (Spagnolo and Cottin 2017). Activated alveolar cells release different cytokines and growth factors that stimulate the recruitment, proliferation, and differentiation of lung fibroblasts into myofibroblasts. This leads to excessive collagen deposition, tissue scar formation, and irreversible loss of function (Bellaye and Kolb 2015; Mei et al. 2022).

According to current understanding, genetic susceptibility, in addition to environmental risk factors, contributes significantly to the risk of developing IPF (Kropski, Blackwell, and Loyd 2015; García-Sancho et al. 2011). IPF occurs most often in individuals without a known family history of the disease. Familial interstitial pneumonia (FIP) is usually defined as a case of ILD in which the patient has a family history of two or more relatives with ILD (Kropski, Blackwell, and Loyd 2015; García-Sancho et al. 2011). However, no consensus definition exists. Early studies suggested that familial forms of the disease accounted for 2%–4% of IPF (Hodgson, Laitinen, and Tukiainen 2002). Later evidence suggests that this percentage may be higher. Approximately 20% of IPF patients report a family history of idiopathic interstitial pneumonia at diagnosis (García-Sancho et al. 2011; Fernández Pérez et al. 2010). Patients with FIP are indistinguishable from sporadic IPF patients in terms of clinical presentation, radiographic findings, and histopathology, although familial forms may develop at an earlier age (Krauss et al. 2019).

The strongest and most well-replicated single genetic risk factor for both familial and sporadic IPF is a polymorphism in the distal promoter region of the MUC5B gene rs35705950 (Seibold et al. 2011; Conti et al. 2016). The gene encodes mucin 5B, a glycosylated macromolecular component of mucus, and is expressed in the normal bronchiolar epithelium (Seibold et al. 2011). The rs35705950 variant is neither necessary nor sufficient to cause the disease, and approximately half of all IPF patients do not carry the variant. Therefore, it is suggested that other genetic or environmental factors are involved in the disease development. Subsequently, many more common and rare risk variants have been identified: genes related to innate immune function (TOLLIP, TLR3, IL1RN, IL8, TGFB1), epithelial barrier function (DSP, DPP9), telomerase maintenance (TERT, TERC, OBFC1, TINF2, DKC1, RTEL1, PARN), surfactant production (SFTPC, SFTPA2, ABCA3), and cell cycle regulation (KIF15, MAD1L1, CDKN1A) (Borie et al. 2019). Active research is ongoing in this area. Several biobanks have been established globally, and also in Finland (FinnGen study). The FinnGen study combines genome data with digital health care data. One of the clinical research aims is to improve and advance diagnosis of IPF. According to recently published results of a large meta-analysis

from 13 biobanks including the FinnGen study (Partanen et al. 2022), seven novel genome-wide significant loci have been identified recently.

Cigarette smoke is the most studied risk factor for IPF, although the studies have had small sample sizes. More than 20 years ago, Baumgartner et al. (1997) published a study in which tobacco smoke was considered an important risk factor for the development of IPF even many years after cessation. A more recent prospective cohort study using UK Biobank data (Bellou, Belbasis, and Evangelou 2021)concluded that smoking and maternal smoking around birth increase the risk of IPF, and they work synergistically. A dose-response relationship exists between pack years and IPF (Bellou, Belbasis, and Evangelou 2021). An Australian study by Abramson et al. showed that passive smoking in the workplace also increases the risk of developing IPF (Abramson et al. 2018).

Besides tobacco smoke, various exposures have been suggested to associate with the development of IPF: gastroesophageal reflux disease (Tobin et al. 1998), viruses (Stewart et al. 1999; Tang et al. 2003), metal/wood dust (Hubbard et al. 1996), and combined exposures (vapor, dust, gas, and fumes, VDGF) (Blanc et al. 2019). Additionally, growing evidence supports the causal relationship between ambient air pollution and IPF. Through several potential mechanisms, air pollutants may contribute to the onset of the disease, impact disease severity, accelerate progression, trigger acute exacerbation and hospitalization as well as affect mortality (Majewski and Piotrowski 2020).

A growing body of evidence suggests that the lung microbiome may influence the pathogenesis and progression of ILDs, particularly IPF (Spagnolo et al. 2019). Microbial imbalance, meaning increased bacterial load and/or loss of diversity, has been reported in IPF patients (Phillip L. Molyneaux et al. 2014; Han et al. 2014) and it is associated with disease progression and immune response (Philip L. Molyneaux et al. 2017; Huang et al. 2017), and probably contributing to acute exacerbations, hospitalizations, and decreased survival.

2.3 Diagnosing idiopathic pulmonary fibrosis

To clarify the terminology of IPF, it should be noted that the term ‘idiopathic pulmonary fibrosis’ refers to the clinical condition, whereas usual interstitial pneumonia is a histopathologic and radiologic pattern in IPF. The term UIP (usual interstitial pneumonia) is sometimes used as a synonym for IPF, but there are other etiologies associated with UIP. Thus, the diagnosis of IPF requires the exclusion of possible underlying conditions.

2.3.1 Current classification of idiopathic interstitial pneumonias

IPF is classified as an idiopathic interstitial pneumonia (IIP), which includes a heterogenous group of diffuse parenchymal lung diseases. IPF is often reported as the most common of the IIPs. Data from a Danish ILD study suggest that IPF accounts for 28% of all ILD diagnoses (Hyldgaard 2015).

According to the latest revision of classification in 2013 (Travis et al. 2013), IIPs are grouped as major, rare and unclassifiable (**Table 2**). The major IIPs are subdivided into chronic fibrosing IIPs, smoking-related IIPs, and acute/subacute IIPs. Idiopathic pulmonary fibrosis together with idiopathic nonspecific interstitial pneumonia (NSIP) form a subdivision of chronic fibrosing IIPs. Infrequent cases of isolated, reversible cellular NSIP exists (Travis et al. 2013). Strong evidence supports a causal role for cigarette smoking in the development of respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) and desquamative interstitial pneumonitis (DIP) (Caminati et al. 2012). Cryptogenic organising pneumonia (COP) is in many cases secondary when the use of the generic term organising pneumonia (OP) is suggested. Acute interstitial pneumonia (AIP) is a severe, rapidly progressing hypoxemic IIP with high mortality. AIP should be distinguished from the clinically similar acute respiratory distress syndrome (ARDS), which has a known cause. Rare IIPs are idiopathic lymphocytic interstitial pneumonia (LIP) and pleuroparenchymal fibroelastosis (PPFE). It is estimated that the prevalence of unclassifiable IIPs is around 10–15% of all IIP cases (Ryerson et al. 2013; Skolnik and Ryerson 2016).

Table 2. Current classification of Idiopathic Interstitial Pneumonias (2013). Modified from Travis et al 2013.

IIP CATEGORY	
MAJOR IIPS	
	Chronic fibrosing: IPF, idiopathic NSIP
	Smoking related: RB-ILD, DIP
	Acute/subacute: AIP, COP
RARE IIPS	
	Idiopathic LIP
	PPFE
UNCLASSIFIABLE	

AIP, acute interstitial pneumonia; COP, cryptogenic organizing pneumonia; DIP, desquamative interstitial pneumonia; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; LIP, lymphoid interstitial pneumonia; NSIP, nonspesific interstitial pneumonia; PPFE, pleuroparenchymal fibroelastosis; RB-ILD respiratory bronchiolitis-associated interstitial lung disease

2.3.2 Evolution of diagnostic criteria for idiopathic pulmonary fibrosis

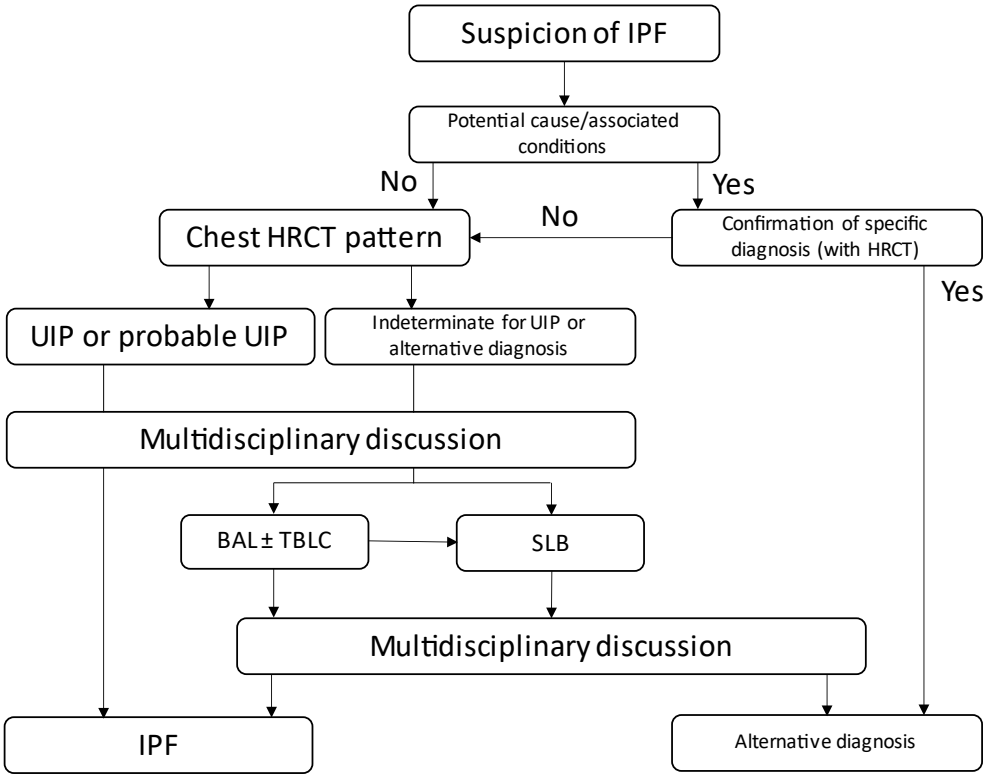
The first statement on the clinical management of IPF, was published in 2000 ('Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment: International Consensus Statement' 2000). At that time the evidence available was minimal, consequently the statement was based on the consensus of a few expert opinions. The diagnostic criteria in 2000 included major and minor criteria. For IPF diagnosis, all four major criteria and three of the four minor criteria were required. The major criteria were: 1. Exclusion of other known causes of ILD, such as certain drug toxicities, environmental exposures, and connective tissue diseases. 2. Abnormal pulmonary function studies that include evidence of restriction and impaired gas exchange. 3. Bibasilar reticular abnormalities with minimal ground glass opacities on high-resolution computed tomography (HRCT). 4. Transbronchial lung biopsy or bronchoalveolar lavage showing no features to support an alternative diagnosis. Minor criteria were: 1. Age >50 yrs. 2. Insidious onset of otherwise unexplained dyspnoea on exertion. 3. Duration of illness ≥3 months. 4. Bibasilar, inspiratory crackles (dry or "velcro" type).

Significant changes happened in 2011 when ATS/ERS/JRS/ALAT published new clinical practice guidelines for the diagnosis and management of IPF (G. Raghu et al. 2011). The guideline introduced diagnostic criteria for radiological and histological findings. The patterns were classified into three categories: UIP, probable UIP, and inconsistent with UIP. However, the 2011 criteria have since been shown to have significant limitations in clinical practice and therefore, a revision was published in 2018 (G. Raghu et al. 2018).

According to the ATS/ERS/JRS/ALAT 2018 guidelines, the diagnosis of IPF requires (#1 and #2 or #3):

1. Exclusion of other known causes of ILD.
2. The presence of the HRCT pattern of UIP.
3. Specific combinations (**Table 3**) of HRCT patterns and histopathology patterns in patients subjected to lung tissue sampling.

The updated diagnostic algorithm (Ganesh Raghu, Remy-Jardin, et al. 2022) for IPF was published in 2022 and is presented in **Figure 1**.



BAL, bronchoalveolar lavage; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; SLB surgical lung biopsy; TBLC, transbronchial lung cryobiopsy; UIP, usual interstitial pneumonia;

Figure 1. Diagnostic algorithm for IPF, modified from Raghu et al. 2022.

Table 3. Diagnosis based upon radiological and histopathological patterns, modified from Raghu et al. 2018.

	HISTOPATHOLOGICAL DIAGNOSIS			
HRCT PATTERN	**UIP**	**PROBABLE UIP**	**INDETERMI-NATE FOR UIP**	**ALTERNATIVE DIAGNOSIS**
UIP	IPF	IPF	IPF	Non-IPF dx
PROBABLE UIP	IPF	IPF	IPF (likely)	Non-IPF dx
INDETERMI-NATE FOR UIP	IPF	IPF (likely)	Indeterminate for IPF	Non-IPF dx
ALTERNATIVE DIAGNOSIS	IPF (likely)/ Non-IPF dx	Non-IPF dx	Non-IPF dx	Non-IPF dx

dx, diagnosis; HRCT, high-resolution computed tomography;
UIP, usual interstitial pneumonia

2.3.3 Clinical assessment and diagnostic tools

Thorough clinical evaluation is necessary for diagnosing interstitial lung diseases. A detailed history of smoking, medication use, and environmental exposures at home, work, and other places the patient frequently visits should be taken to exclude potential causes of ILD (Raghu et al. 2018).

The most frequently reported symptoms of IPF are a prolonged dry cough and progressive exertional dyspnea. An extensive study by Hewson et al. (2017) concluded that symptoms may be present 4–5 years before diagnosis.

Typical findings in a physical examination – although not specific for IPF – are basal and symmetrical velcro crackles at lung auscultation. Velcro crackles may occasionally be heard in healthy subjects from the anterior side of the chest disappearing after a few deep breaths (Thacker and Kraman 1982). Lung auscultation may also reveal crackles in patients with asymptomatic congestive heart failure (Kataoka and Matsuno 2008). Digital auscultation of respiratory sounds combined with artificial intelligence may contribute to earlier diagnosis of IPF in the future (L. Richeldi et al. 2019). Digital lung sound auscultation may also have potential as a quantitative methodology for monitoring disease progression (Sgalla et al. 2018). Finger clubbing is present in approximately one-third of IPF patients (Bando et al. 2015). Body mass index (BMI) and mid-arm circumference are independently associated with a low fat-free mass index (Jouneau et al. 2019). Nearly one-third of IPF patients are undernourished (Jouneau et al. 2019).

Connective tissue diseases (CTD) should be excluded by careful clinical investigation. Multi-joint arthralgias, proximal myalgia, skin lesions, Raynaud phenomena, dry mouth, and dry eyes are suggestive of CTD. Serological testing is recommended to aid in the exclusion of CTDs as a potential cause of ILD (G. Raghu et al. 2018).

A high-resolution CT scan of the chest is superior to other diagnostic imaging techniques. The hallmark pattern of IPF is usual interstitial pneumonia. See section 2.3.4 Radiological diagnosis.

According to current knowledge, the pathological processes in IPF affect not only alveoli but also conducting airways and lung vasculature (Plantier et al. 2018). As a result, the mechanical properties of the lungs are altered in many ways. These alterations are mainly seen as a reduction of lung compliance and diffusing capacity, and restriction in lung volume. Therefore, in clinical practice, spirometric values and DLCO (diffusing capacity of the lung for carbon monoxide) should be measured in patients with suspected ILD. Lung function testing is also an important tool in the follow-up of IPF patients.

In diagnosing IPF, the role of bronchoscopy and BAL (bronchoalveolar lavage) are limited but they may assist in the diagnosis of ILDs such as chronic hypersensitivity pneumonitis (HP). Surgical lung biopsy (SLB) carries considerable

risks. In a recent extensive analysis, the rate of mortality for elective and non-elective SLB was 1.7 % and 16 % respectively (J. P. Hutchinson et al. 2016).

The 2018 diagnostic guideline gives a conditional recommendation for BAL and cellular analysis, and for SLB in patients with suspected IPF and patterns other than UIP on HRCT. No recommendation for or against the use of transbronchial biopsy is given (G. Raghu et al. 2018). The new updated diagnostic guideline gives a conditional recommendation for t. It is an acceptable alternative to surgical lung biopsy in centres with appropriate expertise (Ganesh Raghu, Remy-Jardin, et al. 2022).

The available tools for genetic testing are increasing. In clinical practice, the role of genomic testing is unclear. A genetic consultation may be considered at least for young patients (under 60 years) with a family history of IPF.

2.3.4 Radiological diagnosis

Earlier, the 2011 ATS/ERS guidelines classified three degrees of diagnostic certainty for UIP in CT-scans: typical UIP, possible UIP, and inconsistent with UIP (G. Raghu et al. 2011). Yet, the possible UIP pattern proved problematic because the category included plenty of patients who theoretically had to be subjected to potentially risky lung biopsy. Over the years, research in this field encouraged the division of possible UIP patterns into probable UIP and indeterminate UIP. Studies (Raghu et al. 2014; Chung et al. 2015) have shown that 82%–94% of patients with possible UIP had a probable or definite UIP histopathological pattern at surgical lung biopsy.

In 2018, two multinational publications on the diagnosis of IPF were published by major respiratory and radiological societies: The ATS/ERS/JRS/ALAT (Raghu et al. 2018) and the Fleischner Society statement (Lynch et al. 2018). Both publications reached similar conclusions and recommendations. The guidelines expanded the HRCT classification for UIP to four categories: typical UIP, probable UIP, indeterminate for UIP, or suggestive of an alternative diagnosis (**Table 4**).

Table 4. International guidelines for radiological patterns and features for IPF. Based on the references Raghu et al. 2018, Lynch et al. 2018.

HRCT PATTERN	DESCRIPTIONS
TYPICAL UIP	Subpleural and basal distribution of fibrosis, distribution often heterogenous, characterized by honeycombing, with/without peripheral traction bronchiectasis or bronchiolectasis, and the absence of findings that suggest a diagnosis other than IPF
PROBABLE UIP	Lacks honeycombing but otherwise shows a typical UIP pattern
INDETERMINATE FOR UIP	Peripheral and basal predominant reticulation without features that suggest a specific etiology. The reticular abnormality is often mild and there may be associated ground glass opacity
ALTERNATIVE DIAGNOSIS	Upper-lung or mid-lung predominant fibrosis, peribronchovascular predominance with subpleural sparing, or in any of the following features: predominant consolidation, extensive ground glass opacity (without acute exacerbation), extensive mosaic pattern with air trapping on expiration, and nodules or cysts other than in a honeycomb formation.

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

In addition, the presence of small nodular calcification foci within areas of fibrosis may suggest IPF. Mediastinal lymphadenopathy was reported in 70% of IPF patients (Lynch et al. 2018).

2.3.5 Histological diagnosis

If the finding in HRCT is a typical or probable UIP pattern and the clinical context is appropriate, the diagnosis of IPF can be made without additional procedures. A surgical lung biopsy or transbronchial lung cryobiopsy (TBLC) should be considered when the radiological pattern is indeterminate for or inconsistent with UIP (Raghu et al. 2022). Moreover, a biopsy is recommended when clinical features suggest an alternative diagnosis (e.g., exposure history suggesting hypersensitivity pneumonitis) (Lynch et al. 2018). **Table 5** summarizes the descriptions of different patterns according to recent guidelines.

Table 5. International guidelines of histopathological patterns and features. Based on the references: Raghu et al. 2018, Lynch et al. 2018.

HISTOPATOLOGICAL PATTERN	DESCRIPTION
TYPICAL UIP	Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing), predominant subpleural and/or paraseptal distribution of fibrosis, patchy involvement of lung parenchyma by fibrosis, fibroblast foci, absence of features to suggest an alternative diagnosis.
PROBABLE UIP	Some histologic features described above (see UIP) are present but to an extent that precludes a definite diagnosis of UIP/IPF and the absence of features to suggest an alternative diagnosis or honeycombing only.
INDETERMINATE FOR UIP	Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause. Some histologic features described above (see UIP), but with other features suggesting an alternative diagnosis.
ALTERNATIVE DIAGNOSIS	Features of other histologic patterns of IIPs (e.g., absence of fibroblast foci or loose fibrosis) in all biopsies, histologic findings indicative of other diseases (e.g., hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, LAM)

IPF, idiopathic pulmonary fibrosis; LAM, lymphangioleiomyomatosis; UIP, usual interstitial pneumonia

2.3.6 Multidisciplinary discussion and differential diagnosis

Diagnosing interstitial lung diseases can be challenging as separate disease entities share overlapping findings on imaging and lung tissue sampling. To gain an accurate and early diagnosis of ILD, a multidisciplinary discussion (MDD) is widely recommended (Raghu et al. 2018; Lynch et al. 2018). In clinical practice, multidisciplinary team (MDT) usually includes a clinician (pulmonologist), a radiologist, and a pathologist. In addition, other professionals can participate on demand: a specialist in rheumatology, a thoracic surgeon, a lung transplant expert, and an occupational medicine expert.

Since IPF is defined by a radiological and/or histological pattern of UIP, these findings are not specific to IPF. Several other clinical conditions are also associated with UIP, mimicking IPF. Conditions to be considered in the differential diagnosis are listed in **Table 6**. IPF is frequently confused with chronic HP. Morell et al. (2013) published results of a single-center case-cohort study, which showed that up to 43% of patients diagnosed with IPF were misdiagnosed with chronic hypersensitivity

pneumonitis. Hermansky-Pudlak syndrome (HPS) is a rare multisystemic, hereditary disorder characterized by oculocutaneous albinism, bleeding diathesis, and lethal pulmonary fibrosis (PF) in some HPS subtypes (HPS-1, HPS-2, and HPS-4). Fibrosis typically develops in middle adulthood. Ground-glass opacities, reticulation, and traction bronchiectasis develop with the progression of PF. The prevalence of HPS is 1 in 500 000 to 1 000 000 individuals worldwide, though the prevalence is 1 in 1 800 in individuals with Puerto Rican heritage (El-Chemaly and Young 2016).

Table 6. Clinical conditions, other than IPF, associated with UIP. Based on the references: Wuyts et al. 2014, D. J. Lederer and Martinez 2018).

ILDS MIMICKING IPF
CHRONIC HYPERSENSITIVITY PNEUMONITIS
CONNECTIVE TISSUE-RELATED ILDS rheumatoid arthritis (UIP most common) systemic sclerosis (UIP more common) polymyositis/dermatomyositis (also NSIP) mixed connective tissue disease (also NSIP)
DRUG-INDUCED ILDS amiodarone lung
FAMILIAL IPF
PNEUMOCONIOSIS (OCCUPATIONAL ILDS) asbestosis
HERMANSKY-PUDLAK SYNDROME

ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia

Real-world data on the effect and impact of MDD are sparse. An Italian study (Biglia et al. 2019) showed that 42% of ILD diagnoses were revised and the number of unclassifiable ILDs was significantly reduced. Another study by Grewal et al. (2019) reported that after MDD review, treatment was started in 45% of patients with no prior ILD therapy, and treatment was changed in 45% of patients on ILD therapy.

2.4 Comorbidities

IPF is associated with multimorbidity. A recent study by Kreuter et al. (2016) estimated that approximately 60% of IPF patients have one to three comorbidities, 30% have four to seven comorbidities, and only 10% have no comorbidities. A real-world study, the EMPIRE registry study (Jovanovic et al. 2022), showed that increasing numbers of comorbidities were associated with worse survival.

Comorbidities/medical conditions which are frequently associated with IPF are listed in **Table 7**.

Table 7. Comorbidities and medical conditions associated with IPF. (C. S. King and Nathan 2017).

PULMONARY	EXTRAPULMONARY
Pulmonary hypertension	Coronary artery disease
Chronic obstructive pulmonary disease	Diastolic dysfunction
Emphysema	Gastroesophageal reflux disease
Lung cancer	Obstructive sleep apnea
Venous thromboembolism/pulmonary embolism	Psychiatric disturbances
	Endocrine disorders

As summarized in a systematic review by Raghu et al. (Raghu, Amatto, et al. 2015) the prevalence of different comorbid diseases varies widely between studies. Variation is mainly due to heterogeneity in data and differences in disease definitions (both IPF and comorbid diseases). Some comorbidities, especially lung cancer, negatively influence survival in IPF, while others such as gastroesophageal reflux disease (GERD) may have a more favorable effect on survival (Lee et al. 2011; Kreuter et al. 2016). The possible explanatory factors are unclear, but they may be related to an earlier diagnosis due to GERD-related pulmonary symptoms and thereby longer survival. Another controversial argument is the potential impact of antacid therapy, mainly proton pump inhibitors on the course of IPF (Michael Kreuter, Ehlers-Tenenbaum, et al. 2016; H. E. Jo et al. 2019).

Pulmonary hypertension

Pulmonary hypertension (PH) is currently defined as increased pulmonary vascular resistance (≥3 Wood units) associated with an increased mean pulmonary arterial pressure (> 20 mmHg) at rest in right heart catheterization (Simonneau et al. 2019). According to a previous review 3%–86 % of patients with IPF develop pulmonary hypertension (Raghu, Amatto, et al. 2015). PH usually develops as the fibrosis progresses to a more advanced stage. Transthoracic echocardiogram is often used as a screening tool, even though it might overdiagnose pulmonary hypertension in chronic lung disease (Arcasoy et al. 2003). Pulmonary hypertension has been associated with poor prognosis (Nathan, Noble, and Tuder 2007; Caminati, Cassandro, and Harari 2013).

COPD and emphysema

The majority of IPF patients have a smoking history. Therefore, it is not surprising that emphysema and/or COPD may occur among IPF patients. The prevalence of COPD (including emphysema) ranges from 6% to 67% (Raghu, Amatto, et al. 2015). When emphysema is a relevant component of the condition, it is referred to as "combined pulmonary fibrosis emphysema" (CPFE) seen as a distinct phenotype of IPF (V. Cottin 2005). Patients with CPFE are generally middle-aged male, heavy smokers with HRCT showing typical or atypical fibrosis at the base of the lung and emphysema in the upper lobes (V. Cottin 2005).

Lung cancer

IPF patients are at risk of developing lung cancer. The prevalence of lung cancer is significantly higher than in the general population, it ranges from 2.7% to 48% (Ballester, Milara, and Cortijo 2019). IPF itself is a risk factor for lung cancer, irrespective of smoking (H. Y. Lee et al. 2021). Lung cancer with concomitant UIP appears to have special clinicopathological features such as squamous cell subtype and peripheral location predominantly in the lower lobes compared with lung cancer without UIP (Watanabe et al. 2017).

Obstructive sleep apnea

Sleep is significantly altered in IPF patients. Recent sleep studies have revealed alterations in sleep architecture and breathing patterns, as well as desaturations, especially during vulnerable REM sleep (Mermigkis, Bouloukaki, and Schiza 2017). Prevalence of obstructive sleep apnea (OSA) is reported from 5.9% to 91% (G. Raghu, Amatto, et al. 2015). OSA appears to be more common among patients with a higher BMI (G. Raghu, Amatto, et al. 2015). The use of a positive airway pressure device has been shown to improve sleep quality and alleviate symptoms such as sleepiness and fatigue in IPF patients as well (Papadogiannis et al. 2021). IPF patients with ≥6-hour positive airway pressure use had better survival compared with patients with <6-hour use (Papadogiannis et al. 2021).

Gastroesophageal reflux disease

The relationship between gastroesophageal reflux disease and idiopathic pulmonary fibrosis is controversial. Several studies have shown that GERD and hiatal hernia occur frequently in IPF patients (G. Raghu 2006; Noth et al. 2012). It is hypothesized that GERD followed by microaspiration possibly leads to alveolar injury. However, other studies have explained GERD as an expected phenomenon resulting from

increasingly negative intrathoracic pressure in restrictive pulmonary fibrosis (J. S. Lee et al. 2010). A recent meta-analysis agrees that GERD and IPF may be related, but this association is most likely confounded, especially by smoking (Bédard Méthot, Leblanc, and Lacasse 2019).

Cardiovascular diseases

IPF and cardiovascular diseases share several risk factors, including increased age, male gender, and smoking history. The estimated prevalence of coronary artery disease (CAD) in those with IPF ranges from 4% to 25% (Oldham and Collard 2017). Nathan et al. (2011) have investigated the value of high-resolution CT in the detection of CAD. They compared coronary artery calcification on CT scans with left heart catheterization and concluded that routine CT has very good performance characteristics in predicting underlying significant coronary artery disease in patients with IPF (Nathan et al. 2011). Moreover, IPF is associated with several other cardiovascular conditions, such as atrial fibrillation, other arrhythmias, congestive heart failure, cerebrovascular incidents, and systemic arterial hypertension (G. Raghu, Amatto, et al. 2015)

Venous thromboembolism and pulmonary embolism

Prior animal models and laboratory studies have suggested that activation of the clotting cascade occurs in fibrotic lungs (Chambers and Scotton 2012). Recent epidemiological research has confirmed a strong association between IPF and venous thromboembolism, and consequently pulmonary embolism. Navaratnam et al. (2014) reported an approximately fourfold higher prevalence of prothrombotic state in IPF patients compared to age-matched controls.

Diabetes mellitus

Several studies (C. S. King and Nathan 2017) have reported an increased prevalence of diabetes mellitus in patients with IPF compared with matched controls even after controlling for corticosteroid use. The prevalence of diabetes mellitus among IPF patients is reported to range from 10 % to 40 %, but the reason is unclear. It is also unknown, whether glycemic control affects the progression of fibrosis (C. S. King and Nathan 2017).

Hypothyroidism

According to a recent retrospective case-control analysis (Oldham et al. 2015), hypothyroidism was more common among IPF patients than in COPD controls (16.8% vs 7.1%). It is speculated that there may be common pathogenic mechanisms between autoimmune thyroid disease and IPF.

Anxiety and depression

The prevalence of anxiety and depression is high, 31% and 23%, respectively, among IPF patients (Holland et al. 2014). Recently Glaspole and colleagues (Glaspole et al. 2017) reported results from an Australian IPF registry study which concluded that dyspnea and cough, the key symptoms of IPF, are important contributors to anxiety and depression. Moreover, the risk of anxiety and depression worsened, as cough and dyspnea became more severe. All patients with IPF should be screened for these disorders.

2.5 Disease course and acute exacerbations

According to studies published in the 1990s, the median survival of IPF patients is 2–3 years from diagnosis. However, post-diagnosis survival time has increased as patients are diagnosed at an earlier stage of the disease.

Disease progression is highly variable and difficult to predict at the individual level (Ley, Collard, and King 2011). Some patients experience periods of stability followed by acute deteriorations in lung function known as acute exacerbations (AE) (Cottin and Richeldi 2014).

AE is defined as “an acute, clinically significant respiratory deterioration (both idiopathic and triggered events) characterized by evidence of new widespread alveolar abnormality” (Collard et al. 2016). The criteria require a previous or simultaneous diagnosis of IPF, an acute worsening or development of dyspnea typically less than 1 month in duration and new bilateral ground-glass opacity and/or consolidation superimposed on a background imaging pattern of UIP not fully explained by cardiac failure or fluid overload on chest CT (Collard et al. 2016).

Several factors have been suggested as a trigger for acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF): infections, procedures, operations, drug toxicity, and aspiration (G. Raghu et al. 2011). Most commonly the etiology of AE is unknown.

AE-IPF is more common in patients with advanced disease (Collard et al. 2016). Low forced vital capacity (FVC) is the most consistent risk factor for exacerbations. Other parameters associated with increased risk include low DLCO, low 6-minute-

walk distance, pulmonary hypertension, poor baseline oxygenation, increased dyspnea, and a recent decline in FVC (Collard et al. 2016).

AE-IPF usually carries a poor prognosis. A recent Japanese study (Natsuizaka et al. 2014) reported that acute exacerbations accounted for 40% of IPF deaths. When a patient has had an episode of AE, the in-hospital mortality has been reported as high as 50.0%, and the 1- and 5-yr survival rates from the initial diagnosis are 56.2% and 18.4%, respectively (Song et al. 2011).

2.5.1 Prediction of mortality

Several clinical, physiological, radiographic, histologic, and molecular biomarker predictors have been associated with the prognosis of IPF (Biondini et al. 2021; Jacob et al. 2017). These include e.g., gender, age, change in lung function, radiological/histological pattern, blood/BAL biomarkers, and symptoms (dyspnea score) (Nishiyama et al. 2010). Some multidimensional staging systems have been developed for these variables (du Bois et al. 2011). However, complicated predictive models have not been widely adopted as they are difficult to use or lack external validation.

In 2012, Ley et al. proposed a novel staging system for IPF to determine the average risk of mortality (Ley et al. 2012). The GAP index and staging system use four variables: gender (G), age (A), and two pulmonary physiological parameters (P): FVC % of predicted, and DLCO % of predicted. The GAP index was derived and validated based on data from 558 IPF patients from three academic centers in the United States and Italy. GAP is validated at both presentation and during follow-up, thus it can be used throughout the disease course (Tran et al. 2020). Calculation of the GAP index produces 1-, 2-, and 3-year mortality estimates, which may guide management decisions.

2.6 Management of idiopathic pulmonary fibrosis

2.6.1 Pharmacotherapy

Until the beginning of the 2010s, treatment of IPF focused on immunosuppressant therapy despite the lack of evidence to support its efficacy and safety in this patient population. In 2012, the PANTHER-IPF trial (Raghu et al. 2012) showed that the triple therapy with prednisone, azathioprine and *N*-acetylcysteine was associated with an increased risk of hospitalization and death. Currently, after decades of drug development and failed clinical trials, two antifibrotic compounds, pirfenidone and nintedanib, are approved for idiopathic pulmonary fibrosis.

The most recent clinical practice guideline for pharmacotherapy in IPF was updated in 2015 (G. Raghu, Rochwerg, et al. 2015). The guideline gives conditional recommendations for treatment with pirfenidone, and nintedanib. The evidence supporting the use of pirfenidone and nintedanib is based on prospective, RCTs. The guideline stresses the need for physicians to discuss both medications with patients. The decision to initiate one of the medications should be a shared decision based on the patient's preferred choices, potential benefits, and risks. The intolerance of antifibrotics in the real world seems to be high when compared with clinical trials. Wright and colleagues (2021) showed in their study that over half of all treated patients had stopped the medication (nintedanib or pirfenidone) within 18 months. The predictors for discontinuation were age 75 years or over, female sex, and a BMI of 25 or under. There are also studies showing frequent side effects but with discontinuation rates of only under 10 % (Cameli et al. 2020).

2.6.1.1 Pirfenidone

Pirfenidone is an orally administered antifibrotic and anti-inflammatory product approved for IPF. It has taken several years for its antifibrotic and anti-inflammatory effects to be recognized. Pirfenidone works by inhibiting collagen synthesis, downregulating the production of multiple cytokines, and blocking fibroblast proliferation and stimulation in response to cytokines (Schaefer et al. 2011).

The encouraging results on the antifibrotic effect of pirfenidone were first published over 20 years ago (Ganesh Raghu et al. 1999). Later, these results were tested in a double-blind, placebo-controlled phase II study of Japanese IPF patients (Azuma et al. 2005). The study was stopped early at 9 months because an interim analysis showed a reduced deterioration in lung function in pirfenidone-treated patients. Pirfenidone was further studied in three phase III studies – one in Japan (Taniguchi et al. 2010) and two across North America, Australia, and Europe (Noble et al. 2011; T. E. King et al. 2014).

In the Japanese, randomized, double-blind, placebo-controlled phase III study (Taniguchi et al. 2010) of 275 IPF patients, pirfenidone reduced mean change in vital capacity (VC) at week 52 (absolute difference 70 mL, relative difference 44%, $p=0.042$), and improved progression-free survival time ($p=0.028$). Pirfenidone was relatively well tolerated. These results, with the results of the phase II study, led to regulatory approval of pirfenidone in Japan for the treatment of idiopathic pulmonary fibrosis.

In addition, pirfenidone was evaluated in three pivotal, concurrent, randomized, placebo-controlled phase III trials: the CAPACITY program (Noble et al. 2011), including two similar multinational trials (studies 004 and 006) and ASCEND (T. E.

King et al. 2014). These studies were designed to confirm the effect of pirfenidone on the reduction of decline in lung function.

CAPACITY 004 and CAPACITY 006 (Noble et al. 2011) assessed patients who had an FVC ≥50% of predicted and DLCO ≥35% of predicted. The primary endpoint in the CAPACITY trials was a change in FVC % of predicted from baseline to week 72. In study 004, patients were assigned in a 2:1:2 ratio to pirfenidone 2403 mg/day, pirfenidone 1197 mg/day, or placebo, whereas in study 006, patients were assigned in a 1:1 ratio to pirfenidone 2403 mg/day or placebo. In study 004, pirfenidone significantly reduced decline in FVC compared with placebo at week 72 in (–8.0% versus –12.4%, respectively; p = 0.001). In study 006 the difference between groups in FVC change at week 72 was not significant. However, a consistent pirfenidone effect was apparent until week 48 (p=0.005) The difference between primary endpoint results at week 72 for study 004 and study 006 is unclear. Analyses of pooled data from the two studies supported pirfenidone treatment's effect on FVC % predicted, progression-free survival, and 6-minute walk test (6MWT) distance. Analyses of pooled data from the two studies (004 and 006) supported the pirfenidone treatment's effect on the percentage predicted FVC at week 72 (p=0.005): mean change was −8.5% in the patients in the pirfenidone 2403 mg/day group and −11.0% in those in the placebo group. In the pooled analysis, pirfenidone prolonged progression-free survival by 26% compared with placebo and in 6MWT distance, a 31% relative difference was noted between treatment groups at week 72.

ASCEND (King et al. 2014) assessed patients who had an FVC of 50%–90% of predicted and DLCO of ≥30% of predicted. 555 IPF patients were randomly assigned to receive either oral pirfenidone (2403 mg per day) or a placebo for 52 weeks. The primary endpoint was the change in FVC or death at week 52. A 10% decline in FVC in an individual IPF patient is considered clinically meaningful and strongly predicts mortality (Paterniti et al. 2017). At week 52, 16.5% of patients in the pirfenidone group experienced an FVC decline of 10% or more or death, compared with 31.8% in the placebo group, representing a 47.9% reduction in the proportion of patients who experienced a significant change in FVC or death. In addition, at week 52 the data demonstrated that 22.7% of patients in the pirfenidone group experienced no decline in FVC, compared with 9.7% in the placebo group, representing 132.5% increase in the proportion of patients whose FVC did not decrease between baseline and week 52.

In a pooled analysis of the CAPACITY trials and the ASCEND trial (Ley et al. 2017), pirfenidone was associated with a reduced risk of respiratory-related hospitalization compared with placebo (7% vs. 12%) within 52 weeks. Among those hospitalized for any reason, treatment with pirfenidone was associated with a lower risk of death after hospitalization for up to 52 weeks after randomization, but this association was no longer significant with longer follow-up.

Another extensive study combining analytical approaches (pooled analysis and meta-analyses of clinical trials) was conducted to determine the effect of pirfenidone on mortality outcomes over 120 weeks (Nathan et al. 2017). At week 52, the relative risk of death for all four mortality outcomes (all-cause mortality, treatment-emergent all-cause mortality, idiopathic pulmonary fibrosis-related mortality, and treatment-emergent idiopathic-pulmonary fibrosis-related mortality) was significantly lower in the pirfenidone group than in the placebo group in the pooled analysis. Similarly, meta-analyses for all-cause mortality at week 52 also showed a significant reduction in mortality in the pirfenidone group compared with the placebo group. Over 120 weeks, significant differences were noted in the pooled analysis favouring pirfenidone compared with placebo in mortality outcomes. Similar results were shown by the meta-analyses.

The safety and tolerability of pirfenidone have been acceptable in RCTs. The most reported adverse events due to pirfenidone are dermatological and gastrointestinal (Lancaster et al. 2017). Unwanted dermatological effects are skin rashes and photosensitivity. Severe sunburn of the skin may develop if the skin is not protected. Common gastrointestinal side effects are diarrhoea, nausea, stomach discomfort/pain, and vomiting. Liver function should be monitored during pirfenidone treatment. According to analysis of clinical trials, gastrointestinal and skin-related adverse events tend to occur early in the course of treatment and decrease over time (Valeyre et al. 2014). In the phase III trials, elevations of alanine transaminase and aspartate transaminase levels to >3 x the upper limit of normal occurred in 3.2% of patients (Noble et al. 2016).

2.6.1.2 Nintedanib

Nintedanib is an intracellular triple tyrosine kinase inhibitor that targets fibrogenic growth factors. Nintedanib inhibits platelet-derived growth factor receptors, fibroblast growth factor receptors, and vascular endothelial growth factor receptors. In vitro studies have shown that nintedanib inhibits fibroblast proliferation, migration and differentiation, and the secretion of extracellular matrix. (Wollin et al. 2015)

The TOMORROW (Luca Richeldi et al. 2011) and INPULSIS trials (Richeldi et al. 2014) were designed to evaluate the safety and efficacy of nintedanib in patients with idiopathic pulmonary fibrosis. The TOMORROW trial was a randomized, double-blind placebo-controlled, dose-defining study phase II study in which daily doses of tyrosine kinase inhibitors, BIBF 1120 50 mg, 100 mg, 200 mg, and 300 mg were evaluated. In 52 weeks, the use of BIBF 1120 150 mg twice daily was associated with reduced FVC decline, fewer acute exacerbations, and a small increase in quality of life.

The INPULSIS-1 and INPULSIS 2 studies (identical design) were randomized, double-blind, placebo-controlled phase III studies that investigated the safety and efficacy of nintedanib 150 mg given twice daily to patients with IPF (Richeldi et al. 2014). Included patients were ≥ 40 years with IPF diagnosed within five years before randomization. Lung function requirements were: FVC ≥ 50% of predicted and DLCO 30%–79% of predicted. Nintedanib slowed disease progression, measured as an annual decline in FVC. In INPULSIS-1, the annual rate of decline in FVC was –114.7 ml with nintedanib versus –239.9 ml with placebo. In INPULSIS-2 the annual decline in FVC was –113.6 ml (nintedanib) and –207.3 ml (placebo). Time to first acute exacerbation over 52 weeks was a secondary endpoint, which was met in INPULSIS-2 but not in INPULSIS-1. In the secondary endpoint "time to first acute exacerbation over 52 weeks", results were contradictory between the two studies. In INPULSIS –1 there was no difference between the nintedanib and placebo group but in INPULSIS-2 there was a benefit in the nintedanib group compared with the placebo group. The most reported adverse event was diarrhea.

Pooled analysis of INPULSIS-1 and INPULSIS -2 was performed to investigate the effect of nintedanib in different phenotypes of IPF (Costabel et al. 2016). A total of 638 nintedanib- and 423 placebo-treated patients were included. Prespecified subgroups were analyzed by sex, age (<65, ≥65 years), race (white, Asian), baseline FVC % (≤70%, >70%), baseline St. George's Respiratory Questionnaire (SGRQ) total score (≤40, >40), smoking status (never, ex/current), systemic corticosteroid use (yes/no), and bronchodilator use (yes/no). The primary endpoint was the annual rate of decline in FVC, and the secondary endpoints were time to first acute exacerbation and change from baseline in SGRQ total score, both over 52 weeks. Results showed that there was no statistically significant difference in the effect of nintedanib for the primary or the secondary endpoints in any group. It was concluded that nintedanib was effective across a wide range of phenotypes in IPF.

Pooled and meta-analyses of the TOMORROW and INPULSIS trials (Luca Richeldi et al. 2016) were conducted to obtain the treatment effect of nintedanib. 1231 patients were included (n=723 nintedanib, n=508 placebo). The annual rate of decline in FVC, time to first acute exacerbation, change from baseline in SGRQ total score and mortality over 52 weeks were assessed. Nintedanib significantly reduced the annual rate of decline in FVC compared with placebo. The treatment effect of nintedanib on change from baseline in SGRQ total score was modest and consistent across the pooled and meta-analyses. In the pooled analysis, a significant benefit in favor of nintedanib on time to first acute exacerbation was observed. In all models, the hazard ratio estimates were associated with wide confidence intervals (CI) due to the small number of acute exacerbations observed. In the meta-analysis the results were consistent.

In RCTs, the most frequent adverse events during nintedanib treatment were gastrointestinal. Around 62% of IPF of patients in the treatment group reported diarrhoea (compared with 18% in the placebo groups) (Luca Richeldi et al. 2014). However, diarrhoea was mild or moderate in intensity in almost all cases and led to treatment discontinuation in fewer than 5% of patients. Liver function should be monitored during nintedanib treatment. In the INPULSIS trials, elevations of alanine transaminase and aspartate transaminase levels to >3 x the upper limit of normal occurred in 5.0% of the patients. According to Japanese study, individuals with a lower body mass index (BMI≤22) may be at risk developing of liver dysfunction (Ikeda et al. 2017).

2.6.1.3 Treatment of acute exacerbation

Currently, there is no guideline regarding the therapy of AE-IPF, as data from clinical trials are sparse and there are no large RCTs available. In clinical practice, steroids are used based only on expert opinion. No guidance on dose, route, or duration exists.

To assess clinical practices in the management of AE-IPF, a large-scale global survey was conducted between 12/2017-4/2018 (Michael Kreuter, Polke, et al. 2020). A questionnaire was sent and 509 pulmonologists from 66 countries responded. According to the results, high-dose steroids were widely administered (94%), mainly, methylprednisolone or equivalent with a dosage of 500-1000 mg/day, for three days followed by slow tapering. Other immunosuppressive therapies (cyclophosphamide, cyclosporine, tacrolimus, rituximab) were rarely used. Very few (4%) responders never use immunosuppression. In patients without previous antifibrotic therapy, most participants would have initiated such therapy (nintedanib: 21%; pirfenidone: 14%; either nintedanib or pirfenidone: 32%), while 33% did not see an indication for antifibrotic treatment in an acute setting. Most physicians (71%) would have waited until clinical stabilization before initiating antifibrotic therapy. In patients already on antifibrotic therapy at the time of AE-IPF, 76% of respondents recommended its continuation, while a minority would have advised differently (4% discontinue, 3% reduced dose, 10% switch the antifibrotic drug). Antimicrobial therapy was initiated regularly by 56% with other broad-spectrum antibiotics combined with macrolides.

2.6.1.4 Potential future therapies

Because neither nintedanib nor pirfenidone can cure pulmonary fibrosis, there is still a need for finding more effective treatments with fewer side effects. Dozens of

promising molecules are under investigation (ClinicalTrials.gov). A portion of them have reached phase II or phase III clinical trials (some listed below).

Phosphodiesterase 4B inhibitor is a selective phosphodiesterase inhibitor associated with anti-inflammatory and antifibrotic properties. In phase II, an oral phosphodiesterase 4B inhibitor, either alone or with background antifibrotic use, prevented lung function decline in 12 weeks compared to placebo (Luca Richeldi et al. 2022).

Pentraxin 2 (purified serum amyloid P) inhibits monocyte differentiation into proinflammatory macrophages and production of transforming growth factor –β1, which is a key mediator in pulmonary fibrosis. In phase II, intravenous recombinant human pentraxin-2 (rhPTX-2) significantly decreased the decline in FVC % of predicted (change in FVC % of the predicted value of −2.5% compared with −4.8% with placebo) and stabilized 6MWT (Raghu 2018). An open-label extension study showed that long-term treatment (up to 128 weeks) with rhPTX-2 was well tolerated, and no new safety signals emerged. Efficacy data was limited but suggested a trend toward treatment effect (Ganesh Raghu, Hamblin, et al. 2022).

Pamrevlumab is a fully recombinant human monoclonal antibody against connective tissue growth factor, which has a central role in the process of fibrosis. In phase II (PRAISE trial), pamrevlumab reduced the decline in FVC % predicted by 60.3% at week 48 (mean change from baseline -2.9% with pamrevlumab vs -7.2% with placebo) (Luca Richeldi et al. 2020).

GB0139 (initially known as TD139) inhibits galectin-3, a molecule found on the surface of inflammatory cells (including macrophages). GB0139 is administered as a once-daily inhalation via a generic dry powder inhaler. Phase IIB is ongoing. Completion is estimated in May-June 2023. (ClinicalTrials.gov, identifier: NCT03832946)

PLN-74809 blocks activation of the TGFbeta pathway. Oral, small molecule, once daily. Phase IIa study is in progress, evaluating the safety, tolerability, and pharmacokinetics. (ClinicalTrials.gov, identifier: NCT04396756)

Treprostinil is a prostacyclin analog, which dilates blood vessels in the lung. Study RIN-PF-301 (phase III) is designed to evaluate the safety and efficacy of inhaled treprostinil 3 breaths 4 times daily. Completion is estimated in June 2024. (ClinicalTrials.gov, identifier: NCT04905693)

2.6.2 Non-pharmacological therapy

2.6.2.1 Lung transplantation

Interstitial lung disease is the most common indication for lung transplantation in Finland. Yet only a small minority of IPF patients receive a lung transplant due to significant comorbidities and high age. According to FinnishIPF data, the transplantation rate was 3% among IPF patients diagnosed during 2011–2015 (Kaunisto et al. 2019).

Historically, IPF patients have had higher waiting list mortality than patients with other indications for lung transplantation. Mortality on a waiting list has been reported between 14%-54% (David J. Lederer et al. 2006; Mackay et al. 2007; ten Klooster et al. 2015).

Referral to a transplantation center should be made at the time of diagnosis, even if a patient is being initiated on therapy, in case of histopathological UIP or radiographic evidence of a probable or definite UIP pattern (Leard et al. 2021).
Recent data suggest that antifibrotic use before lung transplantation may improve survival; one center reported 5-year survival for up to 100 % of antifibrotic users (Tuyls et al. 2019). Moreover, it seems that antifibrotic treatment does not increase surgical complications or post-operative mortality (Leuschner et al. 2018).

2.6.2.2 Oxygen therapy, high-flow nasal cannula

There is scant evidence with no RCTs to assess the benefit of long-term oxygen therapy in IPF. However, the treatment guideline (G. Raghu et al. 2011) strongly recommends supplemental oxygen for IPF patients. An oxyhemoglobin saturation of 88% or less at rest, during exertion, or during sleep should lead to the initiation of home oxygen therapy. This recommendation is extrapolated from experience with COPD.

In acute respiratory failure, oxygen therapy is the mainstay of treatment. When conventional high oxygen therapy is inadequate, a high-flow nasal cannula (HFNC) may be an alternative (Spoletini et al. 2015). Thus far, only some case series (Horio et al. 2016) and retrospective descriptive studies (Lee et al 2020) have assessed the effectiveness of HFNC with promising results (in acute respiratory failure of IPF/ILD.

2.6.2.3 Non-invasive and mechanical ventilation

The question of how and when to use ventilatory support in acute respiratory failure (ARF) of IPF or ILD remains challenging. Faverio and colleagues (2018) reviewed

the current literature concluding that non-invasive ventilation (NIV) did not seem to change the poor outcome associated with advanced stages of ILDs. Nevertheless, in selected patients with less severe ARF or reversible causes of ARF, NIV trial may be considered.

The 2011 ATS/ERS treatment guideline recommendation for mechanical ventilation is as follows: "The majority of patients with respiratory failure due to IPF should not receive mechanical ventilation, but mechanical ventilation may be a reasonable intervention in a minority" (G. Raghu et al. 2011). For example, mechanical ventilation may be appropriate as a bridge to lung transplantation. This recommendation was based on earlier studies reporting a high mortality of up to 90% among IPF patients admitted to the intensive care unit with acute respiratory failure (Mallick 2008). The more recent studies suggest improved survival rates except for those who end up in invasive mechanical ventilation for IPF exacerbation. Smith and colleagues (Smith et al. 2021) reported an overall hospital mortality rate of 43.8%. In those IPF patients who required invasive mechanical ventilation of any cause, the overall mortality rate was 56.7%. In those patients requiring IMV for IPF exacerbation, the mortality rate was 81.3%.

2.6.2.4 Pulmonary rehabilitation

A Cochrane review was recently published summarizing recent literature on pulmonary rehabilitation in ILDs (Dowman et al. 2021). Altogether 16 studies were included in the meta-analysis. A subgroup analysis for studies on idiopathic pulmonary fibrosis was executed as the disease has a worse prognosis than many other ILDs. The certainty of the evidence was low to moderate due to limitations in the studies. It was concluded that pulmonary rehabilitation can be implemented safely in people with ILD. Pulmonary rehabilitation probably improves functional exercise capacity, quality of life and mitigates dyspnea in short term. Benefits are also probable in IPF. Sustained improvements in functional exercise capacity are less certain in IPF but benefits regarding dyspnea and quality of life may sustain long term.

2.6.2.5 Palliative care

It is estimated that 50%-80% of IPF patients experience cough, usually dry or nonproductive (Guenther et al. 2018; Bargagli et al. 2019). Cough may arise from other (comorbid) conditions, such as GERD, obstructive lung disease, OSA, and upper airway cough syndrome, or it may be due to IPF itself. Wakwaya and colleagues (2021) recently summarized the current evidence for the treatment of chronic cough in IPF. First other causes should be eliminated or addressed. If the

cough continues, it may signal IPF progression. In these cases, Wakwaya et al. suggest referral to speech therapy, prescription of a neuromodulator and/or consideration of moderate to low dose prednisone for 2-3 weeks.

Few publications have reported on the pharmacological therapy of dyspnea. Low-dose oral morphine reduces dyspnea without causing respiratory depression and may be used in palliative care (Allen et al. 2005). The role of benzodiazepines is not clear.

According to a Finnish national survey (Rajala et al. 2018), health-related quality of life was reported low among IPF patients already two years before death. The most prominent declines occurred in physical function, vitality, emotional role, and social functioning. Breathlessness and fatigue were reported as the most severe symptoms.

Another study by Rajala et al. (2016) showed that most IPF patients die in a hospital with ongoing life-prolonging procedures until death. At the hospital, opioids are used frequently, which indicates an intention to relieve symptoms. Still, end-of-life decisions are made very late.

3 Aims

The purpose of this thesis was to

1. Identify reliable methodologies used in the epidemiological studies of IPF by reviewing and analyzing the literature.
2. Initiate a national IPF project by describing the demographics and the distribution of IPF cases in five university hospitals in Finland. Re-evaluate prior IPF diagnosis with a multidisciplinary team.
3. Estimate prognosis and predictive variables of survival of IPF using FinnishIPF data.
4. Describe the use of antifibrotic medications and comedications using data collected from FinnishIPF and Social Insurance Institution.

4 Materials and Methods

4.1 Systematic review (study I)

4.1.1 Data sources and search strategy

The initial literature search was conducted in September 2012 through the databases Medline and Science Citation Index with the help of an information specialist at the University of Turku, Medical Library. The search was limited to adults and peer-reviewed English publications published during 1/2001–9/2012. The following search terms were used: idiopathic pulmonary fibrosis, interstitial lung diseases, and epidemiology combined with geographical areas (Americas, Australia, Europe, Asia, and cities). The Embase database became available to the authors after the initial search in 2012. Therefore, an additional search was conducted in June 2013. Embase was searched using the same key terms as initially.

4.1.2 Study selection

The search yielded 214 original articles. The articles were pre-screened based on their titles and abstracts by two authors. 28 out of 214 articles were accepted as they contained demographic data and/or incidence, prevalence, or mortality rates of IPF. ILD studies were also accepted if they included data on IPF patients.

Four authors reviewed the 28 articles. By consensus, the following 16 articles were excluded: seven review articles and one comparative report of ILD registries, two studies identifying racial differences in IPF epidemiology (they did not contain incidence or prevalence figures), and six articles which did not contain demographic data or whose cohort size was regarded as inadequate. 12 articles were considered suitable.

The additional search on Embase resulted in 942 articles. One suitable article was published after September 2012. After the completion of the selection process, 13 epidemiological articles were accepted for the systematic review.

4.2 FinnishIPF studies (studies II-IV)

4.2.1 Study population (studies II-IV)

The FinnishIPF project was initiated in 2012. Patient recruitment has been ongoing from the beginning. Currently, the registry holds data from all 28 pulmonary clinics nationwide. The inclusion criteria have been as follows: 1) adult subjects with a confirmed diagnosis of idiopathic pulmonary fibrosis (ATS/ERS/JRS/ALAT 2011), 2) patient approval (informed consent) to use medical data from hospital records in the study. Patients participating to the study are receiving standard care. Parameters that are collected from the hospital records are listed in **Table 8**. Patient data is preserved in a secure, electronic registry database.

Table 8. Parameters that are collected to the FinnishIPF registry (if available).

IDENTIFICATION AND DEMOGAPHICAL DATA	Identification number Date of birth Height, weight, body mass index Smoking (pack years), occupation, exposures
DIAGNOSTIC BASELINE INFORMATION	Symptoms, date of onset Medication Date of diagnosis FVC (L) FVC% of predicted FEV1(L) FEV1% of predicted DLCO% of predicted DLCO/VA% predicted Chest X-ray HRCT Biopsy, bronchoalveolar lavage samples, Laboratory findings 6-minute walk test (meters) Familial or sporadic IPF
FOLLOW-UP DATA	Changes in condition Medication FVC (L) FVC% of predicted FEV1(L) FEV1% of predicted DLCO% of predicted DLCO/VA% predicted Laboratory findings HRCT 6-minute walk test (meters) Hospitalization Date of lung transplantation Date of death, cause of death

DLCO, diffusing capacity of the lungs for carbon monoxide; DLCO/VA, diffusing capacity of the lungs for carbon monoxide divided by alveolar volume; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography;

4.2.2 Methods and data analysis: study II

In study II, the study population was geographically limited to five university hospital cities. IPF patients were identified with ICD-10 codes J84.1 and J84.9 from the hospital registries. Pulmonary physician evaluated each case by reading through the hospital records. A majority of the cases with ICD-10 diagnoses J84.1 and J84.9 did not meet the criteria of idiopathic pulmonary fibrosis. Instead, other idiopathic

interstitial pneumonias such as NSIP and ILDs associated with connective tissue diseases -were seen.

All IPF patients who gave informed consent and lived during 2012 in the university hospital cities of Helsinki, Turku, Tampere, Kuopio, or Oulu were included. On average 76% of confirmed IPF patients signed informed consent document and were willing to participate in the FinnishIPF study.

All the identified IPF cases were radiologically and histologically re-evaluated. The diagnostic CT scans (N=123) were re-evaluated by two chest radiologists (senior + resident radiologist). As the study was performed in 2015, HRCT findings were categorized into three groups (ATS/ERS 2011): 1) usual interstitial pneumonia (UIP) pattern, 2) possible UIP pattern, and 3) inconsistent with UIP pattern. The available surgical lung biopsies (N=27) were re-evaluated by two experienced pathologists. Samples were categorized into four groups 1) UIP, 2) probable UIP, 3) possible UIP or 4) not UIP. ATS/ERS/JRS/ALAT diagnostic guidelines from 2011 (Raghu et al. 2011)were used in the re-evaluation.

Point prevalence at the end of December 2012 was calculated using the number of citizens with confirmed IPF as a nominator and the reported population in each university hospital city as a denominator.

Data analysis

The statistical analysis was performed by using SPSS 20.0 for Windows (SPSS™ Illinois, Chicago©). Percentages and mean values (95 % CI) were used to describe the data. The Kruskall-Wallis test and X2 test ($p < 0.05$) were used to compare the differences between the groups.

4.2.3 Methods and data analysis: study III

For study III, FinnishIPF data was limited to patients diagnosed between 2011–2015. This resulted in 453 study subjects. Altogether data was taken from 28 Finnish pulmonary clinics: five university hospitals, 15 central hospitals, and eight regional hospitals (see Table 8 Parameters collected into the FinnishIPF Registry). GAP index was calculated using the baseline parameters of gender, age, and pulmonary function. Baseline characteristics were gathered from the date of diagnosis. Use of antifibrotic treatment was analyzed based on the registry data (some data were missing). A 6-month treatment cut-off was used to categorize patients as treated or not treated with antifibrotic medicines. The date of death was obtained from the Population Register Centre at the end of April 2017, and the cause of death was collected from death certificates. Lung transplantation was considered an endpoint equal to death.

Data analysis

Data analysis was carried out with SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA). The differences in age, FVC % of predicted and DLCO % of predicted between sexes were tested with two-sample t-tests. Mean ages between smokers, ex-smokers and non-smokers were compared using a one-way ANOVA with Tukey's test in pairwise comparisons. Transplant-free survival was measured from diagnosis until death or to the date of transplantation. Survival was evaluated using the Kaplan–Meier method and differences in survival curves were evaluated using the log-rank test. The associations of variables with survival were analyzed using a univariate Cox regression analysis. The significant variables in the univariate analysis were included into a multivariate Cox regression model. GAP stage was excluded from the multivariate model due to high correlation with FVC % of predicted and DLCO % of predicted to avoid collinearity problems.

4.2.4 Methods and data analysis: study IV

For study IV, data was combined from two registries: the FinnishIPF registry and the Registry of the Social Insurance Institution (SII). SII provides reimbursements for medical expenses in Finland and holds statistics on the use of reimbursed drugs. Practically all prescription drugs are reimbursed. In Finland pirfenidone and nintedanib have been reimbursable since 1.6.2013 and 1.12.2015, respectively. The spirometric criterion for reimbursement was FVC 50%–80 % of predicted from 1.6.2013. The criterion changed on 1.11.2015 after which it has been FVC % 50%-90% of predicted at the time of application. Annually each patient pays a maximum of 592.16 € (in 2022) for the reimbursed medications and thereafter the prescribed medicines cost only 2.50 euros per purchase. For this study patients were asked for permission to use data from both registries.

Patients that consented to share both registry data (FinnishIPF and SII data) were included. Thus, inclusion criteria were: 1) confirmed IPF diagnosis and 2) consent to use both above-mentioned registries. A significant number of patients did not reply to the request to share SII registry data, thus lowering the number of participants in this study. 263 patients were included in the study.

Data on medication use consisted of the date of purchase and the number of packages of reimbursed medicines. The purchases were made from the beginning of 2011 until the end of 2018. The number of concomitant medications (other than antifibrotic) was calculated for each patient by considering all different products purchased 120 days before and after the date of diagnosis. Medication persistence was defined from the date of initiation to the date of discontinuation of the therapy (no purchases within 60 days).

For the analyses concerning therapeutic delay, the study population was limited to patients diagnosed on 1.6.2013 or after, since then antifibrotics have been available and reimbursable in Finland. Treatment delay was determined as an interval between the date of diagnosis and the date of the first purchase of antifibrotic medicine.

Data analysis

Statistical analyses were carried out using SAS for Windows version 9.4 (SAS Institute Inc., Cary, NC, USA). Continuous variables having normal distribution were summarized with mean and standard deviation (SD), and those not having a normal distribution were summarized with median and lower quartiles (Q1) and upper quartiles (Q3). Categorical variables were summarized with counts (N) and percentages. Background variables were compared between groups using a two sample t-test or Wilcoxon rank sum test and for categorical variables, Chi-Squared test or Fisher's exact test was used.

The number of concomitant medications (other than antifibrotic) was calculated for each patient by considering all different drug purchases 120 days before and after the date of diagnosis.

Univariate associations between the outcome variable "initiation of the antifibrotic medication" and study variables (gender, age, FVC %, DLCO/VA, and number of other medications) were studied using logistic regression analysis. Age and number of other medications were categorized into three categories (age 50–65, 66–75 and over 75 years and 0–1 medication, 2–4 medications and 5 or more medications), and FVC % and DLCO/VA were categorized in two categories (75 % or less and over 75 % and 55 or less and over 55, respectively). The significant variables (age, FVC %, DLCO/VA) in the univariate analysis were included in a multiple logistic regression model. In addition, a subgroup analysis was conducted using the outcome variable "the delay of initiation of antifibrotic treatment ($\leq$ 1 year vs > 1 year)" and only including patients that were diagnosed on 1.6.2013 or later. The Kaplan-Meier method was used with the cumulative discontinuation curve.

Results are presented with odds ratios (OR) together with 95% CI.

All statistical tests were performed as 2-sided, with a significance level set at 0.05.

4.3 Ethical considerations

Ethical Committees from all five university hospitals in Finland have given their positive statement for the FinnishIPF project. The National Institute of Health and Welfare has given authorization for patient screening from the hospital databases

of all Finnish hospitals. All included patients have given their written informed consent. Data are stored in a secure electronic database. Only responsible doctors and educated study nurses can access the registry with electronic identity verification.

5 Results

5.1 Systematic review (study I)

Altogether, 13 articles were accepted for the systematic review. The chosen articles were categorized into three groups according to the methodology used in the study: 1) national registry databases, 2) questionnaire-based studies, and 3) analysis of the health care system's own registry database. A summary of the articles included is presented in **Table 9**.

The two methodologically similar, national registry studies were dependent on the activity of physicians in reporting patient numbers and data. In Spain and Greece, a standardized questionnaire was sent to pulmonary centers to obtain information on patients' clinical and diagnostic data. These studies yielded the lowest prevalence and incidence numbers. The most used method was the use of pre-existing databases (hospital records, death registries), in which the highest prevalence and incidence were reported.

In only six articles (marked with an asterisk in the **Table 9**) the ATS/ERS/JRS/ALAT 2000 diagnostic criteria or classification recommendations of IIP from 2002 were used. The rest of the studies used older criteria/classifications. In three studies, the original data (radiological, histological, and clinical data) were updated according to the ATS/ERS/JRS/ALAT 2000 criteria.

The lowest prevalence was reported in the Taiwanese publication, 0.5/100 000 (Lai et al. 2012). This prevalence was calculated using the narrow case definition from 1998 with the old criteria/classification of IPF. The highest prevalence, 42.7/100 000 (broad case definition), was in the United States (G. Raghu 2006), where a large healthcare claims database was utilized. Broad case definition included age ≥18 years, one or more medical claims with a diagnosis code for IPF (ICD-9-CM 516.3, not specific for IPF). More modern case definitions and guidelines from 2000 were used in the study of Fernández Pérez et al. (2010) They reported a prevalence of 27.9/100 000 in Olmsted County, Minnesota.

By 2013 no epidemiological articles had been published on IPF using the 2011 ATS/ERS/JRS/ALAT guidelines.

Table 9. Summary of the 13 articles included in the data analysis. Modified with permission from original publication I.

TYPE OF STUDY	COUNTRY	STUDY PERIOD	PREVALENCE/100 000 INCIDENCE/100 000 MORTALITY/100 000
NATIONAL REGISTRY STUDY	Belgium/Flanders	1992–1996	Prevalence 1.25 Incidence 0.22
	Italy	1998–2005	only demographical data *
QUESTIONNAIRE BASED SURVEYS	Spain	10/2000–9/2001	Incidence 2.94*
	Greece	2004	Prevalence 3.38* Incidence 0.93*
PRE-EXISTING DATABASES	Finland	1997–1998	Prevalence 16–18*
	Norway	1984–1998	Prevalence 19.7–23.4 Incidence 4.3
	United Kingdom	1991–2003	Incidence 4.6
	United States	01/1996–12/2000	Prevalence 42.7 (broad) Prevalence 14.0 (narrow) Incidence 16.3 (broad) Incidence 6.8 (narrow)
	United States	1992–2003	Mortality 50.8
	Japan	2005	Prevalence 3.44
	United States/ Minnesota/Olmsted county	1997–2005	Prevalence 27.9 (narrow)* Prevalence 63 (broad)* Incidence 8.8 (narrow)* Incidence 17.4.(broad)*
	United Kingdom	1968–2008 (mortality) 2000–2008 (incidence)	Mortality 2.54* Indicence 7.44*
	Taiwan	1997–2007	Prevalence 0.7–6.4 (broad) Prevalence 0.5–4.9 (narrow) Incidence 0.6–1.4 (broad) Indidence 0.5–1.2 (narrow)

* ATS/ERS/JRS/ALAT 2000 diagnostic criteria or classification recommendations of IIP from 2002 were used

5.2 FinnishIPF studies (studies II-IV)

5.2.1 Study II

The search of hospital registries with ICD-10 codes J84.1 and J84.9 resulted in a heterogeneous group of different ILD diagnoses. After screening the patient files, ¼ of cases were considered as IPF.

Most IPF patients, 60.4%, were men. The mean age at diagnosis was 73.5 years. 54 % were ever-smokers. The most common symptoms were a dry cough and dyspnea. 10.6% of study subjects were asymptomatic at diagnosis. The mean delay from the onset of symptoms to the date of diagnosis was 1.9 years (range 0–16 years, SD 2.9). The mean FVC at diagnosis was 80.4 % of predicted.

Most of the baseline CT scans were dated prior to 2010, with the time being range from 2003 to 2012.

Radiological and histological re-evaluation was done by categorizing HRCT and biopsy findings as UIP, possible UIP or inconsistent with UIP (Raghu et al. 2011). Altogether, 123 HRCT scans were re-evaluated and in 23 (19%) of these cases biopsy was available.

First, 11 patients with HRCT findings that were inconsistent with UIP patterns and whose diagnosis was not confirmed by a surgical lung biopsy were dropped out of the study population. From the 11 patients who were excluded from the initial cohort due to radiological re-evaluation, eight had an HRCT pattern more typical of NSIP than UIP. One looked more like sarcoidosis and one patient who had undergone irradiation due to breast cancer was considered to have radiation-induced fibrosis. One patient had an undetermined interstitial lung disease with no exposure history found in the registry data. Radiological honeycombing was initially seen in 80 % of cases and in the re-evaluation in 76 % of cases. The presence or absence of honeycombing was not mentioned in 11 % of the initial readings despite most of these scans being read as typical UIP. The initial readings were mostly done prior to the new ATS/ERS criteria, which can explain why honeycombing was not always mentioned. Ten patients who had a radiological possible UIP pattern but were not biopsied were still included in the study, as all these patients were evaluated in a multidisciplinary meeting to have IPF.

Of the 87 patients who had radiologically typical UIP patterns, 12 had gone through surgical lung biopsy of which 10 samples were available for histopathological re-evaluation. One patient with a “not UIP pattern” in sparse lung biopsy was, however, considered to have IPF after multidisciplinary evaluation and follow-up. “Possible UIP pattern” was seen in 18 HRCT scans, and seven of these were biopsied. Six were histologically UIP and one possible UIP. Eighteen HRCT scans were classified as “inconsistent with UIP”. In this group seven lung biopsies

were performed; histopathological re-evaluation confirmed four UIP patterns, one probable UIP pattern, one possible UIP and one “not UIP”pattern. After a final multidisciplinary evaluation, only the one patient with a “not UIP” pattern in surgical lung biopsy was excluded from the cohort. Thus, after clinical, radiological and histopatological re-evaluation, 111 of 123 (90%) of patients were considered as confirmed IPF cases. This final study population was used for estimating disease prevalence in university hospital cities.

A hiatal hernia was seen in 42.3 % (47/111) of the HRCTs.

Point prevalence (31st December 2012) in the five university hospital cities was as follows: Helsinki 6.0/100 000, Turku 9.4/100 000, Tampere 9.7/100 000, Kuopio 17.0/100 000, and Oulu 8.6/100 000. The overall prevalence was 8.6/100 000.

Familial form, defined as patient reported history of two or more IPF cases in the family, was present in 6.5 % of cases.

Of the 111 confirmed IPF cases, 14 died (6 women, 8 men) before the end of the year 2012. Median survival was 44.9 months after diagnosis. IPF was the immediate cause of death in 7 (50%) cases. IPF was the underlying cause of death in 12 cases.

5.2.2 Study III

In study III, 453 patients from the FinnishIPF registry were included. 65% of the patients were men. At diagnosis, the mean age of the patients was 73.0 years. Men were a slightly younger than women (mean±SD 72.3±8.8 and 74.3±9.3 years, respectively, p=0.026). The smokers were younger at diagnosis than ex-smokers and non-smokers (63.9±9.5, 71.8±8.6 and 75.1±8.3 years, respectively, one-way ANOVA, p<0.0001).

The mean duration from the onset of symptoms to diagnosis was 575±799 days. 56% of the patients were diagnosed within a year of their first symptoms. At diagnosis, women had better FVC (83.3%±18.9% of predicted for women, 78.6%±17.7% of predicted for men; p=0.013) and a trend towards better DLCO (57.9%±16.6% of predicted for women, 54.5%±16.2% of predicted for men; t-test, p=0.063). The frequencies of comorbidities are presented in **Table 10**.

Table 10. Frequencies of comorbidities. 64 % of patients had two or more comorbidities.

Comorbidity	%
Coronary artery disease	43
Other cardiovascular diseases	60
Hypertension	38
Diabetes	38
Asthma	10
Chronic obstructive pulmonary disease	4
Sleep apnea	5

22 (5%) patients reported a family history of pulmonary fibrosis.

117 (26%) patients received antifibrotic treatment. The mean age and lung function in the treatment group were lower than those who did not receive medication and men were overrepresented in the medication group. The mean interval between diagnosis and the start of treatment was 380±416 days. 95 (21%) patients were treated with antifibrotics for >6 months, which we considered to be a significant enough period to change the progression of the disease. 82 (18%) patients received pirfenidone and 13 (3%) patients received nintedanib. The mean duration of treatment was 804±416 days.

Lung transplantation rate was 3% (13 patients).

The follow-up time was 3.2±1.4 years after diagnosis, totalling 1470 person-years. By the end of follow-up, 179 patients had died and 13 underwent a lung transplantation totalling a transplant-free survival of 58% (261 out of 453). The annualized mortality rate was 13.1%. The cause of death was known in 99% of cases. The underlying cause of death was IPF in 66% of patients. The second most common cause of death was cardiovascular disease (in 16% of patients) and the third most common cause of death was malignant tumor (in 11% of patients). 58% of cancer deaths were due to lung cancer.

The overall survival time was 4.5 years. Transplant-free survival at 1, 2, 3, 4, and 5 years was 95%, 83%, 70%, 58%, and 45%, respectively. There was no difference in survival between men and women ($p=0.795$), or between smokers, non-smokers, and ex-smokers ($p=0.167$). In addition, survival in patients who did not receive antifibrotic medication was similar in both sexes and in the different smoking groups.

81% of patients had adequate data for calculations of GAP stage (mortality prediction) at baseline. In GAP 1 stage, the median survival was not reached; in GAP 2 stage, the median survival was 4.5 years; and in GAP 3 stage, it was 2.2 years ($p<0.0001$). The patients with >6 months of antifibrotic treatment had better survival

compared with those who did not receive antifibrotic treatment (p=0.035). When comparing patients with medication to patients who fulfilled the lung function criteria for reimbursement (FVC 50–90% of predicted) but who had no antifibrotic medication (n=187), the survival difference remained in benefit of antifibrotic therapy (p=0.031).

In the Cox univariate analysis (**Table 11**), age, pulmonary function tests, GAP stage and >6 months antifibrotic use were predictors of survival. However, sex and smoking status did not predict survival. In the multivariate Cox regression analysis (**Table 11**), age, FVC % of predicted and DLCO % of predicted were independent factors for survival.

Although patients with antifibrotic medication seemed to have a better prognosis than those without, the difference was not significant after age adjustment in the multivariate Cox regression analysis.

Table 11. Univariate and multivariate cox regression for mortality. Modified with permission from original publication III.

	Univariate		**Multivariate**	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age per year	1.03 (1.01–1.05)	**0.001**	1.02 (1.00–1.04)	**0.046**
Female vs male	1.04 (0.78–1.39)	0.794		
BMI	0.98 (0.95–1.02)	0.353		
Ever-smoker vs never smoker	1.17 (0.88–1.57)	0.284		
DLCO % of predicted	0.96 (0.95–0.97)	**<0.0001**	0.97 (0.96–0.98)	**<0.0001**
FVC % of predicted	0.98 (0.97–0.99)	**<0.0001**	0.99 (0.96–0.98)	**0.006**
GAP stage	1.71 (1.24–2.36)	**0.0010**		
>6 months antifibrotic treatment	0.67 (0.44–0.98)	**0.037**	0.67 (0.43–1.05)	0.078

BMI, body mass index; CI, confidence interval; DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; GAP, gender, age, physiology; HR, hazard ratio

5.2.3 Study IV

Of the 263 patients 132 (50.2%) had started antifibrotic treatment – pirfenidone (92 patients) or nintedanib (40 patients). The baseline data of the study population (treated versus untreated) are presented in **Table. 12**.

Table 12. Baseline characteristics. Data are presented as mean±SD unless otherwise stated.

Variable	Patients with antifibrotic treatment	Patients without antifibrotic treatment	p-value
	N=132	N=131	
Age at diagnosis (years)	68.3±7.8	72.5±9.3	0.0002
50-65 years N (%)	31 (27%)	16 (13.1%)	<0.0001
66-75 years N (%)	60 (52.2%)	47 (38.5%)	
>75 years N (%)	24 (20.9%)*	59 (48.4%)	
Gender			0.21
Male N (%)	96 (72.7%)	86 (65.7%)	
Female N (%)	36 (27.3%)	45 (34.4%)	
BMI (kg/m²) median	28.0 (25.3–30.9)	27.8 (25.6–30.3)	0.65
FVC (% OF PREDICTED)	77.3±14.8	88.1±17.9	<0.001
FVC ≤75% N (%)	42 (43.3%)	27 (25%)	0.0056
FVC >75% N (%)	55 (56.7%)	81 (75%)	
DLCO/VA (% of predicted)	59.5±14.2	64.3±14.9	0.022
DLCO/VA≤55 N (%)	36(40.9%)	30(27.8%)	0.053
DLCO/VA>55	52 (59.1%)	78 (72.2%)	
Smoking at diagnosis			0.93
Never smoker N (%)	46 (36.5%)	50 (38.8%)	
Current smoker N (%)	10 (7.9%)	10(7.8%)	
Ex-smoker N (%)	70 (55.6%)	69 (53.5%)	
Number of medications at diagnosis (other than antifibrotic)	5 (1.0,9.0)	6.0 (2.0,9.0)	0.65
0-1 medications N (%)	34 (25.8%)	32 (24.4%)	0.90
2-4 medications N (%)	21 (15.9%)	19 (14.5%)	
≥5 medications N (%)	77 (58.3%)	80 (61.1%)	

BMI, body mass index; DLCO/VA diffusing capacity of carbon monoxide divided by alveolar volume; FVC, forced vital capacity

The mean treatment duration was 763 days (range 41-2004 days). 18 patients (13.6%) switched the antifibrotic in use once to another product and 1 patient switched back. Discontinuation of therapy was most common during the first year. The one-year persistence was 77.1% for pirfenidone and 78.9% nintedanib.

At diagnosis, 59.7% of patients had five or more simultaneous medications. Cardiovascular medications were the most common (21%). This also includes cholesterol-lowering medicines. 14% used medication classified as nervous system medications. This group includes painkillers, such as paracetamol and paracetamol-codeine, which is often used for cough in Finland, and sleeping pills. 14 % used alimentary tract drugs including proton pump inhibitors and medicines for constipation. Also, 14% used respiratory medicines such as bronchodilators and combination inhalers.

According to the univariate analysis younger age and lower lung capacity (FVC% and DLCO/VA %) were predictors of initiating antifibrotic medication. A tendency of treating patients under 75 years was noticed. Gender and number of concomitant medications were not statistically significant predictors. In the multiple logistic regression analysis, the only independent predictor for initiating antifibrotic use was the age at diagnosis.

For the subgroup analysis the study population was limited to patients diagnosed 1.6.2013 onwards which is when the first antifibrotic treatment became available for IPF patients. The delay from diagnosis to the initiation of the antifibrotic regimen was defined in 92 patients. The mean interval from diagnosis to the first purchase of antifibrotic medication was 367 (SD 429) days. Mean treatment duration was 633 days. Sixty-five percent of patients-initiated medication within a year. The comparison of the patient groups (treatment initiated ≤ 1 year versus > 1 year) is presented in **Table 13**.

Table 13. Comparison of patient groups: treatment initiated ≤ 1 year versus >1 year (patients diagnosed 1.6.2013 or after). Data are presented as mean±SD unless otherwise stated.

Variable	Initiation ≤ 1 y N=60	Initiation > 1y N=32	p-value
Age at diagnosis(years)	70.0±6.1	68.6±8.5	0.41
50-65 years N (%)	12 (21.1%)	7 (23.3%)	0.91
66-75 years N (%)	31 (54.4%)	15 (50.0%)	
>75 years N (%)	14 (24.6%)	8 (26.7%)	
Gender			0.15
Male N (%)	46 (76.7%)	20 (62.5%)	
Female N (%)	14 (23.3%)	12 (37.5%)	
FVC (% of predicted)	70.1±12.4	84.0±12.8	<0.001
FVC≤75% N (%)	24 (63.1%)	7 (23.3%)	0.001
FVC >75% N (%)	14 (36.8%)	23 (76.7%)	
DLCO/VA/VA (% of predicted)	55.6±14.6	60.1±12.1	0.11
DLCO/VA≤55 N (%)	18 (54.6%)	10 (35.7%)	0.20
DLCO/VA>55 N (%)	15 (45.5%)	18 (64.3%)	
Number of medications at diagnosis (other than antifibrotic) median	6.0 (3.0,9.0)	6.0 (5.0,9.0)	0.96
0-1 medication n (%)	6 (1,0%)	3 (9.4%)	0.54
2-4 medications n (%)	13 (21.7%)	4 (12.5%)	
≥5 medications n (%)	41 (68.3%)	25 (78.1%)	

DLCO/VA diffusing capacity of the lungs for carbon monoxide divided by alveolar volume; FVC, forced vital capacity

Twenty-five percent of patients whose FVC% of predicted fulfilled the reimbursement criteria did not receive antifibrotic treatment (reason not known, insufficient data).

In the univariate logistic regression analysis a significant predictor for initiating antifibrotic treatment within a year was low forced vital capacity (FVC ≤ 75% vs FVC > 75%). DLCO, age, gender or number of medications were not significant predictors. The variables age, FVC, and DLCO were selected for the multiple logistic regression analysis. The only independent factor for earlier initiation was forced vital capacity.

6 Discussion

6.1 Challenges in tracking true epidemiological data of IPF

When interpreting prior epidemiological studies, the most notable sources of uncertainty are the case definition of IPF and variation in diagnostic approaches over time. It is noteworthy, that there are only a limited number of epidemiological studies published after the guidelines were revised in 2011.

In the systematic literature review (study I) we identified and compared different study methodologies used in the epidemiological studies of IPF. To our knowledge, the study was the first of its kind – analytical rather than summarizing – in the epidemiological research field of IPF. Pre-existing databases were mostly used as a source of data offering many patients but at the expense of clinical verification of IPF diagnoses. Recently, Kaul and colleagues (2022) searched an extensive database (10 million U.S. veterans) using an ICD-based algorithm but narrowed the case definition with requirements of having a claim for chest CT or lung biopsy. Still, they acknowledged a limitation in their methodology. The study probably produced an overestimation of occurrence including some patients other than IPF.

In study II, we calculated the prevalence of IPF in Finland using modern guidelines. The overall point prevalence of IPF was estimated at 8.6/100 000 in university hospital cities on 31st December 2012. We acknowledge that this is an underestimation of the true value due to the methodology of the study. Although we have surely captured confirmed IPF cases, there are some patients outside of the study. These are patients who have the diagnosis of IPF but who have not consented to the FinnishIPF study.

Recently Salonen and colleagues (2022) published a study on the prevalence of IPF in Finland. In their study, prevalent IPF cases with ICD-code J84.1 treated in specialized care between 2016–2021 were searched for from the Finnish National Hospital Discharge Register (Hilmo). The results showed that the prevalence of IPF was significantly higher than in our study with an increasing trend from 31/100 000 in 2016 to 36/100 000 in 2021. Authors discussed that there may be non-IPF ILDs included in the material as the definition for IPF was based on ICD-10 code J84.1 (as concluded in our study). On the other hand, the authors speculated that some IPF

patients (elderly, multimorbid) treated only in primary care could not be captured as these cases are not registered in Hilmo.

As demonstrated in our study II, the screening of Finnish hospital registries with ICD-10 codes J84.1 and J84.9 resulted in a very heterogenous group of ILDs. This reveals one of the most important challenges in the epidemiology of IPF – the ICD-10 coding system is inadequate in IPF and for many other rare diseases. However, ICD-10 does contain a code for IPF, J84.112, but this three-decimal code is not generally used in clinical practice. WHO has published the ICD-11 (The Lancet 2018), which has a substantial number of improvements compared to ICD-10. Alongside other rare pulmonary diseases, IPF now has a specific ICD-11 code: CB03.04.

Study I showed varying prevalence and incidence between countries. Among other issues discussed in study I, another explanation for this variation is that globally, there are major differences in the opportunities to diagnose IPF. In developing countries, the availability of chest imaging is limited, and there are difficulties in obtaining reliable pulmonary function testing, and in providing treatment access in rural areas. (Luca Richeldi et al. 2015). Underdiagnosis and under-reporting on death certificates may be behind the lower incidence and mortality rates in developing countries (Rivera-Ortega and Molina-Molina 2019). Thus, when comparing data collected from different registries, caution should be used given the differences in the patient populations enrolled and the methodologies used to collect and categorize the data.

6.2 Real-world data on IPF

6.2.1 Diagnosis

To assess the diagnostic accuracy of IPF in Finnish university hospitals, prior diagnoses were retrospectively re-evaluated according to 2011 guidelines (study II). After a multidisciplinary discussion, 12 out of 123 of the diagnoses were changed. Radiological and histopathological re-evaluations dropped out 9% and 1% of cases, respectively. Considering that many of the original diagnoses were done before the ATS/ERS 2011 guidelines were used, the diagnostic accuracy in university hospitals can be considered good. However, the results indicate that the differential diagnosis with other interstitial fibrotic diseases is occasionally very challenging and therefore the role of multidisciplinary teams cannot be over-emphasized.

Based on well-preserved lung function (study II) and baseline GAP stage (study III), IPF is diagnosed early in Finland. A narrow majority (54.1%) of patients in study III were regarded as GAP 1 at diagnosis. Yet, there is a room for improvement. As the symptoms of pulmonary fibrotic diseases are nonspecific, a diagnostic delay

in referral from primary care to tertiary centers is common (Cordier and Cottin 2013). According to study II, the mean delay from symptoms to diagnosis was 1.9 years. Early diagnosis is crucial as the delay has been associated with poorer survival (Hoyer et al. 2022), especially now that potentially effective treatments are available. According to a recent study by Hoyer et al. (2019), male sex, older age, and treatment attempts for alternative diagnoses were risk factors for delayed diagnosis of IPF.

6.2.2 The use of antifibrotics and their effect on prognosis

Both pirfenidone and nintedanib were approved for use based on the slowed decline in FVC at RCTs. The use of FVC as an efficacy measure has been both supported and criticized in the past (Ganesh Raghu et al. 2012) and the threshold for a clinically meaningful decline in FVC has been uncertain. Previous studies (Reichmann et al. 2015; Paterniti et al. 2017) have suggested that decline in FVC is a poor predictor of future decline in FVC but a powerful predictor of mortality in patients with IPF (surrogate for death). In the INPULSIS trials, which tested nintedanib on IPF patients and their open-label extension, INPULSIS-ON, Richeldi and colleagues (2019) explored the impact of FVC decline on subsequent FVC declilne and mortality. Conclusions were that FVC decline over 24 weeks did not predict FVC decline between weeks 24 and 52. FVC decline ≥10% predicted over 24 weeks was associated with mortality at week 52. The authors concluded that these data do not support ending the use of nintedanib based solely on FVC decline.

RWD have shown that the use of antifibrotic drugs is associated with prolonged survival (Helen E. Jo et al. 2017; Guenther et al. 2018; Zurkova et al. 2019; Behr et al. 2020; W. A. Wuyts et al. 2019). Supporting this, survival in the FinnishIPF cohort was longer in patients with antifibrotic therapy than in those without. In mortality analysis, age and pulmonary function were independent predictors of survival. Antifibrotic treatment did not quite reach statistical significance in predicting mortality.

During the long study period, the use of antifibrotics has become more common in Finland. In study III (period 2011–2015), 26% of patients were antifibrotic users and in study IV (period 2011–2018) 50% of patients had initiated antifibrotics. Still, the other half of the patients remained untreated with antifibrotics. Maher and colleagues (Maher and Strek 2019; Maher et al. 2017) have studied the reasons for reluctance to initiate antifibrotic treatment. Possible obstacles were diagnostic uncertainty, stable or mild disease, reimbursement/availability issues and worry about the adverse effects and interactions of antifibrotics. The results from another survey (Maher et al. 2018) suggested that physicians with less experience in diagnosing and managing IPF as well as a lack of confidence in the efficacy of

antifibrotic treatments (particularly for patients with a less-advanced disease), might contribute to lower IPF treatment rates.

Study IV indicated that younger age was the most important patient-related clinical predictor for initiating antifibrotic drugs. This finding is supported by other RWD (Pesonen et al. 2018; Salisbury et al. 2020; Holtze et al. 2020). Moreover, lower FVC predicted earlier initiation. Currently, the reimbursement limit in Finland (FVC 50–90%) restricts early initiation of this expensive medication as physicians must wait for the FVC to decline below 90% of predicted. In advanced stages (FVC below 50%), antifibrotic cannot be initiated at all. However, post hoc analyses have demonstrated clinically relevant benefits in advanced stages of IPF as well (Nathan et al. 2019; Michael Kreuter, Wuyts, et al. 2020).

According to study III, the transplant-free survival at five years was 45%, which was better than previously thought. This may be explained by the exclusion of the most advanced cases which had no time to be included in the registry. Moreover, improved diagnostic processes and treatment may have had an influence on earlier diagnosis and better survival. On the other hand, the delay between diagnosis and treatment initiation was still quite long, and thus with timely diagnosis and treatment, the prognosis could be improved in the future.

For comparison, **Table 14** summarizes data from Swedish IPF registry (SIPFR) and the FinnishIPF registry. Results from SIPFR may be considered suitable for comparison as Sweden shares similarities in healthcare and geography. In the Swedish cohort, 64% of patients were using antifibrotics (Gao et al. 2021). Currently, the prognosis of IPF patients seems somewhat similar in both countries.

Table 14. Comparison of Swedish and Finnish registry data. Data are presented as mean±SD unless otherwise stated. Based on the references Gao et al 2021 and Kaunisto et al. 2019

Variable	Swedish IPF registry	FinnishIPF
Patients (n)	662	453
Age (years)	72.7 (7.5)	73.5 (9.0)
Male (%)	74.0	65.1
BMI (kg/m^2)	27.0 (4.1)	28.4 (5.2)
Ever-smoker (%)	64.8	66.7
FVC % of predicted	72.7 (17.1)	80.2 (18.0)
DLCO % of predicted	48.4 (14.7)	55.6 (16.5)
GAP stage 1 (%)	40.9	54.1
The cumulative rate of death (%) 1 year 2 year 3 year 4 year 5 year	 7 16 30 39 48	 5 17 30 42 55

BMI, body mass index; DLCO, diffusing capacity of the lungs for carbon monoxide; GAP, gender, age, physiology

6.3 Strengths and limitations

The FinnishIPF project has provided an extensive amount of real-world data on IPF patients from 28 pulmonary clinics across Finland. During the long study project, valuable clinical data from over 900 IPF patients have been collected, which is a large sample size considering the rarity of the disease. One of the major advantages of the FinnishIPF study (like in other similar studies) is the long follow-up time, which has enabled the assessment of disease course, survival, and continuation of treatment. In Finland, all permanent residents are entitled to public health care (regardless of their financial situation). Therefore, the FinnishIPF study is unique, as data is not skewed by socioeconomic grounds.

For ethical reasons, we have only included patients who have given informed consent ruling out some of the patients who were unwilling or unable to participate. It is likely that the patients with the most rapid progression and worst prognosis could not be reached due to the study design. Moreover, despite the high quality of health care in Finland, there surely still are some (elderly, multimorbid) patients in primary care, which are not recognized as having this rare fibrotic pulmonary disease.

We acknowledge that there is a substantial amount of missing data for some variables, which complicates the analysis and interpretation of longitudinal analyses. We tried to consider this with statistical techniques and in the design of studies.

In study II, the FinnishIPF cohort was limited to university hospitals where the quality of diagnosis is the highest in Finland. Therefore, results may not reflect the situation in smaller hospitals with fewer patients.

FinnishIPF was not designed to compare the treatment effect (study III). The results should interpreted cautiously due to differences in the compared groups (size and characteristics), non-randomization, and other undetected confounders.

In study III, the updated Finnish reference values for spirometry were used (Kainu et al. 2016). As the old reference values were derived from a selective occupational group in the 1980s (Viljanen et al. 1982) with only extrapolated reference values for adults over 65 years, there was a need for an update. It is acknowledged that in the Finnish population, the predicted lung volumes are higher than those obtained by the 2012 Global Lung Function Initiative predictions for the Caucasian subgroup for FVC. Therefore, lung function test results are not fully comparable with other national registries using other reference values.

In study IV the antifibrotic medication use was objectively evaluated with data from the SII registry, which offers the most reliable data source for drug purchases in Finland. Whether patients have taken their purchased medicines, could not be assessed within the framework of this study.

6.4 Future

There is a continuing need for real-world data on IPF and other progressive fibrosing ILDs (PF-ILD) in the future. Despite, frequent RWD studies being conducted in past years, the epidemiology of different ILDs is still not well defined. As IPF is the prototype of all PF-ILDs, the results of this dissertation may be used for comparison with future RWD studies on PF-ILDs.

Currently, nintedanib is also indicated for the treatment of systemic sclerosis-associated interstitial lung disease and for chronic fibrosing interstitial lung diseases with a progressive phenotype. Moreover, there are studies investigating the safety and efficacy of pirfenidone for PF-ILD (Behr et al. 2021) and in rheumatoid arthritis-associated ILD (Solomon et al. 2022). There is a need for RWD studies on the management and healthcare utilization of PF-ILDs as the use of antifibrotics is increasing.

No doubt, the implementation of data collection in clinical practice is changing as new information technology tools are emerging. In recent years, home monitoring and home spirometry have been increasingly studied among ILD patients. Studies in IPF have shown that home spirometry is highly feasible and predicts disease

progression (Russell et al. 2016). Home monitoring is shown to improve psychological well-being and enable individually tailored treatment decisions (Moor et al. 2020).

Different genetic and molecular biomarkers are under evaluation in clinical trials. In the future, we may identify at-risk individuals or use biomarkers to predict treatment response in IPF and in other PF-ILDs.

IPF has been reported to cause large economic and health burdens (M. Kreuter et al. 2019; V. Navaratnam et al. 2013; Lassenius et al. 2020). Future therapies should aim to palliate symptoms and improve the quality of life of patients. In the long term, the goal is to discover novel ways to stabilize disease progression and to eventually find a cure.

7 Conclusions

1. Different methodologies for executing epidemiological research in the field of IPF are identified, but none are without limitations. The comparative analysis of different study types has formed a basis for later studies investigating the prevalence and incidence of IPF.
2. To execute accurate epidemiological research using large databases (e.g., hospital registries), the data should be validated by revising the diagnoses. Multidisciplinary discussion improves diagnosis according to real-world data.
3. In the FinnishIPF cohort, the overall survival was 4.5 years. Independent predictors of survival were age and pulmonary function. Patients treated with antifibrotics had a better prognosis, but this was explained by younger age.
4. Antifibrotics were initiated for every second IPF patient in Finland. Age at diagnosis was the most important predictor for initiating the medication. Drug discontinuation was most frequent during the first year of therapy. Polypharmacy was common among IPF patients which reflects the multimorbidity of these patients.

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