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CLINICAL CHARACTERISTICS OF PROGRESSIVE PULMONARY FIBROSIS IN PATIENTS WITH AUTOIMMUNE ASSOCIATED ILD

PhD thesis

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LIST OF ABBREVIATIONS

6MWT	6-minute walk test
ABG	Arterial blood gas test
AE	Acute exacerbation
ANA	Antinuclear antibody
ATS	American Thoracic Society
AZA	Azathioprine
BAL	Bronchoalveolar lavage
BID	Twice daily
BMI	Body mass index
CI	Confidence interval
CS	Corticosteroid
CTD	Connective tissue diseases
CTD-ILD	Connective tissue disease-associated interstitial lung disease
CYC	Cyclophosphamide
dcSSc	Diffuse cutaneous systemic sclerosis
DL_{CO}	Diffusing capacity of the lungs for carbon monoxide
DM	Dermatomyositis
DMARD	Disease-modifying antirheumatic drug
ECM	Extracellular matrix
EMPIRE	European Multipartner IPF Registry
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
GAP	Gender-Age-Physiology
GERD	Gastro-esophageal reflux disease
GGO	Ground-glass opacity
HP	Hypersensitive pneumonitis
HRCT	High-resolution computed tomography
IIM	Idiopathic inflammatory myopathy
IIP	Idiopathic interstitial pneumonia

ILD	Interstitial lung disease
INBUILD	Efficacy and Safety of Nintedanib in Patients With PF-ILD trial
INPULSIS	Safety and Efficacy of Nintedanib at High Dose in IPF Patients trial
IPAF	Interstitial pneumonia with autoimmune features
IPF	Idiopathic pulmonary fibrosis
ISU	Immunosuppressive
JAK	Janus kinase
KLco	Transfer coefficient of the lung for carbon monoxide
lcSSc	Limited cutaneous SScsystemic sclerosis
LTOT	Long-term oxygen therapy
MA-ILD	Myositis-associated interstitial lung disease
MCTD	Mixed connective tissue disease
MDD	Multidisciplinary discussion
MMF	Mycophenolate mofetil
MTX	Methotrexate
NSIP	Non-specific interstitial pneumonia
OP	Organizing pneumonia
OR	Odds ratio
OSA	Obstructive sleep apnea
PDGF	Platelet-derived growth factor
PF-ILD	Progressive fibrosing interstitial lung disease
PFT	Pulmonary function test
PH	Pulmonary hypertension
PM	Polymyositis
PPF	Progressive pulmonary fibrosis
pSS	Primary Sjögren’s syndrome
pUIP	Probable usual interstitial pneumonia
QoL	Quality of life
RA	Rheumatoid arthritis
RA-ILD	Rheumatoid arthritis-associated interstitial lung disease
RTX	Rituximab
SENSCIS	Safety and Efficacy of Nintedanib in Systemic Sclerosis trial

SLB	Surgical lung biopsy
SLE	Systemic lupus erythematosus
SLE-ILD	Systemic Lupus Erythematosus-related interstitial lung disease
SLS	Scleroderma Lung Study
SS	Sjögren's syndrome
SSc	Systemic sclerosis
SSc-ILD	Systemic sclerosis-associated interstitial lung disease
sSS	Secondary Sjögren's syndrome
TBLC	Transbronchial lung cryobiopsy
TGF-β1	Transforming growth factor beta -β1
TID	Three times a day
TLC	Total lung capacity
TNF-α	Tumor necrosis factor alpha
UIP	Usual interstitial pneumonia

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1. INTRODUCTION

Interstitial lung disease (ILD) describes a group of conditions consisting of over 200 subtypes, each sharing the common characteristic of irreversible fibrotic scarring of the lung parenchyma (1). The most common subtype of fibrosing ILDs is idiopathic pulmonary fibrosis (IPF), which is a chronic progressive ILD with poor survival of a median of ~3 years (2, 3). ILDs with autoimmune features, including connective tissue disease-associated (CTD)-ILDs and interstitial pneumonia with autoimmune features (IPAF) show varying rates of progression. In case of disease progression in non-IPF ILDs, the characteristics of the disease course are like the untreated IPF patients, such as respiratory symptoms' worsening, lung function loss and early mortality (4). Furthermore, progressive ILDs have a significant impact on patients' quality of life (QoL) and represent a socioeconomic burden on the healthcare systems (5). There is an emerging need to raise the awareness among treating physicians in order to detect the progression and highlight the requirement for standardized diagnosis and treatment guidelines. Early identification of progression is of utmost importance even with patients with preserved lung function to decrease lung function decline and improve the outcome through the introduction of targeted antifibrotic agents.

1.1. Interstitial lung diseases (ILDs)

1.1.1. Definition and classification

ILD is a heterogeneous group of diseases including more than 200 different non-neoplastic disorders (1). Common characteristics of ILDs are lung parenchyma destruction caused by varying patterns of inflammation and fibrosis, and consequently impaired alveolar gas diffusion (6). The different etiologies are accompanied with specific clinical, radiological, and histopathological features. The current guideline of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) classifies ILDs into the following 4 main categories: ILDs of known association, granulomatous ILDs, idiopathic interstitial pneumonias (IIPs), and miscellaneous ILDs (6, 7).

The subgroup of ILDs with known cause includes CTD associated ILDs, occupational exposures, or side effect of certain drugs or irradiation. The most frequent autoimmune conditions responsible for CTD-ILDs are rheumatoid arthritis (RA), systemic sclerosis (SSc), and idiopathic inflammatory myopathies (IIMs) as dermatomyositis (DM) and polymyositis (PM) (8). Environmental exposure to inhaled irritants or lung toxic fumes, such as mold, bird, domestic animal, and livestock allergens; metal (e.g., brass, lead, steel); wood (pine); vegetable dust; and stone polishing materials are significant risk factors for the development of occupational ILDs, including hypersensitive pneumonitis (HP) (9). Furthermore, several widely used drugs - bleomycin (a chemotherapeutic drug), nitrofurantoin (an antimicrobial agent) and amiodarone (an antiarrhythmic drug) – have a significant lung toxic effect and thus can lead to drug-induced ILD (10, 11). It is important to note, that methotrexate (MTX) is no longer considered as a profibrotic agent in CTDs (12).

IIPs are divided into major, rare, and unclassifiable subgroups. Major IIPs consist of chronic fibrosing [IPF and idiopathic non-specific interstitial pneumonia (NSIP)], smoking-related (respiratory bronchiolitis–interstitial lung disease and desquamative interstitial pneumonia), and acute/subacute (cryptogenic organizing pneumonia and acute interstitial pneumonia) groups. Rare IIPs include idiopathic lymphoid interstitial pneumonia and idiopathic pleuroparenchymal fibroelastosis (7).

The group of granulomatous ILDs primarily includes sarcoidosis – a multi-systemic condition with 20% risk of lung involvement -, and HP with similar clinical, radiological, histological characteristics to IPF and NSIP (7, 13).

Other forms without any specific ILD definition are lymphangioleiomyomatosis and pulmonary Langerhans cell histiocytosis (6). The classification of the major ILD subtypes is summarized in Figure 1. IPAF is considered as a research entity and defined as an underlying ILD associated with an undifferentiated CTD (14).

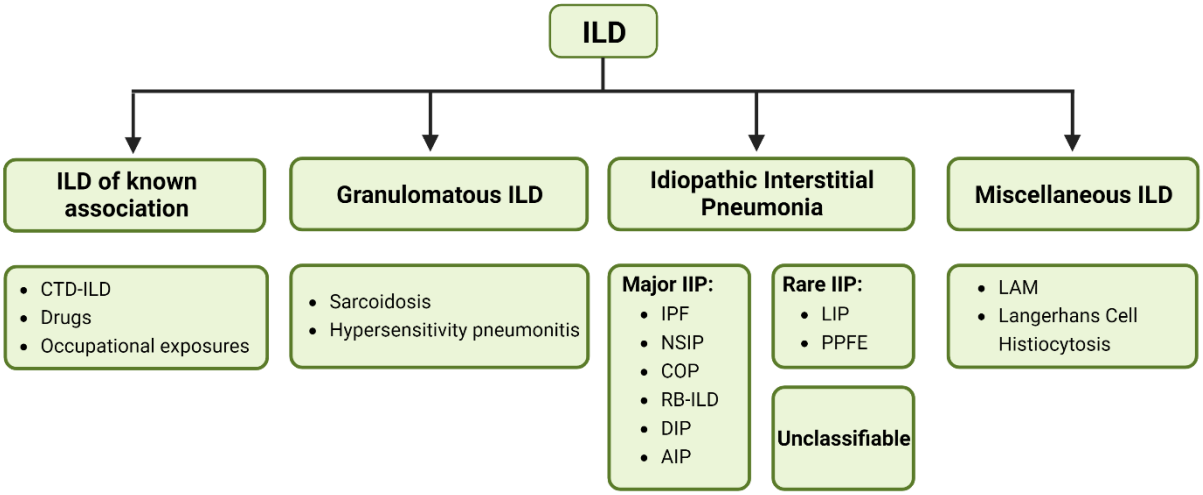

Figure 1. International classification of ILDs. Abbreviations: AIP, acute interstitial pneumonitis; COP, cryptogenic organizing pneumonia; CTD-ILD, connective tissue disease-associated interstitial lung disease; DIP, desquamative interstitial pneumonia; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LAM, lymphangioleiomyomatosis; LIP, lymphocytic interstitial pneumonia; NSIP, non-specific interstitial pneumonia; PPFE, pleuroparenchymal fibroelastosis; RB-ILD, respiratory bronchiolitis-interstitial lung disease. This figure was created with biorender.com and modified from source (6, 7).

1.1.2. Epidemiology

ILDs are rare diseases with a total prevalence of 98/100.000 and an incidence of 19/100.000 per year. According to a French multi-center study, the three most common forms of ILDs by prevalence are sarcoidosis (30/100.000), CTD-ILDs (12/100.000), and IPF (8/100.000); however, in the literature prevalence shows geographic heterogeneity (15, 16). Although, the distribution and epidemiology of ILD cases from the Eastern European countries are scarce, a considerable part of the available data were provided by our ILD center (17). Despite the heterogeneous nature of different ILDs, sex related differences can have a pivotal impact on the prevalence, susceptibility and even disease severity (18). During the neonatal period and early childhood, sex hormones play an important regulating role in lung maturation (19). As an example, a significant difference was found in the surfactant production and alveolar surface area growth between male and female neonatal lung development (20). Moreover, estrogens may have a stimulative effect on autoimmunity, while androgens have a protective effect (21). Additionally, sex

hormones have been associated with differing responses to lung injury (22, 23). Female predominance is characteristic for CTD- ILDs with the highest ratio of SSc, RA, systemic lupus erythematosus (SLE), Sjögren's syndrome (SS) and for IPAF (24, 25). In contrast to autoimmune-associated ILDs, a male predominance is detected in IPF, and male sex is considered a risk factor for the disease development and progression (26, 27).

1.1.3. Clinical characteristics

Despite the heterogeneity of ILD subgroups and etiologies, shared pathophysiological features including structural remodeling and architectural changes of the lung parenchyma contribute to the common, but non-specific clinical symptoms, including exertional dyspnea with or without chronic dry cough (2).

Breathlessness in ILDs is one of the most important limiting factors, that significantly deteriorates the patients' QoL and associates with a decreased general functional status, thus might lead to depression (28). Exertional dyspnea and reduced exercise tolerance are commonly observed introductory symptoms from an early stage, while in a more advanced condition shortness of breath remains constant even at rest (29). These symptoms have a complex pathophysiological background including altered respiratory mechanics due to reduced lung compliance and decreased alveolar gas diffusion as a consequence of the thickened alveolocapillary membranes. Additionally, the hypoxic pulmonary vasoconstriction and microvasculature destruction result in cardiovascular abnormalities, such as pulmonary hypertension (PH) and right heart failure. Because of the above-mentioned factors, the peripheral muscle (e.g., quadriceps) strength also declines, which further affects the physical performance negatively (30). Dyspnea in patients with fibrotic ILDs can cause the frightening experience of breathlessness and can provoke anxiety (31, 32). Chronic cough is a frequent symptom with a substantial effect on the physical and psychosocial status, thus impairing the QoL (33). Although, the exact pathophysiology of the cough is not well-established yet, various factors might be responsible (34). Structural changes and traction forces to the lung parenchyma might lead to diminished inhibitory nerves and result in cough reflex hypersensitivity due to the upregulation in sensory nerve fibers (35). Transpulmonary pressure changes during coughing are most pronounced in the peripheral and basilar lung areas, therefore it may have a role in fibroproliferative progression through the

mechanical injuries and the stretch activated transforming growth factor beta 1 (TGF-β1) (36-38). The evaluation of cough is challenging given that either the underlying ILD, or the comorbid conditions, such as gastro-esophageal reflux disease (GERD) can be the cause (39). Moreover, chronic cough can also aggravate comorbidities, which may worsen the cough. There is a well-established complex connection between cough and GERD, obstructive sleep apnea (OSA) and IPF (35). As an example, traction of the fibrotic lung can weaken the lower esophageal sphincter and leads to GERD associated with microaspiration thus contributing to the ILD pathogenesis/worsening (35). Chronic cough is associated with chest pain and sleep disturbances, adding more problems to social, work, and daily activities (33, 40). Other nonspecific symptoms of ILDs are fatigue and weight loss. Physical and mental fatigue are characterized by reduced physical performance and the subjective sensation of tiredness or lack of energy (41). Fatigue is a significantly limiting symptom regarding social interactions and work capacity (42). Additionally, weight loss is a strong prognostic factor for poor outcome (43). In advanced disease stages finger clubbing due to chronic hypoxia can be observed (44, 45).

Besides the negative impact of ILDs on patients' QoL, the significant economic burden should be taken into consideration (46). Comorbidities have their cost-driving factors, while productivity loss at workplace contributes to the socioeconomic effect (47, 48).

1.1.4. Comorbidities

Common and significant comorbidities associated to ILDs are summarized in Table 1.

Table 1. Most common ILD associated comorbidities.

Acute and chronic infections
GERD
Pulmonary hypertension
Cardiac disease
Pulmonary embolism
Lung cancer
OSA
Depression

Abbreviations: GERD, gastro-esophageal reflux disease; ILD, interstitial lung disease; OSA, obstructive sleep apnea. Modified from source (49).

Acute exacerbations (AEs) of ILDs are responsible for a high mortality, especially in IPF patients. They are characterized by an acute clinical worsening with a new bilateral ground-glass opacity (GGO) superposed on the underlying CT pattern when cardiac failure is excluded (50). Although the exact pathophysiology is unknown, infections might be important triggers (51). Additionally, the risk of acute and chronic lower airway infections including *Mycobacterium spp.* and *Aspergillus spp.* is high in the CTD-ILD population, often due to the immunosuppressive (ISU) treatment and lung colonization (52).

GERD is a frequent comorbidity in ILDs and is bi-directionally related to them. Microaspiration of gastric acid damages the lung parenchyma through chemical irritation and chronic inflammation, while intrathoracic pressure changes due to chronic cough can contribute to the development of GERD (53). Accordingly, SSc-ILD patients' high-resolution computed tomography (HRCT) scan verified an increased esophageal diameter, which was associated with more severe ILD and pulmonary symptoms (54).

Cardiovascular comorbidities are commonly associated with ILDs. Firstly, PH is frequently observed in ILDs, which is caused by various mechanisms affecting the large and small vessels, including hypoxic pulmonary vasoconstriction and pulmonary vascular bed destruction mainly as a result of fibrotic scarring. It consequently leads to a reduced diffusing capacity of the lungs for carbon monoxide (DL_{CO}) and a decreased exercise tolerance in 6-minute walk test (6MWT) with rapid desaturation and dyspnea (55). According to the international guideline, PH by definition is an abnormal pulmonary vascular resistance elevation as mean pulmonary arterial pressure >20 mmHg at rest. Group 3 PH is caused by lung diseases – as obstructive, and restrictive pulmonary conditions including ILDs – and/or hypoxia (56, 57). Additionally, the procoagulant features of IPF and CTDs propose an increased risk for venous thromboembolic disease and pulmonary embolism (58-60). Other factors that can be responsible for cardiovascular diseases include elevated pulmonary vascular resistance in PH, smoking, and cardiomyopathy due to cardiac involvement in SSc (61-63). Pulmonary malignancies are also comorbidities of ILDs: lung carcinogenesis is promoted by the fibrotic scarring and different genetic factors (64, 65). OSA is predominantly associated with IPF, and in ILD

patients OSA and hypoxemia increased the risk of disease-related mortality (66, 67). Anxiety and depression strongly affect ILD patients, especially with the concomitant dyspnea and cough, that strongly deteriorate the patients' QoL (32).

Moreover, the treatment of comorbid conditions may have enormous costs as a result, increases the economic burden of ILDs (68). Therefore, prevention, early detection and adequate treatment of the comorbid conditions are of utmost importance even with the understanding of their role in disease progression (69). Management of comorbidities is as important as the ILD-specific treatment considering the outcome (70).

1.1.5. Nature of ILDs

The disease course of fibrosing ILDs varies greatly, thus it is challenging to predict progression especially in early stages. The crude prevalence of progression in non-IPF ILDs is approximately 70/100 000 (46). According to Hambly *et al.*, disease progression was detected in a total of 50% of the study population, while among them 59% had IPF, and 45% had CTD-ILD (3).

According to the ATS/ERS guideline, the progressive non-IPF ILDs should be referred to as "progressive pulmonary fibrosis" (PPF) instead of the previously used term of "progressive fibrosing ILD" (PF-ILD), due to the parenchymal dimension of progression (4, 71). IPF is a benchmark disease of fibrosing ILDs with an irreversible progression regarding lung function decline, exercise intolerance, respiratory failure, and poor outcome (44). Similar to IPF, the clinical characteristics of PPF include worsening of respiratory symptoms, loss of lung function and early mortality (4, 71).

It is of high importance that clinicians pay a close attention to the clinical symptoms and can therefore recognize the signs of early disease progression. The clinical symptoms have a substantial impact on the QoL and are essential in the diagnosis and progression detection.

1.1.6. Diagnosis

The heterogeneity of the ILDs requires an accurate diagnosis according to medical history, clinical signs, and symptoms with radiological and/or histological patterns, as treatment modalities can be different based on the underlying disease (72). It is of utmost

importance to differentiate any known underlying cause such as CTDs or drug related ILD. If the cause remains potentially unknown, then that refers to IPF (9).

Firstly, a thorough exploration of the recent or previous medications and pertinent environmental exposures should be carried out, including the typical recreational/avocational, residential, and occupational exposures (73). Symptoms and physical findings can refer to lung involvement. For instance, patients with definitive CTD and chronic non-specific pulmonary symptoms such as cough or exertional dyspnea should raise the suspicion on having lung involvement related to ILD (74). Additionally, in advanced stages velcro-like crackles on chest auscultation primarily heard in the basal regions are often observed in ILDs (75).

The main diagnostic workup includes pulmonary function tests (PFTs) and HRCT scan. PFTs (spirometry and body plethysmography) are baseline functional measurements to establish the diagnosis, as well as for staging and monitoring of ILDs (76-78). Forced vital capacity (FVC) and DL_{CO} are pivotal parameters in the detection of progression and/or control of treatment efficacy (71, 79). Imaging with inspiratory and expiratory HRCT scan is the cornerstone of ILD diagnosis. HRCT scan is the most specific tool to establish lung parenchymal changes, such as inflammation and architectural deterioration along with the lung volume loss (9, 80).

Even from the early stages of a developing ILD, it is possible to detect specific HRCT patterns. The two dominant HRCT patterns include probable (p) or definite usual interstitial pneumonia (UIP) and NSIP, while other patterns like organizing pneumonia (OP) are less frequently seen (Table 2.) (9, 14, 81). The UIP pattern consists of predominantly subpleural and basal lung involvement with the distinguishing feature of honeycombing, which may be accompanied with peripheral traction bronchiectasis or bronchiolectasis (9). Honeycombing is characterized by cystic airspaces in a cluster with thick, well-defined walls (1-3 mm) and an average diameter of 3–10 mm (82, 83). Traction bronchiectasis/ bronchiolectasis manifests as an irreversible dilatation of the bronchial/bronchiolar wall resulting in an airway distortion and varicosity - this often presents around distorted architectural areas of the lung parenchyma (84). Coexisting traction bronchiectasis and bronchiolectasis are regarded as important indicators of severity and prognosis in ILDs (85). GGO is defined as an increased attenuation of the lung tissue with preserved bronchial and vascular margins (86). NSIP pattern includes

GGO with the characteristic features of symmetrical and bilateral lung involvement with basal predominance (7, 87). Typical imaging features of the fibrotic NSIP pattern subtype are the reticular opacities, bronchovascular bundle thickening and traction bronchiectasis (88). There are potential overlap features on HRCT; therefore, the differentiation between NSIP and UIP is crucial (89). Notably, the NSIP pattern carries a better prognosis than the UIP pattern (7). In case of radiological uncertainty, a lung biopsy may be necessary to differentiate the two patterns (90).

Table 2. Most common HRCT patterns in fibrosing ILDs.

HRCT pattern	Characteristic features
UIP	Subpleural and basal predominance (often heterogeneous distribution) Honeycombing ± traction bronchiectasis/bronchiolectasis on the periphery
pUIP	Subpleural and basal predominance (often heterogeneous distribution) Reticular pattern associated with peripheral traction bronchiectasis/ bronchiolectasis Variably mild GGO
NSIP	Subpleural, basal, and symmetrical distribution on the periphery GGO Lower lobe volume loss

Abbreviations: GGO, ground-glass opacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; pUIP, probable usual interstitial pneumonia; UIP, usual interstitial pneumonia. Modified from source (9, 91).

In the case of indeterminate HRCT patterns, invasive diagnostic approaches including bronchoscopy can be performed according to the advice of the multidisciplinary discussion (MDD). Bronchoscopy is an important diagnostic tool for cellular analysis of bronchoalveolar lavage (BAL) fluid or transbronchial lung cryobiopsy (TBLC) for histopathologic testing. Surgical lung biopsy (SLB) should only be performed following thorough consideration, due to the procedure's high-risk potential for the development of AE (71). As an important diagnostic modality, laboratory analysis of autoantibodies or disease specific biomarkers play a differentiating role in suspected underlying autoimmune conditions (92-95).

Other baseline and follow-up assessment tools include diagnostic modalities to monitor the cardiorespiratory system, such as: arterial blood gas (ABG) test, 6MWT and

echocardiography or right heart catheterization (96). With ABGs pO_2 and pCO_2 levels and the metabolic status can be assessed (96). 6MWT is a physiological test mainly used in chronic lung diseases and PH to measure exercise tolerance, to evaluate prognosis and treatment efficacy (97). Regarding the prevalence of OSA as well as the burden subjected by it on the ILD population, early detection of OSA is significant as it allows for early treatment initiation (98). Specific diagnostic tools should be used depending on the clinical course and the individual needs of the patients (96). The main baseline, follow-up and occasional investigations are summarized in Table 3.

Table 3. Interstitial lung disease diagnostic work-up.

Baseline and follow-up	**According to MDD or clinical status**
PFTs	BAL ± TBLC
HRCT scan	Echocardiogram/right heart
CTD serology (autoantibodies)	catheterization
ABG	Overnight sleep study-polysomnography
6MWT	(SLB)

Abbreviations: 6MWT, 6-minute walk test; ABG, arterial blood gas test; BAL, bronchoalveolar lavage; CTD, connective tissue disease; MDD, multidisciplinary discussion; HRCT, high-resolution computed tomography; PFTs, pulmonary function tests; SLB, surgical lung biopsy; TBLC, transbronchial lung cryobiopsy. Modified from source (71, 96, 99).

According to the ATS/ERS guideline, MDD is considered as the gold standard diagnostic tool for the evaluation of ILD (7, 9). MDD members are specialists from the fields of pulmonology, radiology, pathology and immunology/ rheumatology (100). Patients can benefit from introducing rheumatologists into the MDD, which can improve the diagnostic accuracy and adequate therapy administration (101, 102). Patient evaluation with PFTs (FVC and DL_{CO}) and 6MWT should be carried out every 3–6 months or more often if clinically indicated, in order to detect disease progression (96). The optimal time interval of chest HRCT scans in terms of efficiency is 12–24 months from baseline in functionally stable SSc-ILD patients; however, they can be performed more frequently considering lung cancer risk and clinical signs of AE (96, 103). Although, the optimal time interval between follow-up HRCT scans in progressive non-IPF ILD patients is under discussion, the detection of clinical worsening and the presence of progression predictors can indicate the need for closer patient monitoring (104). If an

increased risk of mortality is verified, evaluation for lung transplantation even at the time of diagnosis or during the follow-ups is indicated according to lung transplantation guidelines (96, 105).

Each ILD case requires a multidisciplinary approach in order to provide a patient centered approach, have better diagnostic and follow-up outcomes and help to improve the therapeutic decision-making (106).

1.1.7. Management

Treatment options for different ILDs can be divided into pharmacological and non-pharmacological therapeutic modalities (71). Pharmacological treatment includes antifibrotic agents (nintedanib and pirfenidone) and conventional ISU drugs. Antifibrotics are indicated for IPF and show effective properties in patients with progressive non-IPF ILDs (107). First-line treatment for ILDs with autoimmune characteristics such as CTD-ILD, IPAF is ISU (108). In this section the common non-pharmacological treatment modalities, including oxygen supplementation and pulmonary rehabilitation, are described in detail. For the best outcome both therapeutic possibilities should be included (71).

Hypoxemia is a key physiological result of the deteriorated gas exchange in ILDs (109). Oxygen supplementation as long-term oxygen therapy (LTOT) is part of ILD treatment for resting hypoxemia and is associated with improvement of symptoms (96, 110). Interestingly, ILD patients have different expectations and experiences with oxygen therapy in terms of dyspnea; however, a beneficial effect was only associated with non–dyspnea-related physical parameters - for example levels of energy and activity - not the dyspnea itself (111). Ambulatory oxygen supplementation showed an improved QoL including better exercise duration, decline in desaturation, and improvement subjective symptoms (112, 113).

Pulmonary rehabilitation plays a crucial role in the management of ILDs and includes a wide spectrum of modalities, such as aerobic performance, strength and flexibility training, patient education, nutritional counselling, and psychosocial support (96). Palliative care aims to improve the symptoms through patient and caregiver education, early intervention, and management of symptoms for an improved or maintained QoL (114). During ILD care, discussing the patients' values and preferences

are extremely important in order to choose the appropriate action for symptom relief (96). Lung transplantation remains the only definitive therapy for non-responder patients and is regarded as a salvage treatment for selected and advanced ILD cases (71). Globally, the most common lung transplantation indication is ILD, predominantly IPF (115-117). Advanced RA, SSc and DM/PM are the most frequent CTD-ILD causes; however, there is insufficient information about this population, including the post-transplant outcomes and complications, as CTDs are often a contraindication for lung transplantation (118, 119). Additionally, the treatment of the associated comorbid conditions, including pulmonary and extrapulmonary diseases, is essential in order to achieve better outcomes (120).

1.2. Idiopathic pulmonary fibrosis (IPF)

1.2.1. Epidemiology

IPF is a rare chronic progressive ILD with the incidence of 3–9/100000 and the overall prevalence of 8/100.000 person per year in Europe (15, 121). However, both the incidence and prevalence show great variability worldwide, and the incidence is still increasing (122, 123). Male predominance is detected with the median age of 65 years at the time of diagnosis. Male sex is associated with a genetic susceptibility due to the telomerase activity, worse lung function parameters and a higher risk of comorbidities when compared to female IPF patients (18, 124). Although, the diagnosis of IPF under 50 years is rare, familial forms or underlying other conditions might be suspected (125).

1.2.2. EMPIRE registry

European Multipartner IPF Registry (EMPIRE) is a non-interventional, multinational registry collecting data of IPF patients from 11 Central and Eastern European countries including Hungary. Primary outcome of EMPIRE is to estimate IPF incidence, prevalence, and mortality in Central and Eastern Europe, while secondary outcome is to describe basic characteristics as age, gender, risk factors of patients with IPF. Hungarian participants have included more than 300 IPF patients among which 201 patients are from the Department of Pulmonology, Semmelweis University. The EMPIRE

registry is currently the largest IPF database in Europe with the purpose of providing valuable information in order to describe the outcome as well as to assess the efficacy and safety of current therapies and provide new potential data for clinical trials (126).

1.2.3. Pathophysiology

IPF is considered a prototype of chronic fibrosing ILDs. According to recent studies, the complex pathophysiological process includes genetic susceptibility and repetitive environmental or endogenous alveolar epithelial microinjuries with the key step of abnormally activated alveolar epithelial cells (2). In IPF alveolar type II epithelial cells lose their function as alveolar stem cells and their role in tissue regeneration and repair mechanisms (127, 128). The increased secretion and activation of profibrotic growth factors - including TGF-β1, platelet-derived growth factor (PDGF) and cytokines - initiate fibroblast activation and a dysregulated epithelial-fibroblast communication (37, 129, 130). Activation and recruitment of myofibroblasts leads to the accumulation of altered extracellular matrix (ECM) in the lung interstitium (131). The process of remodeling impairs the pulmonary architecture and reduces gas exchange. Additionally, the altered ECM components promote a self-sustaining fibrosis (2, 132). With a more accurate understanding of IPF's pathomechanism, new therapeutic targets and opportunities for drug development may be provided (133).

1.2.4. Diagnostic criteria

According to the official ATS/ERS guideline, the diagnosis of IPF is the result of the exclusion of ILDs with known etiology. Firstly, with the presence of IPF suspicious clinical symptoms and PFT parameters, it is essential to exclude other possible known causes (domestic and occupational environmental exposures, drug toxicity). Additionally, autoimmune serology is important to exclude any underlying CTDs and imaging with HRCT can also help in the diagnostic work-up. Any UIP pattern is diagnostic to IPF; however, in case of other specific HRCT patterns, lung tissue sampling is required for the diagnosis. After the result of the diagnostic work-up, IPF is evaluated and diagnosed by MDD (9). "Indeterminate for UIP pattern" describes the combination of a predominant subpleural and basal involvement with a slight reticulation and mild GGO or distortion ("early UIP pattern") (71). Although, imaging uncertainties may call for the histological

evaluation of TBLC or SLB, IPF patients should be assessed carefully due to the coexisting comorbidities and the increased risk of intra-, peri-, or postoperative complications. Cellular analysis of BAL fluid can also help in the differentiating process of IPF and other ILDs, considering the percentage of neutrophils, macrophages, lymphocytes, eosinophils, and the CD4/CD8 ratio (71).

1.2.5. Management

After establishing the diagnosis of IPF by MDD, the treatment includes pharmacological and non-pharmacological therapy, as well as comorbidity management and symptom control (134). First-line pharmacological treatment is antifibrotic therapy with nintedanib and pirfenidone (Figure 2.) (96).

Nintedanib is an intracellular multiple tyrosine kinase inhibitor targeting profibrotic receptors including vascular endothelial growth factor, fibroblast growth factor, and PDGF (135). In the Safety and Efficacy of Nintedanib at High Dose in IPF Patients (INPULSIS) trial treatment efficacy was emphasized by the reduced annual rate of lung function decline in FVC, less AEs, and the preservation of QoL (136). Suggested oral administration is 150 mg nintedanib twice daily (BID), which can be reduced to 100mg BID in the presence of adverse events (137). Adverse events are characterized mainly by gastrointestinal disorders including predominantly mild to moderate diarrhea and nausea, vomiting, decreased appetite, and weight loss. Other adverse events include: nasopharyngitis, bronchitis and upper respiratory tract infections. Hepatic side effects may also occur: elevation of liver enzyme levels of either aspartate aminotransferase or alanine aminotransferase, or both, have been observed (138). Pirfenidone is another approved antifibrotic agent and has complex anti-inflammatory and antifibrotic properties, where the antifibrotic effect is probably mediated through TGF-β and tumor necrosis factor alpha (TNF-α) antagonism (96, 139). Pirfenidone is tapered up, and maintenance dosage is 801 mg three times a day (TID) if tolerated (140). In clinical trials pirfenidone reduced the lung function decline (defined by FVC) and additionally, progression-free survival also improved as compared to the placebo group (141). Gastrointestinal and skin-related adverse events were the most frequent, with mild to moderate severity. Nausea and diarrhea were the most common gastrointestinal adverse effects; however, skin rash was also a frequent event. Liver aminotransferase elevation

was found in a small proportion of patients. Adverse events did not cause premature treatment discontinuation (142).

AEs in IPF are associated with a poor prognosis and high mortality (50). Long-term corticosteroid (CS) therapy is not recommended in IPF considering the increased morbidity; however, AEs are still treated with systemic CS even with a weak recommendation and no clear evidence to support its effectiveness (143).

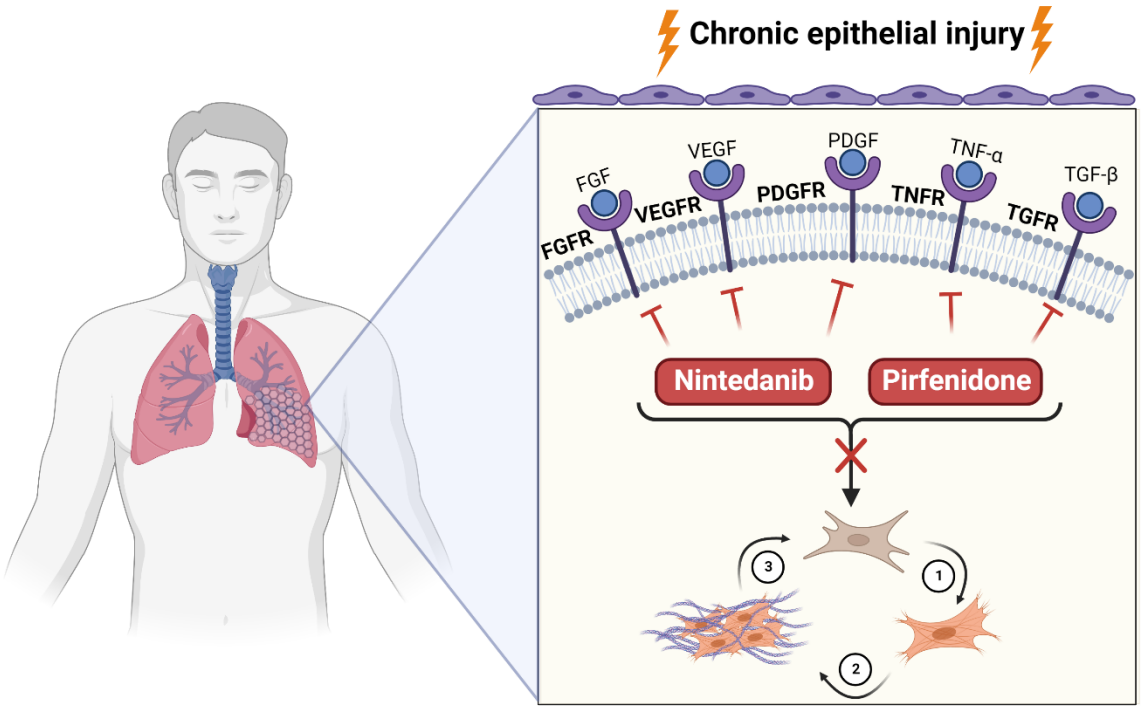

Figure 2. Antifibrotic agents' mechanism of action in ILDs. (1.) The self-sustaining fibrosis includes fibroblast activation and transformation into myofibroblasts; (2.) increased extracellular matrix deposition leading to irreversible fibrosis and (3.) further fibroblast activation as a fibrotic response. Abbreviations: FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; TGF-β, transforming growth factor beta; TGFR, transforming growth factor receptor; TNF-α, tumor necrosis factor alpha; TNFR, tumor necrosis factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. This figure was created with biorender.com and based on (139).

1.3. Autoimmune associated ILDs

Each CTD has its unique clinical features; however, immune-mediated organ damage, such as the extent of the lung involvement, varies among CTD subtypes (71). The three most frequent autoimmune conditions responsible for CTD-ILDs are SSc, RA and IIMs (DM/PM), while other subtypes are less frequently associated with ILD (108). Among the several organ involvements, ILD is one of the leading causes of morbidity and mortality (144). Although ILDs are usually diagnosed simultaneously with CTDs or thereafter, previous manifestation can also be verified (145). The clinical course of the disease regarding progression shows great variability depending on the specific disease (4).

1.3.1. Pathophysiology

The exact pathophysiology is still unknown; however, underlying autoimmune mechanisms with different cytokines play an important role in this complex process. In general, CTDs are characterized by an immune dysregulation with the production of autoantibodies, thus leading to a systemic chronic inflammation affecting different organs. Some etiologic factors of CTD-ILD share similar features when compared to IPF, including the genetic and environmental risk factors; however, immunological, and initiating triggers, including the autoimmune processes, can vary (146). The innate and adaptive immune systems - specifically B cells - both play a pivotal role in the immunopathogenesis of CTD-ILDs (147). As an example, chronic lung microinjuries in SSc-ILD patients are caused by immune complexes and vascular injuries in addition to circulating endothelial cells and endothelin-1 expression (148). IPF and SSc-ILD share the common feature of activation of macrophages with a similar chemokine expression and T-cell profiles, although B-cell profiles and T-cell chemokine profiles are different (149). The common pathway of fibrosing ILDs includes the classical steps of fibroblast migration, epithelial–mesenchymal transition, the production of TGF-β and other cytokines, chemokines. Finally, myofibroblasts contribute to the increased ECM production with interstitial remodeling and architectural changes, as described above in the IPF section (150).

1.3.2. Management

Choosing the adequate treatment for CTD-ILD patients is challenging, due to the underlying autoimmune conditions and simultaneous ILDs requiring personalized treatment (108). Management of different CTD-ILDs calls for a multidisciplinary approach; MDD's pulmonologist and rheumatologist specialists are required to collaborate to decide upon the optimal therapy (9, 100). In order to facilitate early treatment interventions, regular monitoring of progression is essential, despite the application of conventional ISU therapy, disease progression can still occur (151).

According to rheumatology guidelines, first-line therapy of autoimmune conditions includes conventional ISU agents - such as CS, cyclophosphamide (CYC), mycophenolate mofetil (MMF), azathioprine (AZA) and MTX -, the use of which is aimed at reducing inflammatory processes (108). Systemic CSs have potent anti-inflammatory and immunomodulating properties in CTD-ILD patients; however, the most beneficial effect is achieved when combined with other ISU drugs (152). Although, CYC is a strong drug with an alkylating mechanism leading to a lymphocyte cell death; its use is limited due to its toxic properties (153). The pro-drug MMF inhibits lymphocyte functions with the cytostatic effect of the mycophenolic acid (154). Comparing CYC and MMF in the Scleroderma Lung Study (SLS) II trial, MMF had better tolerability and less toxicity in patients with progressive SSc-ILD (155). Furthermore, AZA has non-selective immunomodulating effects on lymphocytes by inhibiting the purine synthesis and DNA replication (156). Although, early AZA intolerability is common, administration to CTD-ILD patients in turn was associated with good drug tolerability (157). The biologic agent rituximab (RTX) targets the CD20 antigen, thereby depleting B lymphocytes, RTX is frequently administered in CTD-ILDs, along with tocilizumab, which, on the other hand, inhibits the interleukin-6 receptor (158). Disease-modifying antirheumatic drugs (DMARDs) are therapeutic agents for inflammatory arthritides, such as RA (159). MTX is an antimetabolite - enzymatic inhibitor of folic acid metabolism - interfering with DNA synthesis by cell division, and protein production, thus inhibiting lymphocyte proliferation and pro-inflammatory cells like T cells, macrophages, endothelial cells and fibroblast-like synoviocytes in RA (160, 161). The biological DMARD abatacept is a selective T-cell co-stimulation modulator, which thereby inhibits T-cell activation (159). TNF-α inhibitors (e.g., infliximab, adalimumab) block cytokine induced cell death and

inflammation in RA (162, 163). Calcineurin inhibitors, such as tacrolimus, are enzyme inhibitors, which block T-cell functions, and are mainly used in transplantation (164). Janus kinase (JAK) enzyme inhibitors (tofacitinib) interfere with the cytoplasmic non-receptor tyrosine kinases, thus inhibiting signal transduction and decreasing the inflammatory processes (165). Antifibrotics nintedanib and pirfenidone have promising results in CTD-ILDs and are described in detail above.

Despite the available treatment guidelines for CTD subgroups, more trials are needed to reveal the optimal therapies for different CTD-ILD subtypes, including those with progressive phenotypes.

1.3.3. Systemic sclerosis-associated interstitial lung disease (SSc-ILD)

Immune dysfunction, vasculopathy and cellular inflammation lead to skin and internal organs fibrosis in SSc patients (166). The extent of the skin sclerosis differentiates the two major subtypes: the diffuse cutaneous (dc)SSc form with skin involvement being proximal to the elbows, at times also involving the trunk; whereas, in the limited cutaneous (lc)SSc form, it is restricted to the hands, forearms, feet and face (167). The major causes of SSc-associated mortality are ILD and PH (168). The most frequent pulmonary involvement on HRCT is ILD, with the prevalence of 63% (169). Although, NSIP is the dominant pattern, a small proportion of patients presents with the UIP pattern (80). Within the SSc population, the dcSSc subtype and Scl-70-, Ro52 antibody positivity increase the risk of ILD development (170, 171). Patients with dcSSc have a higher risk of developing ILD as compared to lcSSc; however, the lack of pulmonary symptoms does not exclude ILD (166). Risk factors for disease progression are low baseline FVC and DL_{CO}, fibrotic score, as well as the extent of fibrosis on HRCT (172-174). Other factors, such as: advanced age, male sex, increased esophageal diameter or GERD as well as desaturation after 6MWT may predict a progressive disease course (175-177). Recently, ILD focused therapies include different ISU agents, tocilizumab and nintedanib (168). According to SSc-ILD clinical trials, first-line treatment includes conventional ISU drugs including CYC and MMF, as both drugs led to a decrease in lung function deterioration as well as in the extent of pulmonary fibrosis seen on HRCT, while an improvement was observed with dyspnea. In the SLS II trial, MMF had more beneficial long-term effects when compared to CYC, due to having fewer toxic adverse

events and overall, a better tolerability (155, 178). Another treatment option is tocilizumab, a potential biological agent, which may have a stabilizing effect on lung function in early SSc-ILD (179). In the Safety and Efficacy of Nintedanib in SSc (SENSCIS) trial, the antifibrotic agent nintedanib reduced the annual rate of lung function decline regarding FVC (180).

1.3.4. Rheumatoid arthritis-associated interstitial lung disease (RA-ILD)

RA is characterized by an autoimmune-mediated polyarthritis with progressive bone destruction and deformation of joints; however, extra-articular manifestations are frequent as well (181). Several parts of the respiratory system can be affected; however, one of the most common extra-articular manifestations is ILD, in addition to being the leading cause of death in the RA population (182). At an early-stage, lung involvement seen on HRCT scans was found in around 60% of RA patients, but only up to 10% had a significant ILD (183, 184). The two most frequent RA-ILD associated HRCT patterns are UIP and NSIP (185). Predictors of ILD development include male sex, advanced age, smoking and anti-cyclic citrullinated peptide positivity (186). Despite the female predominance of RA, RA-ILD is detected more frequently in males (187). The extent of fibrosis seen on HRCT scans, the UIP pattern (as opposed to NSIP), as well as low baseline FVC and DL_{CO} are associated with a high risk for progression (188, 189). A well-established treatment strategy is still needed in RA-ILD patients; however, an effective baseline therapy can be achieved with MTX and other DMARDs, newer biologics and ISU agents (182). Recently, first-line treatment of RA has been MTX as a DMARD, which is administered to suppress autoimmune and inflammatory processes (190). Recent findings have proved that the use of MTX is not a pro-fibrotic risk factor; however, in contrast, evidence shows that it can delay ILD development in RA patients (12, 191). ISU therapy – such as: CS, CYC and MMF – showed efficacy in ILDs. MMF and CYC can have a beneficial effect in RA-ILD patients (as seen in SSc-ILD patients), due to having an improving or stabilizing effect on lung function parameters. However, unfortunately, the toxicity of CYC makes its use limited (192, 193). Other DMARDs and biologic agents show efficacy in the therapy of RA; although, the usage in RA-ILD is still not well-established and patients are at risk of potential drug-induced lung toxicity (182, 194). The use of TNF-α inhibitors is controversial due to their simultaneous profibrotic and

antifibrotic properties (182). Abatacept or RTX, on the other hand, were proved to have a promising effect on RA-ILD, and therefore, may be considered first-line amongst biologic treatment options (195). JAK inhibitors, such as baricitinib and tofacitinib, can be administered safely as well (196). Amongst antifibrotic agents, nintedanib showed promising effects in progressive RA-ILDs, furthermore, the efficacy and tolerability of pirfenidone is recently being studied (4, 197).

1.3.5. Myositis-associated interstitial lung disease (MA-ILD)

Myositis-associated (MA-)ILDs among the heterogeneous group of IIMs are most commonly DM and PM, with the characteristics of a progressive proximal muscle weakness due to muscle inflammation (198). ILD is a frequent extra-muscular organ manifestation and an important prognostic marker for poor outcome as compared to patients without ILD (199). Among patients with DM/PM, MA-ILD was found to be present in up to 48% of the study population (200). The NSIP pattern predominates over UIP and OP (201). Predictors of progression are older age, clinical amyopathic DM, and low baseline PFT parameters (202). The presence of DM with anti-melanoma differentiation-associated gene 5 antibody and antisynthetase syndrome have a higher risk for developing rapidly progressive ILD with a poor prognosis (203, 204). Baseline treatment includes CS, antimetabolic drugs (AZA, MMF, MTX), CYC, calcineurin inhibitors (tacrolimus), and the biologic RTX (205). Notably, clinical, and serological subtypes might have a different response to treatment (206). ISU therapy includes CS mainly combined with agents such as MMF or AZA (207). After the initiation of MMF, AZA and CYC an improvement was found in lung function parameters (192, 208, 209). While tacrolimus showed beneficial effects in non-responder patients to conventional treatment (210). In addition to RTX improving FVC and DL_{CO} values, MA-ILDs responded better to it, as compared to other CTD-ILDs (211). JAK inhibitor tofacitinib improved survival in a high-risk patient group (212). The Efficacy and Safety of Nintedanib in Patients With PF-ILD (INBUILD) trial revealed the beneficial effect of nintedanib in the progressive CTD-ILD population including MA-ILD; however, more studies are needed to support this finding (79).

1.3.6. Other autoimmune associated ILDs

Besides the three most frequent CTDs subtypes, the following systemic autoimmune diseases can present with ILDs as well, although less frequently.

1.1.1.1. Sjögren's syndrome (SS)

SS is characterized by the lymphocytic infiltration of exocrine glands, mainly the lacrimal and salivary glands (213). In the diagnosis of primary (p)SS other CTDs are excluded; however, secondary (s)SS is associated with other CTDs and organ involvements (214). Approximately 10–15% of SS patients develop ILD, which is seen more frequently with pSS patients. On the other hand, a more severe manifestation can be observed in sSS-ILD patients, due to the other potentially coexisting CTDs (8, 215). HRCT findings in pSS patients show heterogeneity with a predominant NSIP pattern or less frequently UIP or OP (216). Increased age or disease duration, anti-Ro/SS-A and anti-Ro52 antibody positivity have a higher tendency for developing ILD, while, on the other hand, the risk of disease progression in ILD patients is increased by the UIP pattern and the extent of reticular abnormality (217-219). Combined therapy of SS-ILD patients primarily includes CS with MMF and CYC to stabilize or improve PFTs (192, 220).

1.1.1.2. Systemic lupus erythematosus (SLE)

SLE has heterogenous clinical characteristics affecting multiple organ systems (221). Despite the various pleuropulmonary complications of SLE, ILD presents only among smaller proportion of patients in approximately 1-2%. However, in case of overlapping with SS or SSc the prevalence is higher (222, 223). Diffuse alveolar hemorrhage is a life treating complication (224). NSIP is the predominant HRCT pattern in SLE-ILD (225). Older age, male sex, and longer disease course are considered as risk factors for ILD development (223, 226, 227). The international management guideline for SLE patients recommends hydroxychloroquine, CS and different ISU treatment depending on the disease severity (228). First-line treatment of SLE-ILD is CS alone or combined with MMF or intravenous CYC, additionally, maintenance AZA or MMF are effective in the treatment of most patients (225, 229).

1.1.1.3. Mixed connective tissue disease (MCTD)

Mixed connective tissue disease (MCTD) is an autoimmune condition associated with overlap features of CTDs such as SLE, SSc, myositis, with the presence of the U1-ribonucleoprotein antibody (230). Lung involvement was found in 52% of the MCTD patients; however, only 35% was diagnosed as ILD with the predominant HRCT pattern NSIP (231, 232). Advanced age at the diagnosis, and the presence of dysphagia, Raynaud's phenomenon, and anti-Smith antibodies are regarded as risk factors for ILD development (233). Although, treatment data of randomized controlled trials in MCTD-ILD patients is lacking, ISU therapy can be beneficial, similarly to other CTD-ILDs (234). First-line treatment of ILD is CS combined with steroid sparing agents, such as MTX, CYC, AZA, MMF, or intravenous CYC in severe ILD cases (235).

1.4. Interstitial pneumonia with autoimmune features (IPAF)

According to ATS/ERS, IPAF is considered as a research condition in order to analyze this special patient group with both interstitial lung involvement and autoimmune characteristics. The diagnostic guideline includes domains with a combination of clinical, serological, and morphological features without meeting the criteria of any CTD. Classification criteria of IPAF is based on the HRCT and/or biopsy verified ILD with the exclusion of alternative etiologies and the absence of definite diagnosis of any CTDs; and the presence of at least two of the three diagnostic domains (14, 236). The most common domains are Raynaud's phenomenon clinically, positive antinuclear antibodies (ANA) serologically and morphologically the predominant radiological and histological NSIP pattern (237). After the diagnosis of IPAF, 50% of the patients developed functional progression during the observational period of 16 months. The presence of UIP pattern and ANA was associated with a progressive disease course (238). Due to its undetermined clinical nature, there are uncertainties about the treatment of IPAF patients. Conventional ISU therapy may be effective, while combinative CS and MMF showed effective properties regarding disease progression (239). Antifibrotic agents proved to have beneficial effect on IPAF patients according to two clinical trials (79, 240). Management

includes conservative ILD treatment with pulmonary rehabilitation, LTOT and in symptomatic GERD, reflux therapy (241).

Different ILD subtypes including CTD-ILD, IPF and IPAF - as being the focus of our research in this PhD thesis - is presented in Figure 3.

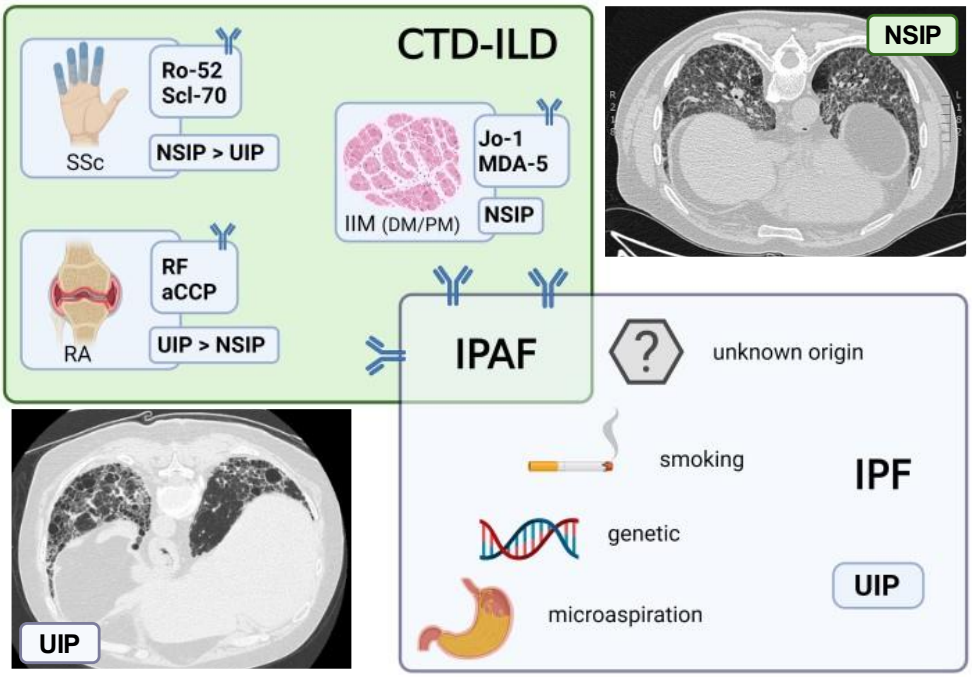

Figure 3. Overview of IPF and autoimmune associated ILDs (CTD-ILD, IPAF). Disease specific features including HRCT patterns, ILD associated autoantibodies and other factors are noted. Abbreviations: CTD-ILD, connective tissue disease-associated interstitial lung disease; NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; IPAF, interstitial pneumonia with autoimmune features; RNP, ribonucleoprotein; RF, rheumatoid factor; aCCP, anti-cyclic citrullinated peptide; MDA-5, melanoma differentiation-associated gene-5. This figure was created with biorender.com and is based on (108, 242).

1.5.Progressive pulmonary fibrosis (PPF)

1.5.1. Definition

PPF, by definition, is the presence of at least two of the three diagnostic criteria: worsening symptoms, radiological, and physiological progression – seen within 1 year and without any alternative explanation in non-IPF ILD patients with radiologically verified lung fibrosis (71).

1.5.2. Epidemiology

As of now, the incidence and prevalence of PPF has not yet been well-established, due to the unique differences regarding the clinical course of the heterogenous groups of the non-IPF ILD population (151). Disease progression was detected in non-IPF ILD patients with a total of 14-27% using the INBUILD criteria (243, 244). A large population investigation detected disease progression in 50% of the study population during a follow-up period of 16 months, more precisely 59% in IPF and 45% in CTD-ILD patients (3).

1.5.3. Diagnostic criteria

Initial diagnostic work-up to establish an accurate diagnosis includes pulmonary symptoms, PFTs and HRCT scans (71). Detailed diagnostic criteria of PPF according to the ATS/ERS guideline are summarized in Table 4.

Table 4. Diagnostic criteria of PPF. Non-IPF ILD patients – with radiologically verified lung fibrosis – presenting with two of the three diagnostic criteria regarding clinical symptoms, PFT and HRCT scans within 1 year with no alternative origin, are defined as PPF.

Criteria of PPF	
Worsening of pulmonary symptoms	Dyspnea Cough
Physiological progression of PFTs (either parameter)	Absolute annual decline in FVC ≥5% of predicted value Absolute annual decline in DL_{CO} ≥10% of predicted value
Radiological progression (one or more)	Increased extent or severity of traction bronchiectasis and bronchiolectasis New ground-glass opacity with traction bronchiectasis New fine reticulation Increased extent or increased coarseness of reticular abnormality New or increased honeycombing Increased lobar volume loss

Abbreviations: DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PFT, pulmonary function test; PPF, progressive pulmonary fibrosis. Modified from source (71).

1.5.4. Monitoring and follow-up

Besides the clinical symptom evaluation, PFTs (FVC, DL_{CO}) and HRCT are key diagnostic tools for disease progression monitoring. The diagnosis of PPF cannot be uniformly applied to all diseases since it varies depending on the specific conditions, and therefore, a personalized approach is recommended (151). The suggested frequency of PFTs including FVC and DL_{CO} is at the minimum of 3-4 months after ILD diagnosis in the first year (96, 245). HRCT scans' frequency should be based on the patient's clinical condition and lung function deterioration; thus, these scans may differ from patient to patient. For most cases, annually repeated imaging is adequate (or even less frequently with a clinically stable or improving condition); however, in some instances more frequent HRCTs are necessary (245). Progression of fibrosis presumed by the deterioration of clinical symptoms and/or PFTs parameters indicate a follow-up HRCT scan (71). It is recommended to discuss additional follow-up investigations, such as echocardiography or 6MWT in each case to assess any potential complications or comorbidities (96). Early detection of progressive cases is of utmost importance because progression can develop even in the population with physiologic lung function parameters (246).

1.5.5. Factors for progression

In non-IPF ILDs different diseases and the variable clinical course makes it difficult to predict individual risk of progression, even with a prognostic scoring systems like Gender-Age-Physiology (GAP) index used in IPF (151). Independent factors of advanced age, male sex, GERD, and baseline lower FVC and DL_{CO} parameters were associated with disease progression in the non-IPF ILD population (3). At baseline, the presence of UIP and/or the traction bronchiectasis' severity on HRCT scan is associated with an increased possibility of progression (151). According to HRCT findings, honeycombing and traction bronchiectasis can lead to a worse prognosis, while the greater extent of lung fibrosis is associated with higher mortality (104). Other risk factor may be post-exercise desaturation at 6MWT, while interestingly, increased body mass index (BMI) is protective against functional progression as compared to normal weight individuals (247-249).

1.5.6. Management

To this day, standard management of PPF is still not available and its establishment is much required. Prior to any treatment initiation, the accurate diagnosis is of utmost importance, and it should be customized on a case-by-case and disease-by-disease basis. Both efficacy and adverse events should be taken into consideration (151).

Conventional ISU therapy is the first-line treatment in many non-IPF ILDs, such as CTD-ILD; however, considering the adverse events of the long-term usage of CSs, other long-term ISU treatments can be administered instead, due to their safer profile (250). Although, the supporting evidence is not extensive, combined antifibrotic and ISU treatment can be effective and tolerable - such as, combined nintedanib and MMF in SSc-ILD patients. However, antifibrotics were found to be sufficient alone, without ISU agents to decrease progression (251). Nintedanib and pirfenidone are seen as equally potent agents in reducing progression and preserving lung function in IPF, in addition, nintedanib has proven efficacy in PPF as well (252-255). In the INBUILD trial, the administered nintedanib decreased the risk of progression in progressive non-IPF ILD patients by reducing the annual FVC decline as compared to the placebo group (79). Pirfenidone may have a promising role in the treatment of PPF by reducing FVC and DL_{CO} decline; however, more clinical research is required to analyze the safety and efficacy of pirfenidone (256). Regular laboratory monitoring should be done in patients on antifibrotic and ISU therapy, depending on the individual clinical context (151). Furthermore, patients can benefit from LTOT and pulmonary rehabilitation; however, early referral to lung transplantation is of utmost importance (110, 118, 151, 257).

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2. OBJECTIVES

In non-IPF ILD patients, PPF shows similar characteristics to IPF, often with rapid lung function decline, worsening of respiratory symptoms and increased mortality. Early detection of functional progression is the key to timely introduce targeted therapies, even in patients with an apparently subtle physiologic change that does not exceed the normal range.

Our aim was to analyze the special population of ILDs with autoimmune features. The publications that are described in detail are our own studies - *Autoimmune Progressive Fibrosing Interstitial Lung Disease: Predictors of Fast Decline* (CTD-ILD Study) (17) and *Clinical Predictors of Lung-Function Decline in Systemic-Sclerosis-Associated Interstitial Lung Disease Patients with Normal Spirometry* (SSc-ILD Study) (246). Primary objectives of my PhD thesis were the following:

1. To describe patient characteristics, clinical symptoms of SSc-ILD patients, and the functional status of *CTD-ILD* and *SSc-ILD Study* subjects.

2. To evaluate HRCT patterns of CTD-ILD and SSc-ILD patients.

3. To investigate the prevalence of functional progression of PPF domain in the Hungarian SSc-ILD populations.

4. To detect possible predictive factors of functional progression in SSc-ILD patients.

5. To analyze applied therapies in the CTD-ILD and SSc-ILD patients. Evaluate the effect of baseline ISU therapy, and the administration of targeted antifibrotic agents.

6. To evaluate adverse events of the applied antifibrotic treatment in the autoimmune associated ILDs in the *CTD-ILD Study*.

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3. METHODS

3.1. Study design

This PhD thesis includes retrospective longitudinal observational studies of predefined CTD-ILD and SSc-ILD patients. The diagnosis of ILD was established based on HRCT scans, PFTs and/or clinical symptoms by MDD at the Department of Pulmonology, Semmelweis University, Budapest, Hungary. Members of the MDD included pulmonology-, rheumatology-, radiology-, and pathology specialists (9). The diagnosis of underlying CTD subtypes were established by rheumatologists according to the current internationally accepted criteria of the American College of Rheumatology/European League Against Rheumatism Collaborative Initiative (198, 221, 258-263). Patient selection for CTD-ILD and SSc-ILD studies is summarized in Figure 4.

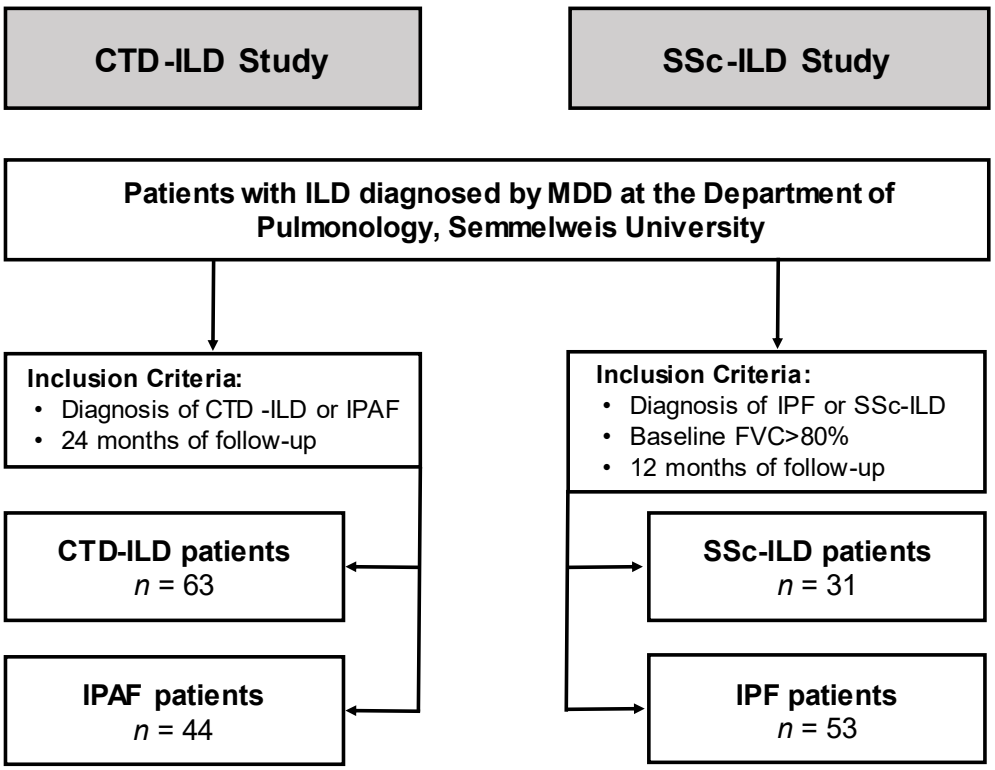

Figure 4. Study population of the PhD thesis. Abbreviations: CTD-ILD, connective tissue disease-associated interstitial lung disease; FVC, forced vital capacity; ILD, interstitial lung

disease; IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis; MDD, multidisciplinary discussion; SSc-ILD, systemic-sclerosis-associated interstitial lung disease. This figure was created based on our publications (17, 246).

The two studies of this PhD thesis were conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committees of RKEB and Semmelweis University (Study No. 69/2015—24 February 2015; 181/2021—23 November 2021).

3.1.1. CTD-ILD Study

Each enrolled subject was diagnosed between January 2017 and June 2019 with the inclusion criteria of having at least 24 months of follow-up after the verification of ILD by the MDD. The two subgroups of ILDs with autoimmune features that we included were CTD-ILD and IPAF, to retrieve real-life data of this special population. Subgroups of CTD-ILD - according to clinical and serologic criteria -, were RA, SSc, SLE, vasculitis, IIM (PM, DM), and other [MCTD and undifferentiated CTD] (198, 221, 258-263). Specific analyzed autoantibodies were described in detail in our publication (17). The diagnosis of IPAF was established based on the 2015 ATS/ERS criteria, including clinical-, serological-, and morphological domains without the diagnosis of CTD-ILD (14). Progressive cases in this study were defined as PF-ILD with the criteria of either a relative annual decline of FVC ≥5 % predicted and/or worsening of clinical symptoms or progression of the fibrosis on HRCT (264).

3.1.2. SSc-ILD Study

Enrolled SSc-ILD and IPF patients were diagnosed with ILD between February 2015 and January 2021 by the MDD. The study population was analyzed and compared to IPF as a benchmark progressive fibrosing ILD. Inclusion criteria were physiologic lung spirometry (FVC >80% of predicted value) and follow-up data of at least 12 months. SSc-ILD subjects were diagnosed between January 2017 and July 2019; however, the underlying SSc was established earlier in Hungarian immunological-rheumatological centers (259). IPF patients were enrolled into the EMPIRE registry according to the 2011 ATS/ERS guideline (96, 126). Subjects in the registry were reviewed for the inclusion criteria and were analyzed according to the diagnosis of IPF. Functional decline of PPF

diagnosis was established as functional deterioration regarding the annual ≥ 5% predicted FVC decline and/or ≥10% predicted of DL_{CO} decline, without other criteria of worsening symptoms and/or HRCT verified fibrotic progression in a 1-year follow-up period (71).

3.2. Clinical and functional parameters

Patient characteristics, including smoking history, symptoms, comorbidities, detailed PFTs values [FVC, forced expiratory volume in 1 s (FEV_1), total lung capacity (TLC), DL_{CO}, transfer coefficient of the lung for carbon monoxide (KL_{CO})], HRCT pattern and treatment data were analyzed and compared between the study populations at baseline and every follow-up. ABG test, BMI and 6MWT results were examined as well. The precise methodology of each measurement (PFTs, ABGs, 6MWT, HRCT) is detailed in our published articles attached to the dissertation (17, 246). Oxygen saturation was measured by pulse oximetry and is abbreviated as SpO_2 in the tables below (265). Reference values were evaluated according to the Global Lung Function Initiative Network (266). The GAP index for each ILD case was calculated (77). This scoring system is used to estimate the 1, 2, and 3-year mortality (27). The GAP index consists of gender (male sex is a positive predictor), age (>60 years) and functional parameters of FVC (<75% predicted) and DL_{CO} (<55% predicted). Treatment data, including different ISUs and/or antifibrotic agents, were recorded. Adverse events were described in more detail, regarding the antifibrotic drugs. Chronic pulmonary and rheumatology/immunology patient care and controls were determined by the individual requirements.

3.3. Statistical analysis

3.3.1. Descriptive statistics

The statistical methods used for both studies are explained here. Graph Pad software (GraphPad Prism 5.0 Software, Inc., La 119 Jolla, CA, USA) and SPSS v25 (IBM Corporation, Armonk, NY, United States) were used for data analysis. Continuous variables were expressed as mean ± standard deviation or median and interquartile range.

Continuous data were compared with a t-test or Mann–Whitney U-test, according to the variable's distribution. Data test for normality was performed by the Kolmogorov–Smirnov test. Categorical variables are presented as percentages (%) expressed for the whole study population (all patients) or respective subgroups as indicated, and the differences were evaluated with Pearson's chi-square test or two-tailed Fisher's exact test. Throughout the thesis, a *p*-value < 0.05 was defined as statistically significant.

3.3.2. Progression analysis

In the *SSc-ILD Study* we used multiple logistic regression analysis to evaluate predictors of functional progression including age (continuous variable), sex (male/female), smoking history (present/absent), cough (present/absent), PH (present/absent), baseline functional parameters FVC, TLC, DL_{CO}, KL_{CO} (% of the predicted value as continuous variables), and treatment (applied/none). Outcome was defined as: observed progression until the end of the 1st year (progression/ stable-improved), *p*-value < 0.05.

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4. RESULTS

4.1. CTD-ILD Study

The study population included 63 CTD-ILD and 44 IPAF patients. The most common CTD-ILD subtypes were SSc and RA. Detailed distribution of CTDs is presented in Figure 5.

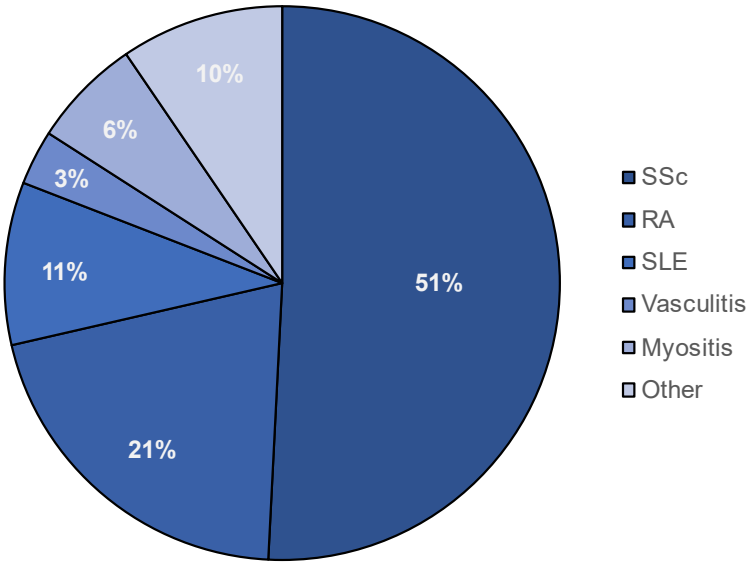

Figure 5. Distribution of CTD subtypes in the whole population. Abbreviations: RA, rheumatoid arthritis; SLE, systemic lupus erythematous; SSc, systemic sclerosis. This figure was created based on our publication (17).

The baseline functional parameters of the study population are summarized in Table 5. The results of PFTs indicate a slight restrictive dysfunction with reduced TLC and CO diffusion parameters. No significant difference was found between the groups regarding the PFTs, ABGs, and 6MWT results.

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Table 5. Functional parameters at baseline.

Variables	All patients (*N*=107)	CTD-ILD (*n*=63)	IPAF (*n*=44)	*p*-value
Lung function				
FEV_1/FVC	0.84 ± 0.08	0.84 ± 0.06	0.82 ± 0.10	0.287
FVC (L)	2.50 ± 0.86	2.49 ± 0.89	2.52 ± 0.83	0.951
FVC (%)	84.41 ± 23.86	85.51 ± 26.93	82.82 ± 18.72	0.577
FEV_1 (L)	2.08 ± 0.72	2.09 ± 0.73	2.07 ± 0.71	0.819
FEV_1 (%)	85.64 ± 24.67	86.82 ± 26.26	83.93 ± 22.36	0.562
TLC (L)	4.31 ± 1.43	4.39 ± 1.54	4.19 ± 1.26	0.683
TLC (%)	80.64 ± 24.82	83.86 ± 26.54	76.13 ± 21.73	0.133
Diffusion parameters				
DL_{CO} (mmol/min/kPa)	5.52 ± 1.87	5.55 ± 1.84	5.47 ± 1.94	0.899
DL_{CO} (%)	70.92 ± 20.88	70.53 ± 20.07	71.48 ± 22.21	0.823
KL_{CO} (mmol/min/kPa/l)	1.26 ± 0.38	1.27 ± 0.37	1.24 ± 0.39	0.943
KL_{CO} (%)	66.19 ± 18.54	65.25 ± 18.12	67.50 ± 19.26	0.551
ABGs				
pH	7.42 ± 0.04	7.43 ± 0.05	7.42 ± 0.02	0.204
pCO_2	40.10 ± 11.13	41.13 ± 11.87	38.86 ± 10.19	0.859
pO_2	66.69 ± 11.82	65.63 ± 13.85	67.96 ± 8.80	0.859
6MWT				
Distance (m)	400.73 ± 108.15	403.45 ± 120.96	397.61 ± 93.02	0.822
SpO_2 baseline	94.51 ± 4.15	95.00 ± 3.35	93.91 ± 4.94	0.490
SpO_2 post-exercise	90.12 ± 8.97	90.69 ± 6.74	89.47 ± 11.06	0.223
Pulse baseline	84.05 ± 14.50	84.75 ± 12.88	83.24 ± 16.37	0.658
Pulse post-exercise	106.71 ± 19.83	109.84 ± 19.56	103.21 ± 19.82	0.158
Borg scale baseline	2.01 ± 11.46	3.23 ± 15.42	0.55 ± 1.25	0.253
Borg scale post-exercise	4.05 ± 11.05	5.33 ± 14.86	2.56 ± 2.15	0.223

Abbreviations: 6MWT, 6-minute walk test; ABG, arterial blood gas test; CTD-ILD, connective tissue disease-associated interstitial lung disease; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IPAF, interstitial pneumonia with autoimmune features; KL_{CO}, transfer coefficient of the lung for carbon monoxide; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; SpO_2, oxygen saturation; TLC, total lung capacity.

Data are presented as mean ± SD. Continuous data were analyzed with a t-test or Mann–Whitney U-test, according to the variable's distribution. The $p<0.05$ was defined as statistically significant. Own data, published in (17).

Predominant HRCT pattern was NSIP in the CTD-ILD group, while a significantly higher proportion of IPAF patients presented with pUIP pattern. The radiological patterns are summarized in Table 6.

Table 6. Radiological patterns on HRCT scan.

HRCT pattern	All patients (*N*=107)	CTD-ILD (*n*=63)	IPAF (*n*=44)	*p*-value
pUIP	27 (25.23)	8 (12.70)	19 (43.18)	**0.001**
UIP	20 (18.69)	10 (15.87)	10 (22.73)	0.370
NSIP	46 (42.99)	38 (60.32)	8 (18.18)	**<0.001**

Abbreviations: CTD-ILD, connective tissue disease-associated interstitial lung disease; HRCT, high-resolution computed tomography; IPAF, interstitial pneumonia with autoimmune features; NSIP, non-specific interstitial pneumonia; pUIP, probable usual interstitial pneumonia; UIP, usual interstitial pneumonia.

Data are presented as *n* (%). Categorical variables were analyzed with Pearson's chi-square test or two-tailed Fisher's exact test. The $p<0.05$ was defined as statistically significant. Statistically significant values were highlighted in bold in the tables. Own data, published in (17).

In the study population, 36 patients (CTD-ILD: *n*=22; IPAF: *n*=14) received CS, RTX, MMF, AZA, CYC, or MTX either in monotherapy or in combination as initial conventional ISU treatment. During the follow-up period, mono- or combined ISU therapies were administered in 25 patients (CTD-ILD: *n*=18; IPAF: *n*=7). In PF-ILD cases, ISU therapy was supplemented with antifibrotic agents. A significant difference was found in the administered antifibrotic therapy (5 CTD-ILD- vs. 13 IPAF patients, $p=0.007$) during the follow-up period. Lung function parameters improved or remained stable in 72.2% of the patients after initiating the antifibrotic treatment (nintedanib *n*=17 with 1 case switched to pirfenidone, pirfenidone *n*=2). The dosage of antifibrotics was administered according to the current international guideline with the goal of maintenance nintedanib 150 mg BID, and 801 mg pirfenidone TID.

Adverse events of antifibrotic agents were mild and transient, and mainly consisted of gastrointestinal symptoms, including nausea and vomiting, diarrhea, and heartburn. Dosage reduction of antifibrotic agents and supportive drugs usually alleviated the adverse events. In one case, liver enzyme elevation led to switching antifibrotic medication from nintedanib to pirfenidone. During the observational period, 11 CTD-ILD and 5 IPAF patients did not receive any treatment.

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4.2.SSc-ILD Study

Baseline characteristics of the study population including therapy are summarized in Table 7. The SSc-ILD population was significantly younger (p=0.001), and the proportion of women was higher (p<0.001). More smokers were found in the IPF group and being overweight was more frequent among these patients. The vast majority of IPF patients presented with ILD specific signs and symptoms including dyspnea (p<0.001), cough, and crackles (p<0.001). Raynaud phenomenon occurred only in the SSc-ILD group. At baseline, according to the GAP index, all patients presented as stage I. No notable difference was found considering the ILD-associated comorbidities, such as PH (p=0.712) and GERD (p=0.345). In the study population, the predominant radiological patterns were UIP/ pUIP in the IPF group and NSIP in the SSc-ILD group. Analyzing the SSc-ILD group, conventional mono or combined ISU treatment was administered in 26 cases, and 9 patients received biological therapy, including 7 patients receiving dual treatment. Antifibrotic agents were not applied in this patient group, while 3 patients did not receive any therapy. In contrast, 39 patients were treated with antifibrotic drugs in the IPF population (n=53); however, in 14 cases no therapy was introduced.

Table 7. Baseline patient characteristics.

Variables	IPF (*n*=53)	SSc-ILD (*n*=31)	*p*-value
Age (years)	68.9 ± 8.5	59.8 ± 13.1	**0.001**
Sex (male:female)	28:25	2:29	**<0.001**
Smoking history			
Ever smoker	33 (62.3)	7 (22.6)	**0.001**
Non-smoker	20 (37.7)	24 (77.4)	
BMI (kg/m^2)	27.7 ± 4.4	25.2 ± 4.4	**0.006**
Overweight (25.0–29.9 kg/m^2)	21 (39.6)	5 (16.2)	**0.025**
Signs and symptoms			
Dyspnea	52 (98.1)	11 (35.5)	**<0.001**
Cough	26 (49.1)	9 (29.0)	0.108
Finger clubbing	12 (22.6)	0	NA
Crackles	47 (88.7)	12 (38.7)	**<0.001**
Raynaud phenomenon	0	23 (74.2)	NA
GAP index			
Stage I	50 (94.3)	31 (100.0)	NA
Stage II	3 (5.7)	0	NA
Stage III	0	0	NA
Specific comorbidities			
PH	7 (13.2)	5 (16.1)	0.712
GERD	6 (11.3)	6 (19.4)	0.345
HRCT pattern			
UIP/pUIP	26/25 (96.2)	0/3 (9.7)	**<0.001**
NSIP	0	26 (83.9)	NA
Other	2 (3.8)	2 (6.5)	0.578
Therapy			
Nintedanib	39 (73.6)	0	NA
Pirfenidone	8 (15.0)	0	NA
ISU	0	26 (83.9)	NA
Biological treatment	0	9 (29.0)	NA
None	14 (26.4)	3 (9.7)	NA

Abbreviations: BMI, body mass index; GAP, Gender–Age–Physiology index; GERD, gastro-esophageal reflux disease; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; NA, not assessed; NSIP, non-specific interstitial pneumonia; PH, pulmonary hypertension; pUIP, probable usual interstitial pneumonia; SSc-ILD, systemic sclerosis-associated interstitial lung disease; UIP, usual interstitial pneumonia; ISU, immunosuppressive therapy. GAP index: stage I = 0–3 points; stage II = 4–5 points; stage III = 6–8 points.

Data are presented as *n* (%) or mean ± SD. Categorical variables were analyzed with Pearson's chi-square test or two-tailed Fisher's exact test. Continuous data were analyzed with a t-test or Mann–Whitney U-test, according to the variable's distribution. The $p<0.05$ was defined as statistically significant. Statistically significant values were highlighted in bold in the tables. Own data, published in (246).

Baseline functional data are summarized in Table 8. Neither of the study populations differed regarding FVC and FEV_1 parameters; however, TLC values were notably lower in the IPF group (p=0.022). Significant differences were detected in lung CO diffusion as IPF patients had more impaired DL_{CO} values (p=0.020), while KL_{CO} values were decreased in SSc-ILD patients (p<0.001). ABG showed notably decreased pO_2 values in the IPF group (p<0.001), while 6MWT parameters, including distance, post-exercise tachycardia, desaturation or Borg scale showed no significant differences compared to the SSc-ILD population.

Table 8. Functional parameters at baseline.

Variables	IPF (n=53)	SSc-ILD (n=31)	p-value
Lung-function parameters			
FVC (mL)	3035.7 ± 836.2	2725.5 ± 655.6	0.080
FVC (% pred)	96.4 ± 13.9	98.7 ± 12.2	0.263
FEV_1 (mL)	2488.5 ± 696.4	2301.6 ± 569.2	0.209
FEV_1 (% pred)	98.6 ± 16.2	99.7 ± 13.3	0.748
FEV_1/FVC (%)	82.6 ± 8.2	84.5 ± 5.2	0.329
TLC (mL)	4648.9 ± 1358.4	4263.9 ± 823.3	0.157
TLC (% pred)	79.5 ± 14.4	88.4 ± 15.4	**0.022**
Diffusion parameters			
DL_{CO} (mmol/min/kPa)	5.9 ± 1.8	6.4 ± 1.6	0.201
DL_{CO} (% pred)	74.1 ± 17.6	83.7 ± 18.3	**0.020**
KL_{CO} (mmol/min/kPa/L)	1.3 ± 0.3	1.4 ± 0.3	**0.042**
KL_{CO} (% pred)	88.8 ± 24.2	71.2 ± 16.4	**<0.001**
ABGs			
pH	7.4 ±0.0	7.4 ±0.0	0.655
pCO_2 (mmHg)	37.7 ± 5.5	37.1 ± 2.3	0.119
pO_2 (mmHg)	67.8 ± 11.0	78.6 ± 8.6	**<0.001**
6MWT			
Distance (m)	454.4 ± 103.1	449.3 ± 70.8	0.502
Initial SpO_2 (%)	95.3 ± 2.9	94.9 ± 3.0	0.463
Final SpO_2 (%)	88.8 ± 9.0	89.2 ± 10.8	0.407
Initial HR (1/min)	81.0 ± 13.9	84.4 ± 14.3	0.425
Final HR (1/min)	111.2 ± 19.7	106.5 ± 20.2	0.443
Initial Borg score (0–10)	0 (0–0)	0 (0–0)	0.885
Final Borg score (0–10)	2 (0–4)	1.5 (1–3)	0.924

Abbreviations: 6MWT, 6-minute walk test; ABGs, arterialized capillary blood gases; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HR, heart rate; IPF, idiopathic pulmonary fibrosis; KL_{CO}, transfer coefficient of the lung for carbon monoxide; pCO_2; partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; SpO_2, oxygen saturation; SSc-ILD, systemic sclerosis-associated interstitial lung disease; TLC, total lung capacity.

Data are presented as mean ± SD, median (IQR). Continuous data were analyzed with a t-test or Mann–Whitney U-test, according to the variable's distribution. The p<0.05 was defined as

statistically significant. Statistically significant values were highlighted in bold in the tables. Own data, published in (246).

Annual median FVC decline for all patients is presented in Figure 6. Median FVC decline in SSc-ILD was -67.5 (-146.0 to -4.0) mL/year, and in the IPF group was -65.3 (-173.8 to -65.3) mL/year. In the study population, 11 (35%) SSc-ILD patients fulfilled the PPF criteria in the following distribution: 7 patients had FVC ≥5% predicted, 7 patients had DL_{CO} ≥10% predicted value decline, including 3 patients who presented with both functional criteria during the observational period. Similarly, functional progression was detected in 16 (30.2%) IPF patients as 14 patients met the FVC-, 7 patients met the DL_{CO} criteria including 5 patients who met both. SSc-ILD subgroups differed significantly regarding the annual median FVC decline. The decline in the functionally progressive subgroup was notably higher than in the stable/improved subgroup (-153.9 (-278.3 to -121.4) mL/year vs. -26.2 (-75.4 to -1.6) mL/year, *p*=0.017). Correspondingly, the IPF population showed a significant difference in the functionally progressive IPF subgroup (-264.7 (-404.9 to -204.6) mL/year) as compared to the stable/improved IPF subgroup (-39.2 (-85.7 to +7.5) mL/year, *p*=0.004).

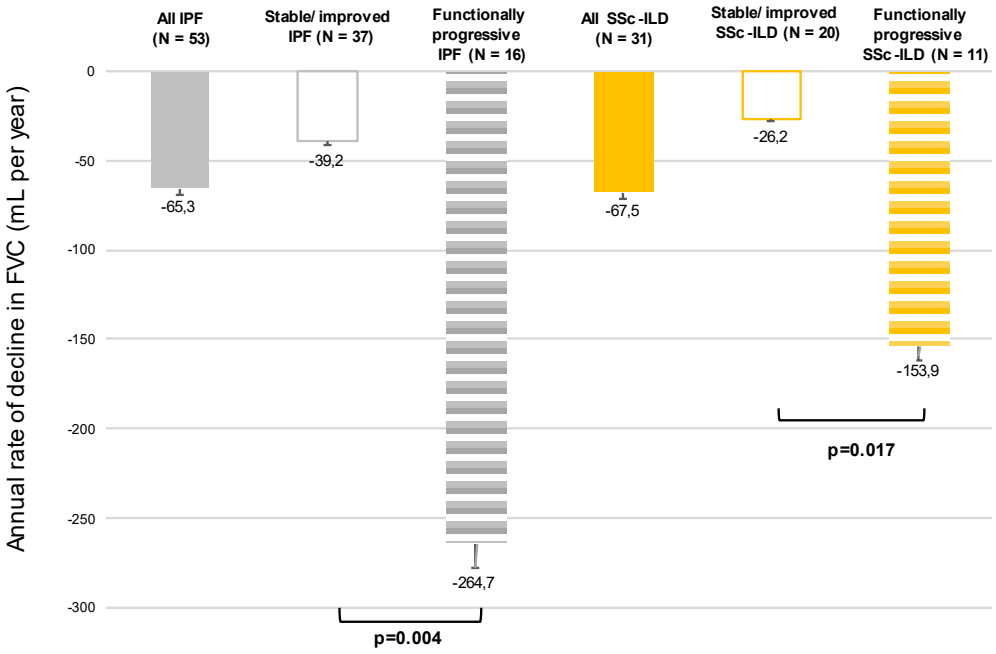

Figure 6. Rate of FVC decline (mL/year) in IPF and SSc-ILD patients. Abbreviations: FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease. Continuous data were analyzed with a t-test or Mann–Whitney U-test,

according to the variable's distribution. The $p<0.05$ was defined as statistically significant. Own representation, published in (246).

Functionally progressive subgroups of IPF patients showed no difference regarding clinical characteristics or treatment at baseline; however, SSc-ILD patients with functional decline over the one-year follow-up, had significantly more frequent cough symptoms ($p=0.002$) and PH initially ($p=0.023$.). In the functionally progressive IPF subgroup, 17 patients received antifibrotics, while no therapy was applied in 25% of the cases. Ten cases of ISU and/or biologic treatment were administered, and 2 patients did not received treatment in SSc-ILD subgroup showing functional progression (Table 9.).

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Table 9. Baseline patient characteristics and functional parameters in the IPF and SSc-ILD subgroups.

Variables	Functionally stable/improved IPF (*n*=37)	Functionally progressive IPF (*n*=16)	Functionally stable/improved SSc-ILD (*n*=20)	Functionally progressive SSc-ILD (*n*=11)
Age (years)	67.6 ± 9.1	71.8 ± 6.5	59.8 ± 13.1	59.7 ± 12.6
Sex (male:female)	20:17	8:8	1:19	1:10
Smoking history				
Ever smoker	23 (62.2)	10 (62.5)	3 (15.0)	4 (36.4)
Non-smoker	14 (37.8)	6 (37.5)	17 (85.0)	7 (63.6)
BMI (kg/m^2)	28.3 ± 4.4	26.8 ± 4.3	25.2 ± 4.4	23.7 ± 4.1
Overweight (25.0–29.9 kg/m^2)	15 (40.5)	6 (37.5)	5 (45.5)	0
Signs and symptoms				
Dyspnea	37 (100)	15 (93.8)	7 (35.0)	4 (36.4)
Cough	19 (51.4)	7 (43.8)	**2 (10.0)***	**7 (63.6)***
Finger clubbing	6 (16.2)	6 (37.5)	0	0
Crackles	33 (89.2)	14 (87.5)	7 (35.0)	5 (45.5)
Raynaud phenomenon	0	0	16 (80.0)	7 (63.6)
GAP index				
Stage I	35 (94.6)	15 (93.8)	20 (100.0)	11 (100.0)
Stage II	2 (5.4)	1 (6.2)	0	0
Stage III	0	0	0	0
Specific comorbidities				
PH	5 (13.5)	2 (13.3)	**1 (5.0)**$^{\#}$	**4 (36.4)**$^{\#}$
GERD	5 (13.5)	1 (6.2)	3 (15.0)	3 (27.3)
HRCT pattern				
UIP/pUIP	16/21 (100)	10/4 (87.5)	0/3 (15.0)	0
NSIP	0	0	16 (80.0)	10 (90.9)
Other	0	2 (12.5)	1 (5.0)	1 (9.1)
Therapy				
Nintedanib	27 (73.0)	12 (75.0)	0	0
Pirfenidone$^{\&}$	3 (8.1)	5 (31.2)	0	0
ISU	0	0	18 (90.0)	8 (72.7)
Biological treatment	0	0	7 (35.0)	2 (18.2)
None	10 (27.0)	4 (25.0)	1 (5.0)	2 (18.2)
Lung-function parameters				
FVC (mL)	3057.0 ± 840.8	2986.3 ± 850.7	2770.5 ± 681.2	2642.7 ± 631.4
FVC (% pred)	95.5 ± 12.8	98.4 ± 16.5	98.9 ± 13.7	98.4 ± 9.7
FEV_1 (mL)	2497.6 ± 707.6	2467.5 ± 692.0	2354.5 ± 609.4	2200.9 ± 510.8
FEV_1 (% pred)	96.8 ± 15.0	102.7 ± 18.5	100.0 ± 14.7	98.6 ± 11.3
FEV_1/FVC (%)	82.0 ± 8.7	82.9 ± 5.2	84.8 ± 4.5	83.6 ± 6.4
TLC (mL)	4683.5 ± 1459.1	4568.8 ± 1130.2	4343.0 ± 884.2	4199.1 ± 635.5
TLC (% pred)	79.7 ± 16.1	78.8 ± 9.5	89.7 ± 17.5	88.1 ± 10.7
Diffusion parameters				
DL_{CO} (mmol/min/kPa)	6.1 ± 1.8	5.3 ± 1.6	6.3 ± 1.5	6.6 ± 1.6
DL_{CO} (% pred)	76.6 ± 18.0	68.3 ± 15.5	82.5 ± 18.4	88.6 ± 14.5
KL_{CO} (mmol/min/kPa/L)	1.3 ± 0.4	1.2 ± 0.2	1.4 ± 0.3	1.5 ± 0.3
KL_{CO} (% pred)	89.2 ± 23.6	87.8 ± 26.3	70.3 ± 16.3	75.6 ± 12.9
ABGs				
pH	7.4 ±0.0	7.4 ±0.0	7.4 ±0.0	7.4 ±0.0
pCO_2 (mmHg)	38.5 ± 2.6	35.3 ± 10.0	37.7 ± 1.9	36.0 ± 2.8
pO_2 (mmHg)	69.7 ± 10.2	62.2 ± 11.8	77.0 ± 6.4	81.4 ± 11.7
6MWT				
Distance (m)	459.7 ± 102.5	442.5 ± 107.1	454.7 ± 68.8	438.4 ± 81.8
Initial SpO_2 (%)	95.6 ± 2.3	94.6 ± 3.8	95.6 ± 1.9	93.6 ± 4.4
Final SpO_2 (%)	89.4 ± 8.9	87.4 ± 9.3	93.6 ± 5.3	82.0 ± 14.0
Initial HR (1/min)	80.4 ± 12.9	82.3 ± 16.4	85.6 ± 15.6	82.4 ± 13.2
Final HR (1/min)	109.7 ± 19.7	114.7 ± 19.7	106.0 ± 16.7	107.2 ± 27.2
Initial Borg score (0–10)	0 (0–0)	0.5 (0–0)	0 (0–0)	0 (0–1)
Final Borg score (0–10)	1.5 (0–4)	2.8 (0–4)	2 (1–3)	1 (0–3)

Abbreviations: 6MWT, 6-minute walk test; ABGs, arterialized capillary blood gases; BMI, body mass index; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GAP, Gender–Age–Physiology index; GERD, gastro-esophageal reflux disease; HR, heart rate; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; ISU, immunosuppressive therapy; KL_{CO}, transfer coefficient of the lung for carbon monoxide; NSIP, non-specific interstitial pneumonia; pCO_2; partial pressure of carbon dioxide; PH, pulmonary hypertension; pO_2, partial pressure of oxygen; pUIP, probable usual interstitial pneumonia; SpO_2, oxygen saturation; SSc-ILD, systemic-sclerosis-associated interstitial lung disease; TLC, total lung capacity; UIP, usual interstitial pneumonia;. GAP index: stage I = 0–3 points; stage II = 4–5 points; stage III = 6–8 points.

Data are presented as *n* (%), mean ± SD or median (IQR). Categorical variables were analyzed with Pearson's chi-square test or two-tailed Fisher's exact test. Continuous data were analyzed with a t-test or Mann–Whitney U-test, according to the variable's distribution. The $p<0.05$ was defined as statistically significant. Statistically significant values were highlighted in bold in the tables ($^{*}p=0.002$; $^{\#}p=0.023$). Own data, published in (246).

[&]All treatment was included: a nintedanib-to-pirfenidone or pirfenidone-to-nintedanib change in therapy resulted in the higher number of treated vs. untreated IPF patients.

Analyzing the baseline predictors of progression with multiple logistic regression, no significant predictor could be identified in the IPF group; however, cough and PH proved to be prognostic factors for functional progression in SSc-ILD patients (odds ratio (OR): 36.2 (95% confidence interval (CI): 1.8–711.9) and OR: 36.4 (95% CI: 1.1–1184.9)), respectively. Dry cough presented in the majority of patients (SSc-ILD: *n*=7; IPF: *n*=17) and was predominant even in the subgroups with functional progression (SSc-ILD: 85.7% vs. IPF: 71.4%). Functional decline with treatment data of the study cases is shown in Figure 7.

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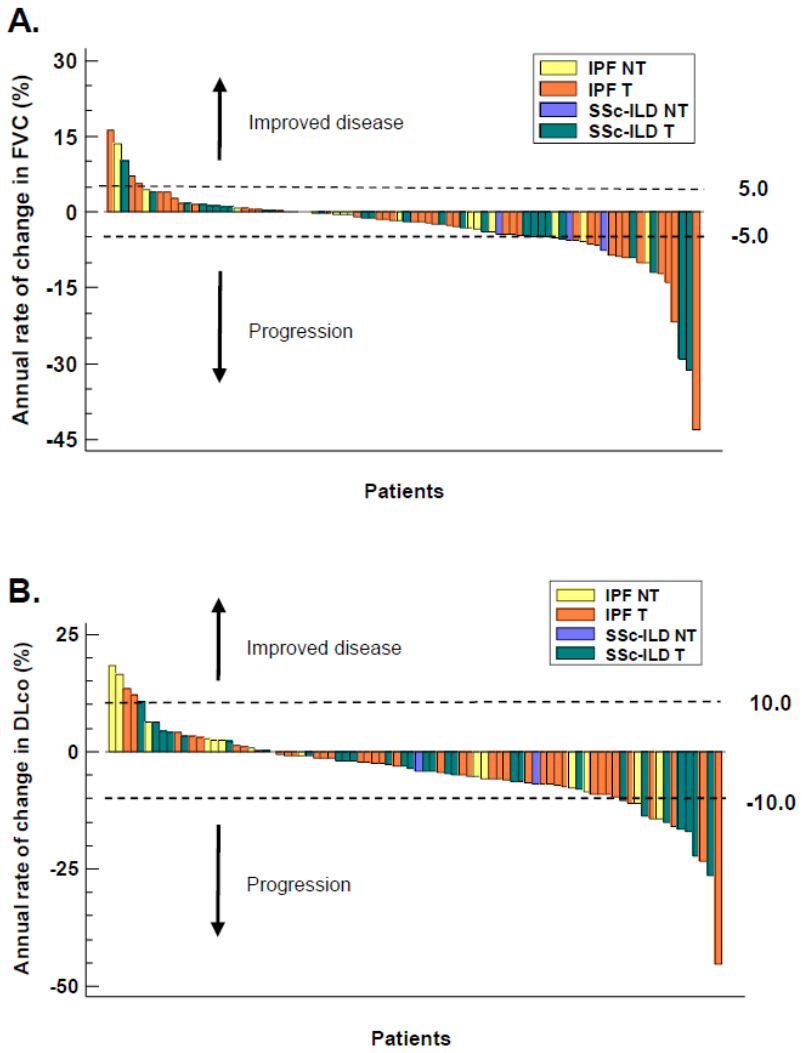

Figure 7. Annual changes in FVC (**A**) and DL_{CO} (**B**) % of the predicted value in all IPF and SSc-ILD patients, according to specific treatment subgroups. Abbreviations: DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; NT, no treatment; SSc-ILD, systemic sclerosis-associated interstitial lung disease; T, treatment. Own representation, this figure was created with Statgraphics 19 software (www.statgraphics.com) and published in (246).

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5. DISCUSSION

The studies of this PhD thesis revealed single-center data of a rare patient population of CTD-ILDs from an Eastern European country focusing on the factors of progression and the administered therapies. The common study aim was to observe clinical characteristics and PPF criteria in the CTD-ILD and SSc-ILD population.

5.1. CTD-ILD Study

Our study described the functional and treatment outcomes related to real-world data retrieved from the rare population of ILDs with autoimmune features (17). While the first line treatment of CTD-ILD patients depends on the specific autoimmune conditions, internationally accepted guidelines are still needed for the treatment of IPAF patients (267, 268).

Population characteristics regarding the distribution of CTD-ILD and IPAF patients - diagnosed by the MDD - and the CTD-ILD subtypes were similar to previous studies (269-271). Despite international data suggesting that the most common radiologic pattern is NSIP; in our study, the majority of IPAF cases exhibited a pUIP pattern (267, 272). This difference could be attributed to the rarity of the disease resulting in a limited number of IPAF patients being included in our study – a limitation, which can be transgressed in multi-center international studies involving larger populations (270). Furthermore, a considerable interobserver variability among radiologists might also have played a role in the conflicting HRCT evaluation results (273, 274). However, it is important to note that the role of the morphological domain is limited, because in IPAF patients the transformation to definitive autoimmune disease was irrespective of the UIP or non-UIP radiologic pattern (275).

The administered ISU therapy - the first line treatment choice in autoimmune associated ILDs - showed efficacy in improving lung function mostly in patients with CTD-ILD (158). The clinical course of SSc-ILDs can be described as either a rapidly progressive-, stable or an improved condition. In line with the SLS I-II and SENSCIS trials, our population also primarily included patients with a stable disease course, in

addition to some cases showing improvement during the 2-year observational period (276, 277).

One of the most important treatment goals is to decrease the rate, and if present, the extent of disease progression into PPF. Antifibrotic agents have the beneficial effect of decreasing disease progression, especially when introduced as early as possible (278). In our study, antifibrotic therapy was initiated based on the decision made by the MDD in cases of rapid progression or detection of IPF-like features. Progressive IPAF patients received antifibrotic treatment more frequently, when compared to CTD-ILD cases with PF-ILD. The initiation of antifibrotics led to the stabilization of lung function in most cases, including CTD-ILD and IPAF. However, 9 patients progressed functionally in the absence of antifibrotic treatment, thereby fulfilling the functional diagnostic criteria of PPF (79). In CTD-ILD patients, observation and follow-ups alone can be used instead of active therapy without the clinical suspicion of functional progression, if their PFTs are within the physiologic range and they do not exhibit respiratory symptoms (151, 279).

There is an emerging need for data regarding the efficacy of combined ISU and antifibrotic therapy, due to the scarcity of the information available. Although, in clinical practice, treatment with ISU and/or immunomodulatory therapy does not rule out the initiation of antifibrotic therapy; in the INBUILD trial, ILD patients with deterioration received restricted therapies only after 6 months of trial treatment (280). The SENSCIS trial revealed the effectiveness of combined MMF and nintedanib therapy in SSc-ILD patients in terms of lung function stabilization; although, the study did not consider the combined treatment's efficacy in the subgroup analysis (180, 251). Mild adverse events were presented in two-thirds of the patients following the treatment with combined ISU and nintedanib. Treatment profile considering safety and tolerability, showed similar characteristics to our previous study (254). Regarding the adverse events, 67% of our patients experienced at least one (17). This is in line with the INBUILD trial, where 67% of the population had diarrhea, and less frequently nausea (29%) (79). Furthermore, in one patient, grade 3 severity of increased liver enzyme led to drug discontinuation and switching to another antifibrotic agent, which resolved the adverse event. A serious complication in ILDs is AE; however, our data was not sufficient to study the impact of AEs on disease progression (281, 282).

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5.2.SSc-ILD Study

In this study, we analyzed treatment and functional outcome real-world data in IPF and SSc-ILD patients with physiologic pulmonary functional parameters at the time of diagnosis (246). Clinical trials mostly focus on advanced ILDs; however, patients with preserved lung function should also be monitored more carefully to prevent the development of early PPF in this special patient group.

During the observational period, approximately one-third of the SSc-ILD patients with physiologic lung function values at baseline had a significant annual FVC and/or DL_{CO} decline (246). The nature of SSc-ILD shows notable variabilities; however, in this special population, PPF may be responsible for the poor outcome and increased mortality (283). Evaluation of PFTs along with clinical symptoms at follow-ups as non-invasive diagnostic tools, are essential as they are two important criteria for PPF diagnosis. Early detection of the decline in lung function is a pivotal step in patients with PPF and might contribute to better clinical decision making in treatment initiation (71).

Although SSc-ILD patients had physiologic lung function parameters at the time of the baseline examination, we found that cough - as a main respiratory symptom - may be associated with an increased probability of PPF (246). In line with our finding, the SENSCIS trial's subgroup analysis revealed that cough is a prognostic factor in SSc-ILD patients considering functional deterioration and disease progression. SSc-ILD patients in the SENSCIS trial had lower baseline PFT values, which accompanied with cough symptoms, and showed an average annual rate of decline of -95.6 mL/year - barely higher than that observed in our study (284). Nintedanib showed a lower therapeutic effectiveness in patients with cough than in patients without cough. Notably, cough proved to be an independent negative prognostic factor for lung function decline, according to two independent observations (40, 155). Similarly, in the SLS II trial, cough was a marker of poor response to treatment and was even firmly associated with the decline in lung function (285). The association between cough and progression might be explained by the frequent changes in intrathoracic pressure and the activation of the stretch-related TGF-β expression, thus being a profibrotic stimulator (37, 38). Highlighting the functional decline in non-progressive patients, prospective cohort studies in healthy subjects found a mean annual rate of FVC decline in men of -47.2 to -

78.4 mL/year, and in women of -14.1 to -65.6 mL/year (286). Our SSc-ILD patients' non-progressive subgroup was in that expected range.

Importantly, PH was found to be a significant prognostic factor of lung function decline in patients with SSc-ILD. Moreover, to the best of our knowledge, this relationship has not yet been described in current literature. Nonetheless, PH - a serious complication -, has been established to have a major impact on survival, according to large-scale international studies (287-289). It is important to emphasize that the brief investigatory period of our study did not allow us to focus on the investigation of mortality, including PH as a possible factor.

Even though SSc-ILD patients were expected to perform better during the 6MWT due to their younger age, and, therefore, superior exercise capacity; there was no significant difference between the patient groups, regarding the 6MWT. Impaired exercise performance could be explained by the associated comorbidities, including vascular involvement, such as PH and/or musculoskeletal manifestations of the underlying SSc (97, 290, 291). Additionally, acral vasculopathy – heterogenous distribution of capillary blood flow - and Raynaud's phenomenon might influence the SpO_2 outcomes in the SSc-ILD group (292).

IPF is considered as a prototypical condition for PPF (5). Although there are many differences between the initial pathophysiology of SSc-ILD and IPF; the final common pathway is similar and consists of activation and recruitment of fibroblasts, their differentiation to myofibroblasts with increased ECM accumulation and the irreversible fibrosis of the lungs (2, 175).

As compared to the INPULSIS trial, we found that our examined IPF population had a lower decline in lung function than the trial's nintedanib-treated IPF patients (-65.3 mL/year vs. -114.7 mL/year FVC decline) (136). Surprisingly, a subgroup analysis revealed no significant difference in lung functional decline between antifibrotic treated and nontreated IPF patients regarding FVC. In some patients, functional progression was found irrespective of the administered targeted antifibrotic drug, thus underlining the importance of the need for further risk factor investigations. It is important to note that large international trials did not take emphasis on ILD patients with lung function parameters in the normal range. The total IPF population (treated and untreated patients), showed a limited functional decline regarding FVC; while in the stable/improved

subgroup, negligible deterioration was found (246). Although, the decline in the functionally progressive subgroup was in line with that of the clinical trials' placebo group (136, 141). Notably, the favorable efficacy of antifibrotic therapy in IPF patients was underlined in our real-world observation, in line with our preceding findings in the analysis of IPF patients at a functionally advanced stage (254).

Selecting the best therapy for SSc-ILD patients, is challenging. Underlining the importance of early therapy initiation, our study has found that SSc-ILD patients on ISU and/or biological treatment had better functional results (17, 293). Subanalysis of SSc-ILD patients in the SENSCIS trial revealed that the antifibrotic agent nintedanib reduced progression in ILD patients with or without initial MMF therapy (251). Inclusion criteria of this trial were the following: FVC ≥40% predicted, DL_{CO} 30-89% predicted and ≥10% extent of lung fibrosis on HRCT. After the observational 52-week period, a significantly lower FVC decline rate was found in the group receiving combined nintedanib and MMF therapy, compared to the placebo and MMF group (-40.2 vs. -66.5 mL/year). Additionally, the functional deterioration was even more pronounced in SSc-ILD patients without any ISU therapy (placebo group: -119.3 mL/year). Combined nintedanib and MMF treatment was found to be the most beneficial in SSc-ILD patients with definitive PPF, regarding the reduction of FVC decline (180, 251).

Finally, therapeutic options in PPF cases are still not well established, nonetheless, antifibrotic agents may be effective and beneficial in a limited patient group. Notably, nintedanib and pirfenidone - two antifibrotic agents - were considered to have similar antifibrotic properties in ILDs; nintedanib was more frequently introduced (151). In large-scale clinical trials, such as INBUILD and INPULSIS 1-2, the effectiveness of nintedanib was verified by lowering the annual FVC decline in patients with PF-ILDs (79, 136). Furthermore, ISU and/or biological therapy introduction is also pivotal in SSc (248). Clinicians should pay close attention to patients with cough or PH, but with physiologic pulmonary functions, as this population is more prone to progression and, therefore, closer pulmonary observation is needed (294).

Our studies of this PhD thesis have two major limitations (17, 246). Firstly, the retrospective observational single-center design clearly led to limited data access. As an example, data about cough was only collected from the clinical anamnestic data. However, several validated questionnaires are available to evaluate cough and its effect

on health-related QoL; including the visual analogue scale, cough symptom score, Short Form-36 Health Survey, St George's Respiratory Questionnaire, Leicester Cough Questionnaire, and Cough-specific QoL Questionnaire (295). In addition, data of dosage change in ISU therapy was also limited, which may have influenced the outcome. Secondly, ILDs are rare conditions, thus the small population included in the study may decrease statistical power. There is an emerging need for more multicenter registries to collect important patient data from these rare pulmonary diseases, for example: the EMPIRE (126).

Further prospective studies are needed to find new possible predictors of disease progression and to optimize treatment regarding adequate therapeutic modalities in order to improve guidelines; accordingly, including initiation, dose, and combination of ISU/biological treatment/antifibrotics (248).

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6. CONCLUSIONS

The focus of this thesis was specifically placed upon the Hungarian ILD population showing progression to PPF, and IPF. We conducted a detailed analysis of our patients at the Department of Pulmonology, Semmelweis University to improve the diagnostic and therapeutic possibilities of this special patient group. Conclusions of this thesis are as follows:

1. In the *SSc-ILD Study* PH and GERD, as comorbidities, presented similarly in the two populations, and functional parameters were similar in the *CTD-ILD Study*. Although, IPF patients had a notably more restrictive PFT (decreased TLC) and reduced CO diffusion (DL_{CO}), KL_{CO} was significantly lower in patients with SSc-ILD, suggesting a worse diffusion per lung units.
2. NSIP was the predominant pattern in definitive autoimmune ILDs, similarly to the *CTD-ILD* and *SSc-ILD Study*; however, the UIP associated pattern dominated in IPAF and IPF cases.
3. Although, similar proportions of patients presented with PPF in the analyzed SSc-ILD and IPF subgroups, antifibrotics were introduced only in IPF patients; however, ISU and/or biologic treatment was applied exclusively in SSc-ILD patients.
4. In SSc-ILD patients with physiologic PFTs, the presence of cough showed an increased risk for PPF development, possibly posing as a prognostic factor for functional decline. Furthermore, PH was found to be a negative prognostic factor for PPF in SSc-ILD patients.
5. Baseline treatment data of the *CTD-ILD Study* showed that administering ISU treatment with or without antifibrotic agents resulted in stable or improved lung functions. In the *SSc-ILD Study*, patients receiving ISU and/or biological-therapy displayed better functional outcomes, which highlights the importance of early and specific SSc therapy.
6. In the *CTD-ILD Study*, administered antifibrotics were associated with tolerable gastrointestinal adverse events, similar to clinical trials.

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7. SUMMARY

ILDs are a heterogeneous group of conditions with various etiologies; however, functional progression can worsen the prognosis and the outcome (1). IPF is regarded as a prototype disease for progression, but ILDs with autoimmune features, such as CTD-ILD and IPAF, can show progressive decline during the disease course, thus deteriorating the QoL and the survival (150). Progressive non-IPF ILD in PPF is characterized by clinical symptom worsening, lung function deterioration and increased fibrosis on HRCT scans (71).

The focus of this thesis and the retrospective studies conducted, was the analysis of clinical characteristics and the identification of possible predictors of progression and treatment options in different ILD populations. In the study population ILDs were diagnosed by MDD at the Department of Pulmonology, Semmelweis University. In the CTD-ILD Study, we included a total of 107 patients with CTD-ILD and IPAF, while a total of 84 IPF and SSc-ILD patients with physiologic lung function parameters were analyzed in SSc-ILD Study. At baseline patient characteristics, functional parameters and imaging were registered, while functional parameters were evaluated at every follow-up (17, 246).

Our results showed that in the study populations most ILD patients receiving ISU and/or antifibrotic treatment - depending on the underlying condition - showed improved functional outcomes. Importantly, patient-reported symptoms, such as cough (especially dry cough), and the presence of PH as a lung-related comorbidity, should be taken into consideration in connection with the disease progression in SSc-ILD patients. Despite the age difference, exercise capacity was similar in IPF and SSc-ILD patients, emphasizing the involvement of additional factors in physical performance. Interestingly, regardless of the typical restrictive parameters of IPF, CO diffusion per alveolar unit - KL_{CO} - was lower in the SSc-ILD population, indicating the presence of altered respiratory mechanisms.

There is emerging need for prospective studies to detect new progression markers of functional deterioration and to develop guidelines for the optimal timing of therapy introduction and treatment of choice in this special ILD population even in early stages with physiologic lung function remaining.

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9. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

9.1. Publications related to the present PhD thesis:

Nagy T, Toth NM, Palmer E, Polivka L, Csoma B, Nagy A, Eszes N, Vincze K, Bárczi E, Bohács A, Tárnoki ÁD, Tárnoki DL, Nagy G, Kiss E, Maurovich-Horvát P, Müller V. Clinical Predictors of Lung-Function Decline in Systemic-Sclerosis-Associated Interstitial Lung Disease Patients with Normal Spirometry. *Biomedicines,* 2022 Aug 31;10(9):2129. doi: 10.3390/biomedicines10092129. PubMed PMID: 36140231, PubMed PMCID: PMC9495755. (Q1)

Nagy A†, **Nagy T**†, Kolonics-Farkas AM, Eszes N, Vincze K, Barczi E, Tarnoki AD, Tarnoki DL, Nagy G, Kiss E, Maurovich-Horvat P, Bohacs A, Müller V. Autoimmune Progressive Fibrosing Interstitial Lung Disease: Predictors of Fast Decline. *Front Pharmacol*. 2021 Dec 22;12:778649. doi: 10.3389/fphar.2021.778649. PubMed PMID: 35002713 PubMed PMCID: PMC8727590. (Q1)
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9.2. Publications not related to the subjects of the thesis

Barczi E, Nagy T, Starobinski L, Kolonics-Farkas A, Eszes N, Bohacs A, Tarnoki AD, Tarnoki DL, Müller V. Impact of interstitial lung disease and simultaneous lung cancer on therapeutic possibilities and survival. Thorac Cancer. 2020 Jul;11(7):1911-1917. doi: 10.1111/1759-7714.13481. Epub 2020 May 13. PMID: 32401433; PMCID: PMC7327688.

Tóth NM, Müller V, Nagy T, Polivka L, Horváth P, Bohács A, Eszes N. Serum Progranulin Level Might Differentiate Non-IPF ILD from IPF. Int J Mol Sci. 2023 May 24;24(11):9178. doi: 10.3390/ijms24119178. PMID: 37298130; PMCID: PMC10252558.

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