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CHARACTERISTICS OF INTERSTITIAL LUNG DISEASES AND FACTORS DETERMINING PROGRESSION - FOCUS ON LUNG DISEASES WITH AUTOIMMUNE FEATURES

PhD thesis

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LIST OF ABBREVIATIONS

6MWT	6-minute walk test
ABG	arterialized capillary blood gases
ACA	anti-centromere antibodies
AIP	acute interstitial pneumonia
ANTI-CCP	anti-cyclic citrullinated peptide antibody
ALAT	Latin American Thoracic Society
ANA	anti-nuclear antibodies
ANCA	anti-neutrophil cytoplasmic antibodies
ANTI-RNP	anti-ribonucleoprotein antibodies
ANTI-SCL-70	anti-topoisomerase I antibodies
APCNA	anti-proliferating cell nuclear antigen
ATS	American Thoracic Society
AZA	azathioprine
BAL	bronchoalveolar lavage
COP	cryptogenic organizing pneumonia
COPD	chronic obstructive pulmonary disease
CTD	connective tissue disease
CYC	cyclophosphamide
dcSSc	diffuse cutaneos systemic sclerosis
DIP	desquamative intersitital pneumonia
DL_{CO}	diffusing capacity of the lungs for carbon monoxide
DMARD	disease modifying antirheumatic drugs
DPLDs	diffuse parenchymal lung diseases
ECM	extracellular matrix
ERS	European Respiratory Society
EULAR-ACR	American College of Rheumatology/European League Against Rheumatism Collaborative Initiative
FEV1	forced expiratory volume in 1 second
FDGF	fibroblast-derived growth factor
FRC	functional residual capacity

FVC	forced vital capacity
GAP	multidimensional gender–age–physiology index
GGO	ground glass opacity
HRCT	high-resolution computed tomography
HP	hypersensitivity pneumonitis
IFN-γ	interferon – γ
IIM	idiopathic inflammatory myopathies
IIPs	idiopathic interstitial pneumonias
IL-6	interleukin-6
ILDs	interstitial lung diseases
ISU	immunosuppression
iNSIP	idiopathic nonspecific interstitial pneumonia
IPAF	interstitial pneumonia with autoimmune features
IPF	idiopathic pulmonary fibrosis
JRS	Japanese Respiratory Society
KL_{CO}	transfer coefficient of the lung for carbon monoxide
LAM	lymphangioleiomyomatosis
lcSSc	limited cutaneous systemic sclerosis
LIP	lymphoid interstitial pneumonia
LTOT	long term oxygen therapy
MCTD	mixed connective tissue disease
MDD	multidisciplinary discussion
MMF	mycophenolate mofetil
MTX	methotrexate
NSIP	nonspecific interstitial pneumonia
PAH	pulmonary arterial hypertension
PDGF	platelet-derived growth factor
PFT	pulmonary function test
pH	potential of hydrogen
PH	pulmonary hypertension
PF-ILD	progressive fibrosing ILD
PPF	progressive pulmonary fibrosis

PPFE	pleuroparenchymal fibroelastosis
pUIP	possible usual interstitial pneumonia
OP	organizing pneumonia
RA	rheumatoid arthritis
RA-ILD	rheumatoid arthritis associated interstitial lung disease
RB-ILD	respiratory bronchiolitis interstitial lung disease
RF	rheumatoid factor
RTX	rituximab
SFTPA2	surfactant Protein A2
SFTPC	surfactant protein C
SLE	systemic lupus erythematosus
SS	Sjögren's syndrome
SSc	systemic sclerosis
ssSSc	systemic sclerosis sine scleroderma
TERC	telomerase ribonucleic acid component
TERT	telomerase reverse transcriptase
TGF-β	transforming growth factor - β
TNF-α	tumor necrosis factor - α
TLC	total lung capacity
tRNA	transfer ribonucleic acid
UCTD	undifferentiated connective tissue disease
UILD	undifferentiated interstitial lung disease
UIP	usual interstitial pneumonia
VC	vital capacity
VATS	video assisted thoracic surgery
VEGF	vascular endothelial growth factor

1. INTRODUCTION

My doctoral thesis focuses on the characteristics of autoimmune disease-associated interstitial lung diseases (ILDs) and the factors determining progression. Following the summary of the literary background, the thesis outlines the main objectives, the methodology of scientific publication, the primary results, and endeavors to discuss them.

1.1. Interstitial lung diseases (ILDs)

ILDs otherwise known as diffuse parenchymal lung diseases (DPLDs) can affect the lung interstitium, terminal bronchioles, alveoli, alveolar capillary network causing diffuse inflammatory and – or fibrous lesions leading to functional worsening of the lungs. ILDs consist of a heterogenous group of patients (nearly 200 distinct often rare diseases) showing similar clinical appearances including symptoms, pulmonary function tests (PFT), radiological manifestations (1-3). From an etiological point of view we differentiate ILDs with known and unknown origin (3-5). The accurately recorded medical history (family and smoking history, occupation, medications, irradiation, exposures to organic and anorganic substances) has an extraordinary importance in finding the diagnosis (3, 6, 7). The categorization of ILDs is shown in Figure 1.

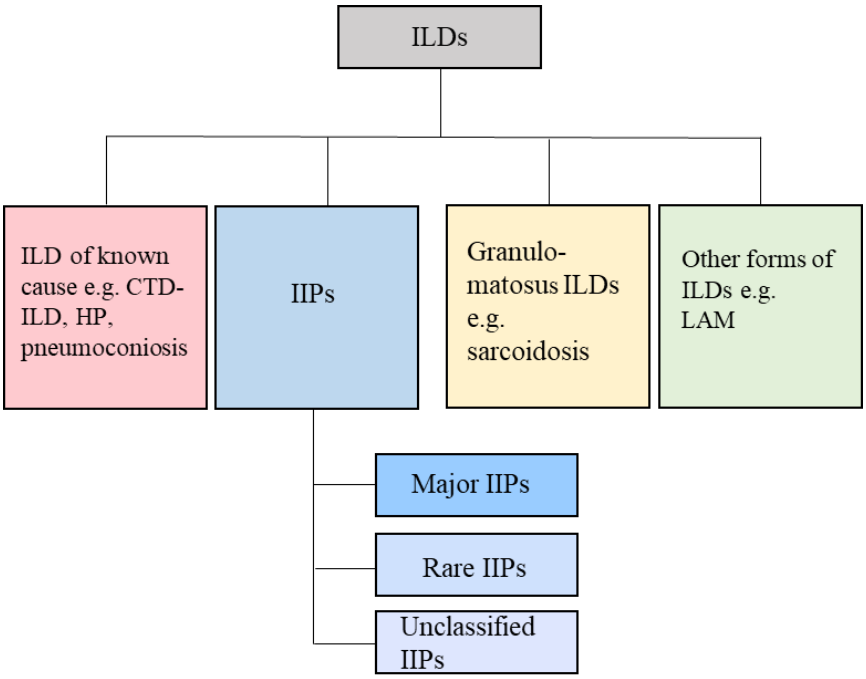


Figure 1. Categorization of ILDs (3, 8, 9). CTD: connective tissue disease, HP: hypersensitivity pneumonitis, IIPs: idiopathic interstitial pneumonias, ILDs: interstitial lung diseases, LAM: lymphangioleiomyomatosis.

Typical clinical symptoms of ILDs are exertional dyspnea and dry cough. Abnormal auscultation findings are often detectable above the lungs, in advanced stages

velcro-like inspiratory fibrotic crackles might be present, predominantly on the lung bases. In cases of a more progressed disease, the use of respiratory accessory muscles and digital clubbing can be present (1, 3, 6, 10). Laboratory tests often show the absence of abnormal changes, immunoserological tests are important in the differential diagnosis of ILD associated with connective tissue disease (CTD) (11-14). PFTs can be normal, however patients are mostly characterized by a mild restrictive ventilatory defect with decreased static parameters: forced vital capacity (FVC), total lung capacity (TLC), vital capacity (VC), functional residual capacity (FRC) and residual volume (RV). A proportionate decline in forced expiratory volume in 1 second (FEV1) may be observed. Consequently, it is generally expected that the ratio of FEV1 to FVC remains normal or even increased. ILDs with simultaneous airway involvement (e.g. asthma bronchiale) show concomitant decrease in FEV1/FVC ratio. The diffusion capacity of the lungs for carbon monoxide (DL_{CO}) is often reduced in ILDs (3). Arterialized blood gases (ABG) can vary from normal to severe hypoxaemia (partial respiratory failure). In the case of normal ABG parameters measured at rest, an ABG analysis during physical exertion is recommended, for which the 6-minute walk test (6MWT) is an excellent and well-defined diagnostic measurement. End-stage global respiratory failure, when associated with decreased carbon dioxide elimination can lead to hypercapnia (15). When ILD is suspected the gold standard diagnostic imaging modality is high-resolution computed tomography (HRCT) (3, 6). Additionally a bronchoscopic procedure for bronchoalveolar lavage (BAL) cellular evaluation (lymphocyte, neutrophil, eosinophil, mast cell counts) is helpful in the diagnosis. In case of appropriate clinical and radiological context the bronchoalveolar lavage (BAL) sample might support the identification or exclusion of certain types of ILDs. BAL fluid lymphocytosis (>15%) might indicate NSIP, sarcoidosis, HP, drug-induced pneumonitis or CTD-ILD, while neurophil pattern might suggest idiopathic pulmonary fibrosis (IPF) (>3%), or possibly CTD-ILD. Usually macrophage predominance with smoking history refers to respiratory bronchiolitis interstitial lung disease (RB-ILD) or desquamative intersitital pneumonia (DIP). Eosinophilic pattern might be related to eosinophilic pneumonia or eosinophilic granulomatosis with polyangitiis (former Churg-Strauss syndrome). Nevertheless, a normal BAL cell distribution does not exclude the presence of disease (16). BAL cellular patterns are summarized in Table 1.

Table 1. Summary of BAL cellular patterns in healthy adults and in patients with ILD based on the Official Clinical Practice Guideline of the American Thoracic Society (ATS) (16).

I. Normal Adults (nonsmokers)		**BAL Differential Cell Counts**
• Alveolar macrophages • Lymphocytes (CD4+/CD8+= 0.9–2.5) • Neutrophils • Eosinophils • Squamous epithelial*/ciliated columnar epithelial cells**		• 85% • 10-15% • <= 3% • <1% • <=5%
II. Interstitial lung diseases		
Disorders associated with increased percentage of specific BAL cell types		
Lymphocytic cellular pattern	***Eosinophilic cellular pattern***	***Neutrophilic cellular pattern***
>15% lymphocytes • Sarcoidosis (CD4/CD8 >4) • NSIP • HP • Drug-induced pneumonitis • CTD • Radiation pneumonitis • COP • Lymphoproliferative disorders	>1% eosinophils • Eosinophilic pneumonias • Drug-induced pneumonitis • Bone marrow transplant • Asthma, bronchitis • Churg-Strauss syndrome • Allergic bronchopulmonary aspergillosis • Bacterial, fungal, helminthic, Pneumocystis infection • Hodgkin's disease	>3% neutrophils • CTD • IPF • Infection: bacterial, fungal • Bronchitis • Asbestosis • Acute respiratory distress syndrome • Diffuse alveolar damage

BAL: bronchoalveolar lavage, COP: cryptogen organizing pneumonia, CTD: connective tissue disease, IPF: idiopathic pulmonary fibrosis, NSIP: nonspecific interstitial pneumonia. * The presence of squamous epithelial cells indicates upper airway secretion contamination. ** Epithelial cells > 5% suggest suboptimal sample (BAL cellular patterns should be interpreted with caution).

Notably, transbronchial cryobiopsy or video assisted thoracic surgery (VATS) might help in establishing the diagnosis when the clinical features are uncertain and the HRCT pattern is non-diagnostic (17). However, it is important to note that surgery of the ILD lung is associated with high risk of exacerbation of the underlying disease, and has a low, but unacceptable mortality rate for a diagnostic procedure (6).

Ultimately, a multidisciplinary discussion (MDD) is considered to be the diagnostic and management reference standard of ILDs. MDDs are participated by pulmonologists, radiologists and a pathologist, if a histopathologic sample is available. Due to the high number of CTD-ILDs in many cases rheumatologists and immunologists are also involved in the work of the MDD. In the future more accurate diagnostic guidelines are required in this field (9, 18-20).

1.1.1. Idiopathic interstitial pneumonias (IIPs)

Idiopathic interstitial pneumonias are characterized by the absence of environmental exposure (e.g., dusts, gases, drugs) and are not associated with autoimmune diseases. IIP-s include major, rare and unclassified groups as it is shown in Figure 2.

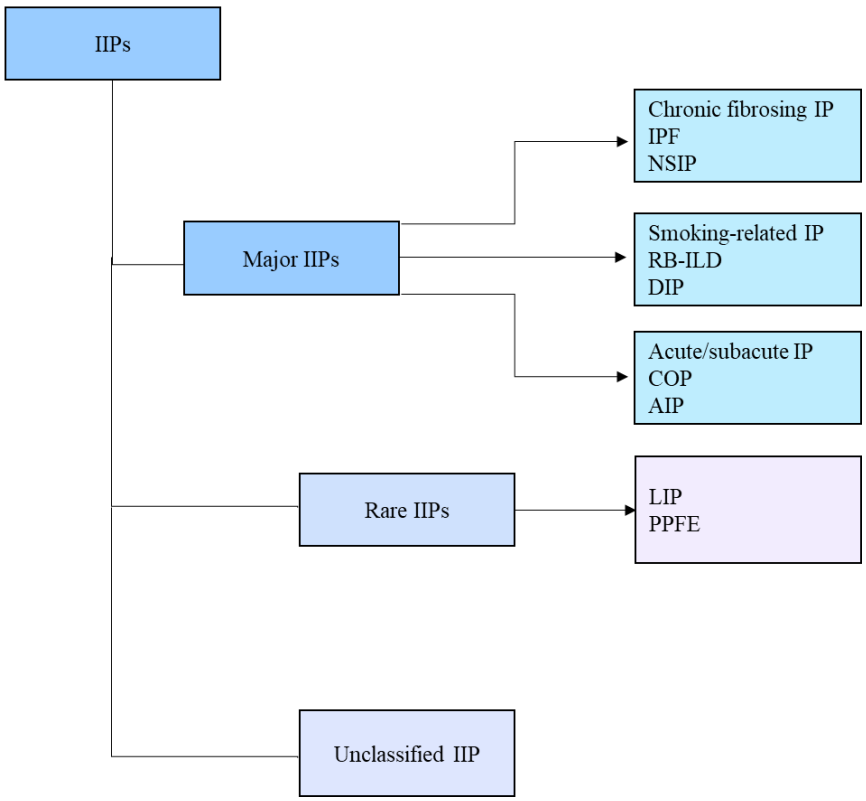


Figure 2. Idiopathic interstitial pneumonias (3, 6, 8-10). AIP: acute interstitial pneumonia, COP: cryptogenic organizing pneumonia, DIP: desquamative interstitial pneumonia, IIPs: idiopathic interstitial pneumonias, IPF: idiopathic pulmonary fibrosis, LIP: lymphoid interstitial pneumonia, NSIP: nonspecific interstitial pneumonia, PPFE: pleuroparenchymal fibroelastosis, RB-ILD: respiratory bronchiolitis interstitial lung disease.

The etiology and pathogenesis of IIPs are still unclear. It is possible to assume some kind of inflammatory process in the background, however, according to recent theories, the structural changes in the lungs are caused by a pathological healing process and regeneration defect. First, the alveolar epithelial cells of the lung and the subepithelial basal membrane get damaged, and due to fibroblast proliferation and an abnormal wound healing response extracellular matrix (ECM) gets deposited leading to fibrotic changes of the lungs. In many ILDs an interaction of environmental damage, infections and genetic risk factors might be the trigger causing structural change in the interstitium as described above (21-23). However, it should be emphasized that not all IIPs develop fibrosis. Key cytokines and molecules involved in pathogenesis are transforming growth factor (TGF) -β (enhances collagen production), platelet-derived growth factor (PDGF), tumor necrosis factor (TNF) – α, vimentin and actin adhesion molecules for excessive ECM deposition), interferon (IFN) -γ deficiency. Familial forms have been associated with α1-antitrypsin inhibitor alleles on chromosome 14 and heterogeneous mutations in SFTPC, SFTPA2, TERT, TERC genes (10, 23-28). Genome-wide analysis researches found an association between a variant of the MUCB promoter (MUC5B) and the appearance of sporadic as well as familial IPF (21-23, 29-31).

The prototype and –very often- a progressive form of IIPs is IPF. IPF occurs typically in men who are former or current smokers over the age of 60, while iNSIP with more favorable prognosis has a female predominance and is more common in non-smokers (10, 23, 32, 33). The most common symptoms are exercise induced dyspnea and dry cough, as described in the introduction (3, 6, 10). The new diagnostic algorithm according to recent clinical practice guidelines is shown in Figure 3 (17). The most common radiological HRCT patterns are listed in Table 2. (6, 23, 34).

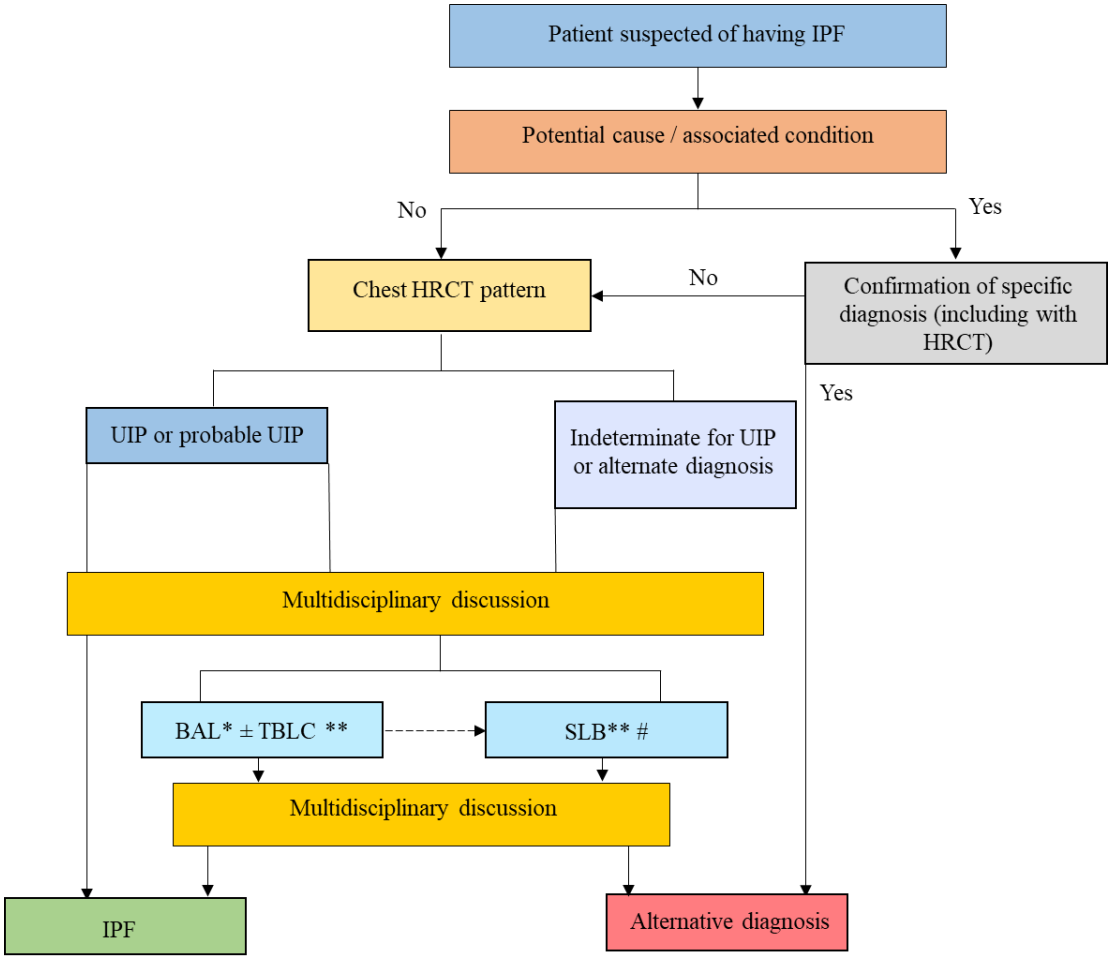


Figure 3. Diagnostic algorithm for idiopathic pulmonary fibrosis (IPF) modified from the Official ATS/ European Respiratory Society (ERS)/ Japanese Respiratory Society (JRS)/ Latin American Thoracic Society (ALAT) Clinical Practice Guideline (2022) (17). BAL: bronchoalveolar lavage, HRCT: high-resolution computed tomography, IPF: idiopathic pulmonary fibrosis, SLB: surgical lung biopsy, UIP: usual interstitial pneumonia, TBLC: transbronchial lung cryobiopsy. *BAL may be performed before MDD in some patients evaluated in experienced centers.** Transbronchial lung cryobiopsy (TBLC) may be preferred to surgical lung biopsy (SLB) in centers with appropriate expertise and/or in some patient populations. A subsequent SLB may be justified in some patients with nondiagnostic findings on TBLC. # Only in exceptional cases.

Table 2. Common radiological patterns of IIPs (modified from references (6, 23, 34)).

	Usual interstitial pneumonia (UIP)	**Probable (p) UIP**	**Indeterminate for UIP**	**Nonspecific interstitial pneumonia (NSIP)**
Distribution	subpleural, basal predominant	subpleural, basal predominant	subpleural, basal predominant, often variable	subpleural, basal predominant
HRCT pattern	reticulation, honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis, GGO (ground glass opacity) only within the fibrotic areas	reticular pattern with peripheral traction bronchiectasis or bronchiolectasis without honeycombing, mild GGO	pattern suggestive of fibrosis, which is only discretely suggestive of UIP	traction bronchiectasis, GGO overspreads fibrosis

Managing IIPs is challenging for respiratory physicians. In ILD-s where inflammatory processes dominate the clinical picture (on HRCT often presenting as alveolitis), corticosteroids and other immunosuppressive agents might have a therapeutic effect (8, 22, 23, 35). Alternatively, azathioprine (AZA) (side effects: hepatotoxicity, bone marrow suppression) cyclophosphamide (side effects: hemorrhagic cystitis, nausea, vomiting, bone marrow suppression) may be given as a second-line drug, even in combination with corticosteroids, especially in acute IIP and cryptogenic organizing pneumonia (COP) (22, 23). Consequently, blood count and liver function tests should be performed at baseline and during treatment. In the case of smoking-related IIP, smoking cessation can lead to regression of the inflammation (22, 23).

In IPF, as frontline therapy antifibrotics are recommended to slow the fibroproliferative progression (35). Nintedanib is a triple intracellular tyrosine kinase inhibitor targeting different growth factor receptors (fibroblast-derived growth factor (FDGF), PDGF, VEGF). Randomized controlled trials confirmed its favorable effects associated with lung function stabilization, exacerbation reduction and maintaining quality of life in IPF. Most frequent adverse events are diarrhea, nausea, nasopharyngitis, cough and elevated liver enzymes (36-38). The other antifibrotic drug is pirfenidone, which mainly inhibits TGF-β-stimulated collagen synthesis and has anti-inflammatory and antioxidant effects. It reduces decline in FVC and improves progression-free survival. (39-44). Possible adverse events are nausea, rash, dyspepsia, dizziness, photosensitivity reaction, anorexia, elevated transaminases (45-47). Additionally, due to increased risk of mortality and hospitalization the use of immunosuppression is not recommended in IPF, only during exacerbations high-dose glucocorticosteroids can be initiated (10, 21, 23, 48-51).

In addition to these specific therapies, long term oxygen therapy (LTOT) can be initiated to support physical activity in the case of hypoxia (52). Lung transplantation is the only option that improves survival in fast progressing fibrotic IIPs. For these patients lung transplantation is a major indication (23, 53). Promising trials are available regarding stem cell-based therapies as novel therapeutic methods (23, 54).

The role of the ILD MDD in differential diagnosis is crucial. It is important to distinguish IIPs from other ILDs of known etiology. Extrapulmonary symptoms like skin, joint, and internal organ involvement are characteristic of autoimmune ILD. A small percentage of patients with iNSIP may develop manifest connective tissue disease (CTD) -ILD. The term interstitial pneumonia with autoimmune features (IPAF) has been established for cases exhibiting autoimmune characteristics but not meeting the criteria for CTDs (23, 55).

1.1.2. Connective tissue disease-associated interstitial lung disease (CTD-ILD)

CTDs, including systemic sclerosis (SSc), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), idiopathic inflammatory myopathies (IIM), Sjögren's-syndrome (SS) might affect the respiratory tract and develop ILD. Notably, in some cases the diagnostic criteria of systemic autoimmune disorders are not completely fulfilled and at this point the definition of "lung-dominant" CTD should be considered (56-58). Moreover, dose-dependent and immune-mediated drug-induced ILDs complicate the verification of the exact etiology (59, 60).

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

SSc is one of the most common systemic autoimmune disorders affecting inflammatory and tissue regeneration pathways. The most common symptoms of SSc are skin sclerosis, puffy fingers and Raynaud phenomenon. Depending on skin localization and internal organ involvement (61) immunologists differentiate limited cutaneous (lc) SSc, diffuse cutaneous (dc) SSc, sine scleroderma (ss) SSc and SSc with overlap syndrome (61-63). Discussing subtypes in detail lies beyond the scope of this thesis. Direct and indirect pulmonary involvements are distinguished, and lung parenchymal abnormalities occur more often in the early period of dsSSc, however they are not as prevalent in lcSSc (64). Table 3. shows a summary of the direct and indirect respiratory manifestations (13, 65).

Table 3. Pulmonary manifestations in SSc (65).

Direct pulmonary manifestations PAH ILD with or without PH Airway disease Pleural involvement
Indirect pulmonary manifestations Gastro-esophageal reflux and aspiration Infection Drug toxicity Malignancy Respiratory muscle weakness Restrictive lung disease from skin involvement Secondary cardiac involvement
Combination of direct and indirect pulmonary manifestations
Other lung diseases unrelated to SSc COPD/emphysema Asthma bronchiale Pulmonary nodules

COPD: chronic obstructive pulmonary disease, ILD: interstitial lung diseases, PAH: pulmonary arterial hypertension, PH: pulmonary hypertension.

Out of these, ILD develops in approximately 80% of SSc patients (in 25-30% a progressive form exists) and together with pulmonary hypertension (PH) - which can manifest in all form in SSc, including isolated pulmonary arterial hypertension (PAH), ILD associated PH and combinations of these - are the leading cause of mortality (13, 66-71). Typical morphological pattern on HRCT is basal and subpleural NSIP, mainly with fibrotic reticulation, traction bronchiectasis and GGO, the latter is rarely reversible. Smaller numbers of patients present with UIP or other scarcer patterns (13, 65, 72-74). Interestingly, honeycombing occurs more in lsSSc (75). Main pulmonary SSc symptoms include dry cough and exercise induced dyspnea. PFT shows restrictive ventilatory defect with the reduction of TLC, FVC, FEV1 and DL_{CO} (13, 76-78) . Using a simple staging system proposed by Goh et al. prognosis of the disease can be estimated based on HRCT extension and FVC (Figure 4.) (79).

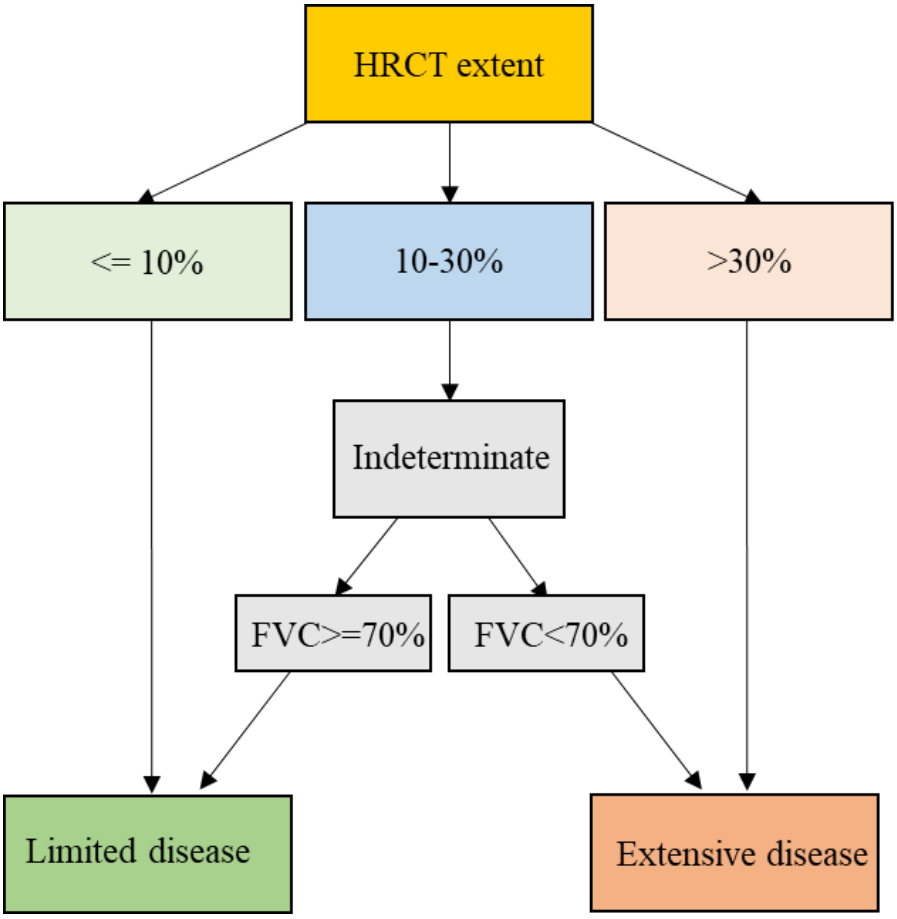


Figure 4. Staging system of limited and extensive disease. Figure is based on HRCT scores and Goh criteria (79). FVC: forced vital capacity, HRCT: high-resolution computed tomography.

Factors favoring the development of SSc-ILD include African-American ethnicity, high skin score, hypothyroidism, cardiac involvement, gastroesophageal reflux and the presence of anti-topoisomerase I (anti-SCL-70), anti-endothelial cell, anti-U11/U12 ribonucleoprotein antibodies (13, 65, 80-82). The showing of anti-centromere is less prevalent in SSc-ILD, but more common in lsSSc and PAH, whereas anti-SCL-70 positivity is more common in dsSSc and Ssc-ILD, but less likely to be associated with PAH (13, 65). Other factors that are linked with severe restrictive lung disease are a decreased baseline FVC and DL_{CO} with an extensive ILD and presence of honeycombing on HRCT. Elevated serum C-reactive protein and Krebs von den Lungen-6 level and younger age at the time of the diagnosis also worsen prognosis. (65, 69, 83-87).

Risk factors of progression and mortality alternate each other as expected (69, 85). The progression of disease in SSc-ILD may differ depending on whether there is a significant, moderate, or major decline in FVC or if FVC remains stable or improves. The rate of progression can be rapid or slow, with a longer duration of stable disease or improvement (87). Notably, a prospective analysis of The European Scleroderma Trials And Research (EUSTAR) database in 2021 found no association between degree of progression and mortality (87). Treatment of SSc is routinely based on immunosuppressive drugs adjusted by immunologists due to the primary disorder and there is no universal treatment guideline for lung dominant SSc (61, 88-90). In SSc-ILD cyclophosphamide (CYC) proved to have benefits on lung function, pulmonary and skin symptoms compared to placebo and AZA (91, 92). Later, in the Scleroderma Lung Study II (SLS II) mycophenolate mofetil (MMF) also showed significant improvement in PFTs, lung radiology, pulmonary symptoms and skin score with having a more favorable adverse event profile compared to CYC and placebo (93-95). As MMF is better tolerated than CYC, it is considered the first therapeutic choice in SSc-ILD (13, 93, 94, 96, 97). In case of side effects, AZA may be an option as it is revealed in a few earlier studies (98, 99). Use of corticosteroids is recommended only in low dosage as corticosteroid therapy can increase the risk of scleroderma renal crisis (100-102). Methotrexate (MTX) is beneficial for skin related symptoms in early dsSSc, but there is no evidence for improvement in any other organ manifestations, including lungs (88). Some promising results are available on biological treatments, such as rituximab (RTX) and Interleukin-6 (IL-6) antagonists showing lung function stabilizing effect (103-106). In a Phase III

randomized controlled trial the drug tocilizumab was found to be effective in preserving lung function and slowing down the decline in FVC in patients with SSc-ILD (105, 107). Randomized trials were conducted to investigate the safety and efficacy of hemopoetic stem cell transplantation, however, it is not a generally accepted treatment protocol (108-110).

In progressive forms of SSc-ILD nintedanib is a promising therapeutic option. In the SENSCIS (A Trial to Compare Nintedanib with Placebo for Patients with Scleroderma Related Lung Fibrosis) randomized, placebo-controlled trial its beneficial effect was proven regarding lung function decline (annual change in FVC amounted -52.4 ml per year with nintedanib and -93.3 ml per year in the placebo group, p=0.04). Notably, during the SENSCIS study numerous patients were on continuous MMF treatment. The side effect profile of nintedanib seemed to be tolerable, with gastrointestinal symptoms being observed in the majority of cases (111). In the ongoing (assessed May 2023) placebo-controlled Scleroderma Lung Study III (ClinicalTrials.gov indicator: NCT03221257) the effects of pirfenidone treatment combining with MMF are currently being investigated. The tolerable adverse event profile of pirfenidone is already known, though we still have to wait for data on its effectiveness (112). In end-stage organ failure lung transplantation can be considered, however, it is a controversial topic as lung transplantations and not routinely performed in systemic autoimmune disorders. Only a few centers worldwide are offering the procedure to a carefully selected group of SSc patients (53, 113-115). Palliation and nonpharmacological care, such as rehabilitation are important for maintaining the quality of life in this special patient group (116).

In summary, slower progression rate of lung function in SSc-ILD may be unnoticed by clinicians leading to a delay in the timing of treatment initiation. Therefore, close monitoring of this population, and considering risk factors of progression is necessary. Combined application of immunosuppressive (ISU) therapy and antifibrotics might be advantageous in the future. However, further randomized controlled trials and optimal initiation of therapy are necessary (87).

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

RA is a systemic inflammatory disorder leading to polyarthritis, joint destruction and synovitis, mainly the metacarpophalangeal and proximal phalangeal joints are involved. In the immunserologic tests rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (anti-CCP) are detectable. Pulmonary manifestation is the most common extra-articular involvement. Normally, pulmonary symptoms begin after symmetric polyarthritis, however, in rare forms of RA respiratory manifestation can overtake joint involvements. The complete respiratory system, such as lung parenchyma (ILD (UIP, NSIP, COP, LIP, DIP) and rheumatoid nodules), pleura (effusion and nodules), airways (obliterative or follicular bronchiolitis, airway hyperreactivity, cricoarytenoid arthritis, laryngeal rheumatoid nodules, vocal cord paralysis) and vasculature (PH, vasculitis) might be affected. ILD occurs mostly in smoking males over the age of 50. The UIP radiological pattern is the most prevalent which is also the main cause of RA disease related deaths (14, 117, 118). After identification of the respiratory symptoms and radiological signs on the chest X-ray examination, HRCT evaluation and MDD are required. In cases where the diagnosis is not clearly established or in cases where infection is suspected BAL and / or transbronchial-, cryo-, or surgical lung biopsy are recommended (117).

Treatment is challenging in RA and a multidisciplinary approach in agreement with rheumatologists is necessary. As frontline therapy conventional synthetic disease modifying anti-rheumatic drugs (DMARD) such as MTX, leflunomide, sulfasalazine or glucocorticoids are approved alone or in combination. With such treatment clinical remission of NSIP and COP is more likely (117, 119, 120). In the case of no significant improvement or when poor prognostic factors are present biological DMARDs, such as tumor necrosis inhibitors, RTX or IL-6 inhibitors are favored for improving joint complaints, disease activity and severity (117, 119). Introduction of new DMARD therapies demands close monitoring due to drug-induced ILDs and increased risk of infections (117). In progressive forms of RA-ILD antifibrotic treatment as a second-line additive therapy might be a good option in reducing FVC decline and lung involvement progression as it is highlighted in section 1.5. (39, 43, 44, 121).

1.1.2.3. Other CTD-ILDs

The respiratory tract and lung parenchyma might also be affected diversely in later stages of other rheumatic disorders with a wide variety of symptoms, from mild to life threatening pulmonary involvement. It has to be pointed out, that in rare forms of the disease the pulmonary manifestation can precede skin and musculoskeletal lesions (122). In SLE pleuritis, pleural effusion, airway manifestations, organizing pneumonia (OP), infections of the lung parenchyma, acute lupus pneumonitis, diffuse alveolar hemorrhage, pulmonary embolism due to antiphospholipid syndrome, often PH can be detected. ILD is only recognized in rare cases of SLE and the disease course is more benign in contrast to other CTD-ILDs. Shrinking lung syndrome in SLE refers to diaphragm dysfunction (122-128). SS mostly causes exocrine gland inflammation and can appear as a primary disorder or in association with other CTDs. In the case of pulmonary manifestation, distal airways might be affected and ILD – most frequently fibrosing NSIP (45%), occasionally OP, UIP or LIP- may be present in this chronic autoimmune disorder (122, 129). The combined presence of the autoimmune diseases that are mentioned above is called mixed connective tissue disease (MCTD). Its main clinical involvement of the respiratory system are serositis, PH and ILD (122, 130-134).

The term of IIM comprises disorders with myositis. Myalgia, skin involvement (periorbital rash, erythematous papules on the chest, neck, extensor surfaces of elbows and, Gottron papules) and extra-muscular manifestations including lung involvement can be present in IIMs. The latter has a significant effect on mortality and morbidity (135-140). ILD is the most common respiratory manifestation in IIM and occurs mostly in dermatomyositis and in anti-tRNA synthetase syndrome. It may be present before musculoskeletal and skin lesions (135, 141). Anti-melanoma differentiation-associated protein 5 (MDA5) positive ILD marks a severe form of acute ILD in dermatomyositis (142, 143). On HRCT, NSIP, OP or their overlapping form are most often visible. UIP pattern is associated with the presence of anti-Jo-1 antibodies (135, 144-146).

Diagnosis is crucial in systemic autoimmune disorders because of treatment benefits. In Hungary specialized treatments are initiated by immunologists. Clinical symptoms, specific serological findings are important pillars in diagnosis. Additionally, in some cases histological biopsy is needed (e.g. in IIMs). Bronchoscopy and BAL cell distribution in existing respiratory involvement is helpful in excluding other pulmonary diseases (e.g. infection, malignancy, diffuse alveolar hemorrhage) (122). PFT supports the differentiation between obstructive airway and restrictive interstitial involvement, decrease in diffusion parameters suggest the presence of ILD or PH. Reduced maximal inspiratory and expiratory pressures refer to diaphragm dysfunction. Surgical lung biopsy or transbronchial cryobiopsy are only considered in a few exceptional cases (135). In SLE, SS and MCTD treatment is needed only in symptomatic forms, and in cases of high disease activity, it tends to be more profitable in NSIP. Nonsteroidal anti-inflammatory drugs and colchicine seem to be beneficial in pleuritis. In progressive forms, the antifibrotic nintedanib is adjustable as it is discussed in Section 1.5. (17, 122). Management in IIM-ILD is based on corticosteroids and ISU drugs (MMF, CYC, RTX, AZA), adjusted and controlled according to disease severity(135).

1.1.3. Interstitial pneumonia with autoimmune features (IPAF)

In recent years, many studies have been conducted on cases where interstitial pneumonia is clinically and serologically associated with autoimmune characteristics and it can be assumed that there is an autoimmune disorder in the background that does not yet meet the definition of obvious CTDs. For this reason numerous nomenclatures were born such as undifferenciated CTD (UCTD), lung-dominant CTD, autoimmune-featured ILD, early CTD, overlap CTD – created by research groups all over the world (57, 147-151). In 2015 Task Force on Undifferenciated Forms of CTD-associated ILD of the ERS and the ATS proposed a new concept for this phenomenon: interstitial pneumonia with autoimmune features (IPAF) (55) (Figure 5).

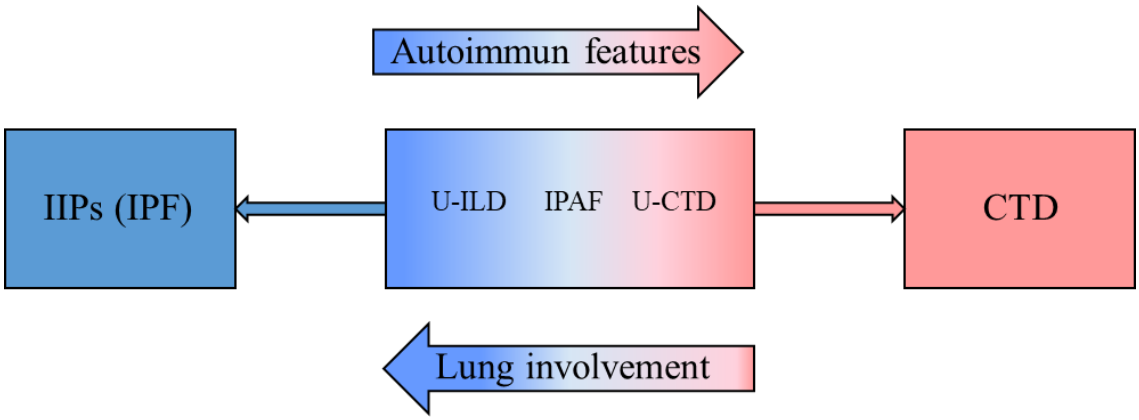


Figure 5. Position of IPAF in ILD continuum (152). CTD: connective tissue disease, IIP: idiopathic interstitial pneumonia, IPAF: interstitial pneumonia with autoimmune features, IPF: idiopathic pulmonary fibrosis, UCTD: undifferentiated connective tissue disease, UILD: undifferentiated interstitial lung disease.

Therefore, IPAF as a research entity is established for a special subgroup of patients characterized by IIP, who have the clinical feature of underlying CTD, but lack the current criteria for CTDs. It is a controversial topic, whether IPAF is a pulmonary manifestation of a systemic disorder or an autoimmune process affecting primary the lungs (153). The classification criteria of IPAF is based on 4 pillars: presence of an interstitial pneumonia on HRCT imaging or surgical lung biopsy, exclusion of alternative ILD etiologies, such as occupational and enviromental exposures, insufficiency for the

criteria of current CTDs, one feature from at least two of clinical, serological and morphological domains (55, 153). Classification criterias and different domains are summarized in Table 4.

Table 4. Classification criteria of IPAF (modified from reference 153).

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) and, 2. Exclusion of alternative aetiologies and, 3. Does not meet criteria of a defined connective tissue disease and, 4. At least one feature from at least two of these domains: A. clinical domain B. serological domain C. morphological domain
A. Clinical domain 1. Distal digital fissuring (i.e. “mechanic’s hands”) 2. Distal digital tip ulceration 3. Inflammatory arthritis or polyarticular morning stiffness ⩾60 min 4. Palmar telangiectasia 5. Raynaud’s phenomenon 6. Unexplained digital oedema 7. Unexplained fixed rash on the digital extensor surfaces (Gottron’s sign)
B. Serological domain 1. ANA ⩾1:320 titre, diffuse, speckled, homogeneous patterns or a. ANA nucleolar pattern (any titre) or b. ANA centromere pattern (any titre) 2. Rheumatoid factor ⩾2× upper limit of normal 3. Anti-CCP 4. Anti-dsDNA 5. Anti-Ro (SS-A) 6. Anti-La (SS-B) 7. Anti-ribonucleoprotein 8. Anti-Smith 9. Anti-topoisomerase (Scl-70) 10. Anti-tRNA synthetase (e.g. Jo-1, PL-7, Pl-12, EJ, OJ, KS, Zo, tRS) 11. Anti-PM/Scl 12. Anti-MDA-5
C. Morphological domain 1. Suggestive radiology patterns by HRCT: a. NSIP b. OP c. NSIP with OP overlap d. LIP 2. Histopathology patterns or features by surgical lung biopsy: a. NSIP b. OP c. NSIP with OP overlap d. LIP e. Interstitial lymphoid aggregates with germinal centres f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles) 3. Multicompartment involvement (in addition to interstitial pneumonia): a. Unexplained pleural effusion or thickening b. Unexplained pericardial effusion or thickening c. Unexplained intrinsic airways disease* (by PFT, imaging or pathology) d. Unexplained pulmonary vasculopathy

ANA: antinuclear antibody, Anti-CCP: anti-cyclic citrullinated peptide antibody, ds: double-stranded, HRCT: high-resolution computed tomography, LIP: lymphoid interstitial pneumonia, NSIP: nonspecific interstitial pneumonia, OP: organizing pneumonia, PFT: pulmonary function testing, SS: Sjögren's syndrome, tRNA: transfer ribonucleic acid * Includes airflow obstruction, bronchiolitis or bronchiectasis.

So far, mainly retrospective researches have been available about IPAF, we are aware of only a few prospective cohort studies (154-159). In most studies the mean age of patients is 60-70 years and the majority of patients are female. (154-158, 160-162). However, in some studies a male predominance was proven (156, 160, 161). In the PFT a slight restrictive pattern with DL_{CO} reduction is characteristic (154-157, 160, 161). Most common clinical symptoms are Raynaud phenomenon and inflammatory arthritis. Most frequently detected antibodies are anti-nuclear antibodies (ANA) and anti-SSA (Ro52 and Ro60) and NSIP is the predominant radiological pattern (163). UIP pattern was not added to morphological domains as there is a probability that there is an underlying autoimmune process with UIP pattern. However, patients with UIP might have IPAF, if they meet at least one clinical or serological domain or other morphologic involvement (55). Notably, when UIP pattern is confirmed, a worse, IPF-like prognosis is expected. In comparison to non-UIP pattern, which is associated with a much more favorable, CTD-ILD like prognosis and survival (151, 153, 164). In a prospective nationwide multicentre cohort study IIP patients were divided according to their presentation of the IPAF criteria. This study shed light on, what autoimmune characteristics are accompanied with more favourable prognosis (159).

Only a few studies focused on treatment approach for IPAF. Therapeutic strategy is mainly based on ISU drugs due to CTD similarity and encouraging results are available for CYC, while MMF effectiveness requires more clinical investigations (163, 165-168). In case of UIP pattern, patients might benefit from the progression moderating effect of antifibrotics, such as pirfenidone and nintedanib (39, 44).

The boundary between early or incomplete CTDs, UCTD and IPAF is probably very uncertain and the criteria systems of the latter two groups might overlap with each other. In many cases, IPAF and UCTD might progress into real CTD (RA, SS, IIM) (151, 169). There would be a great demand for accurate differentiation and the exact establishment of criteria systems, in order to better understand the nature of the diseases, as well as the correct therapeutic approaches (153).

1.1.4. Progressive pulmonary fibrosis (PPF)

While IPF is the most common form of progressive ILD, a progressive fibrosing phenotype can develop in conditions other than IPF, despite clinicians choosing the best available treatment. Progressive pulmonary fibrosis (PPF) is accompanied by similar disease course like IPF, with worsening and/or severe respiratory symptoms, reduced lung function, deterioration of quality of life and ultimately increased risk of mortality. Previously, the literature and clinical trials referred to these entities as progressive fibrosing ILD (PF-ILD). However, the classification criteria were not uniform leading to much confusion. The most widely accepted diagnosis included worsening of clinical symptoms (dyspnea), an increase in the extent of the radiological pattern, and impaired PFT values (35, 42, 170, 171). In 2022, an unified definition was created under the name of progressive pulmonary fibrosis (PPF) published in the clinical practice guideline of the world's major respiratory societies (ATS, ERS, JRS, ALAT) (17). For setting up diagnosis two of the following three points must be fulfilled:

1. Worsening of respiratory symptoms within 1 year
2. Physiological progression
   - Absolute decline in FVC ≥ 5% predicted within 1 year of follow-up
   - Absolute decline in DL_{CO} (corrected for hemoglobin) ≥10% predicted within 1 year of follow-up
3. Radiological progression in extent or severity within 1 year (e.g. of traction bronchiectasis or bronchiolectasis, GGO, reticular abnormality, honeycombing, increased lobar volume loss) (17).

There is no guideline for the monitoring of PPF, but it is preferable to use the IPF protocol and repeat PFT-s and 6MWT-s every 4-6 months, accompanied by HRCT every 12-24 months. Or if clinically indicated (worsening of symptoms or suspicion of exacerbation), earlier (17). In the therapeutic point of view, the guideline makes a clear recommendation to apply the antifibrotic drug nintedanib, if the patient progresses to PPF despite standard treatment of the underlying disease. Efficacy of nintedanib was proven in the Efficacy and Safety of Nintedanib in Patients with Progressive Fibrosing Interstitial Lung Disease (INBUILD) trial. In this randomized, double-blind study patients from 15 countries, with different types of PPF (CTD-ILD, hypersensitivity pneumonitis (HP),

iNSIP, unclassifiable IIP) received nintedanib or placebo during a 52-week follow-up period. The annual rate of FVC decline was significantly lower in patients on the nintedanib arm compared to placebo treatment group (mean: -80.8 ml vs. – 187.8 ml/year) for the entire population (39). At the same time, the new guideline encourages further research on the field of using pirfenidone as its application in PPF has insufficient evidence so far (17, 43).

2. OBJECTIVES

1. Determination of the patient characteristics, clinical symptoms and serological findings in CTD-ILD and IPAF population in Hungary

2. Evaluating the decline in functional stability and estimating the prevalence of PF-ILD* in the CTD-ILD and IPAF population

3. Investigation of factors influencing progression of disease in CTD-ILD and IPAF

4. Determining patient characteristics and clinical symptoms in the Hungarian SSc-ILD population

5. Analysis of HRCT pattern and involvement, lung function abnormalities and serological findings in SSc-ILD

6. Evaluating the distribution of PF-ILD according to treatment subgroups in SSc-ILD and factors of functional decline

* At the time of the studies PPF guideline was still not in place, PF-ILD is representing functional decline as in later PPF guideline.

3. METHODS

3.1. CTD-ILD/IPAF study population

Our study cases were chosen from ILD patients who were discussed during MDD at the Department of Pulmonology at Semmelweis University (172). Data were processed between the evaluation period of January 2017 and June 2019, retrospectively. During this time our MDD viewed 511 ILD suspected cases. Out of these ILD was confirmed among 380 subjects (74.4%) and these were divided into four groups by MDD experts: (1) ILDs with known etiology (N=136, 26.4 %) including mainly confirmed CTD-ILD (N=107, 20.9%) and HP (N=29, 5,7%) cases; (2) IIPs including idiopathic pulmonary fibrosis (IPF), idiopathic non-specific interstitial pneumonia (iNSIP), and other IIPs; (3) granulomatous diseases; and (4) other rare forms of ILDs according to current guidelines (8, 10) (Figure 6.). IPAF subjects were classified into the first group due to their autoimmune traits, in spite of that, IPAF was taken into consideration as a separate entity. In summary, this study focused on ILDs with autoimmune features and the study population consisted of 63 CTD-ILD [32 SSc (50.8%), 13 RA (20.6%), 6 SLE (9.5%), 4 DM/PM (6.4%), 2 vasculitis (3.2%)], 6 other type of ILD (9.5%) and 44 IPAF patients. (Figure 6.) (173). CTD diagnosis was set up according to the internationally accepted American College of Rheumatology/European League Against Rheumatism Collaborative Initiative (EULAR-ACR) clinical and serologic criteria by rheumatology specialists working at specific centers in Central Hungary. CTDs consisted of RA, SSc, SLE, vasculitis, IIM (PM/DM), and other categories (MCTD and UCTD) (63, 174-180). IPAF diagnosis was made using the classification criteria proposed by ERS/ATS in 2015, considering clinical, serological and morphological domains as described in the Introduction chapter (55, 153). To examine the suspicion of underlying CTD, all IPAF patients were referred to rheumatologists at the time of diagnosis or later on, when clinical symptoms appeared. During the observational period none of them progressed manifest CTD (173).

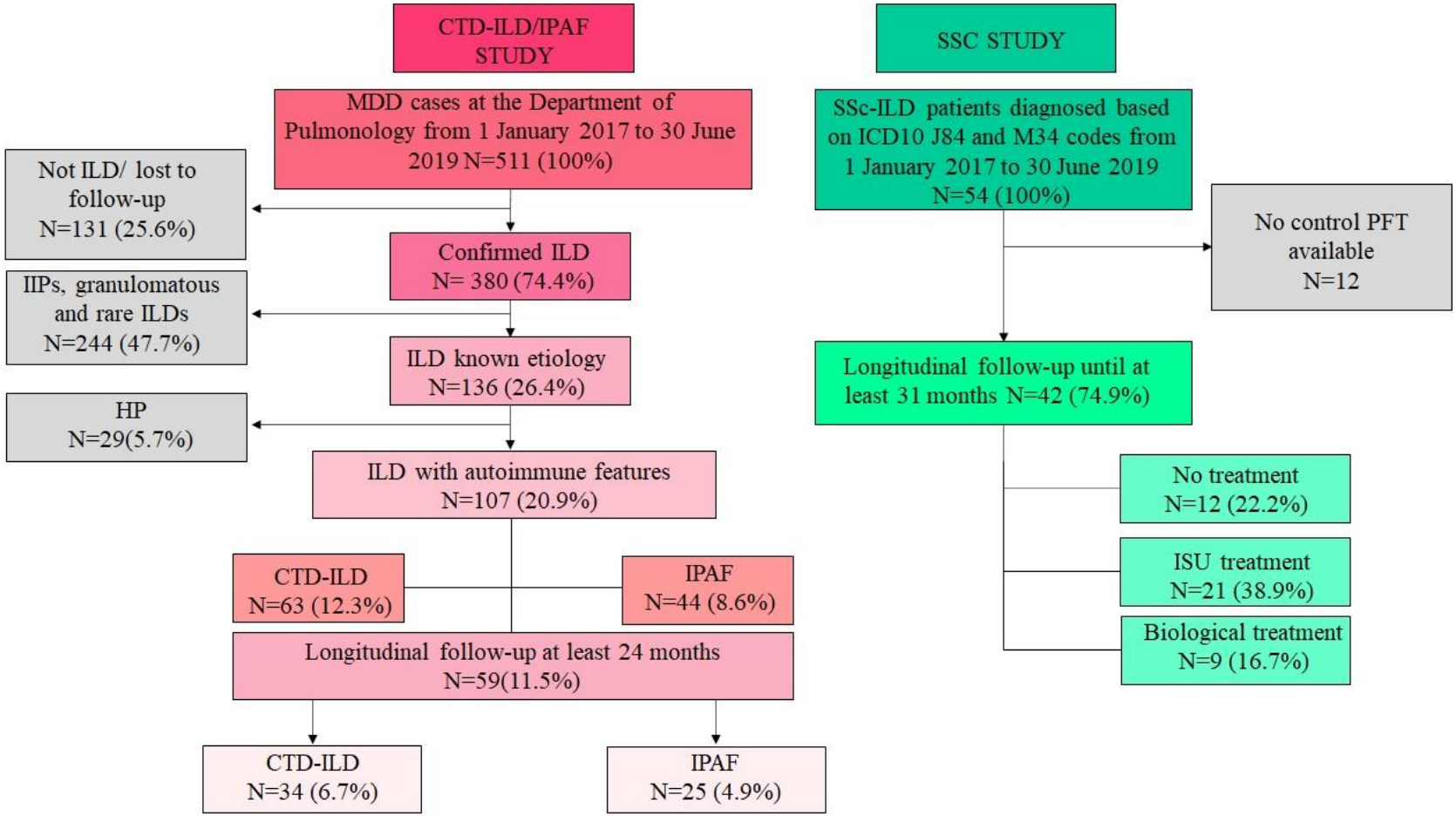


Figure 6. Study population (173, 181). CTD-ILD: connective tissue disease-associated interstitial lung disease, HP: hypersensitivity pneumonitis, IIP: idiopathic interstitial pneumonia; ILD: interstitial lung disease, IPAF: interstitial pneumonia with autoimmune features, ISU: immunosuppression, MDD: multidisciplinary discussion, PFT: pulmonary function test, SSc: systemic sclerosis.

In each case a detailed medical history including comorbidities and physical examination was performed at baseline. The follow-up visits focused on clinical symptoms, such as dry or productive cough, sputum production, chest and joint pain and infections were assessed thoroughly. Baseline PFT, HRCT and ABG measurements were completed at the time of ILD diagnosis. 6MWT as performed to assess functional exercise capacity. This test checks how far a person can walk quickly on a flat surface in 6 minutes. It helps understand how the body responds during exercise, involving breathing, heart, circulation, muscles, and nerves. During the 6MWT, dyspnea at baseline and post-test was assessed using the Borg scale, where a score of 0 indicated no dyspnea, and a score of 10 represented dyspnea at its most severe (181). HRCT examination was also performed in both inspiration and expiration phase using Philips Ingenuity Core 64 and Philips Brilliance 16 CT scanners. The radiological features of each ILD morphology, such as NSIP, pUIP and UIP can be reviewed in details in the Introduction section. The extent of GGO, fibrosis, bronchiectasis and honeycombing were identified by MDD specialists for all the 5 lung lobes based on visual scoring method (182). PFTs consisted of the measurement of FVC, FEV1, FEV1/FVC and TLC according to ATS and current ERS guidelines (183, 184). DL_{CO} was assessed with the single breath CO method and transfer coefficient of the lung for carbon monoxide (KL_{CO}) was also determined (PDD-301/s, Piston, Budapest, Hungary). Multidimensional gender–age–physiology (GAP) index was calculated which is originally an important tool in IPF to predict mortality, but it is also validated for CTD-ILD (185, 186). Blood sampling for autoantibodies consisted of ANA, RF, anti-CCP, anti-RNA polymerase, anti-centromere, anti-proliferating cell nuclear antigen (APCNA), anti-Ku, anti-P-ribosomal, anticytoplasmic, anti-cytoskeleton, anti-chromatin, anti-Smith, anti-myeloperoxidase, anti-proteinase-3, anti-Jo-1, anti-SS-A, anti-SS-B, anti-SCL-70, anti-ribonucleoprotein (RNP), and anti-neutrophil cytoplasmic antibodies (ANCA). The long-term follow-up included pulmonary (PFT measurements, blood samplings, ABG, chest X-ray or HRCT) and rheumatology controls according to the patients' disease requirements. PF-ILD was determined as annual relative FVC decline ≥5% and parallel deterioration of clinical symptoms or progression of fibrosis on HRCT (170). Follow-up time was available in 59 cases (CTD-ILD=34, IPAF=25), an average of 24 months(173).

3.1.1. Statistical analysis

Analysis was performed using the GraphPad software (GraphPad Prism 5.0 Software, Inc., La Jolla, CA, United States) and SPSS v25 (IBM Corporation, Armonk, NY, United States). Parametric variables are expressed as mean ± standard deviation. Normality of the data was examined with Kolmogorov–Smirnov test. Student's t-test for normally distributed data; a Mann–Whitney U-test was used for evaluation the differences between subgroups. Comparison of categorical variables was implemented with Chi squared test and two-tailed Fisher's exact test. Cox proportional hazards regression model was used to detect possible prognostic factors of progression. All % values are expressed for the whole study population (all patients) or respective subgroups as indicated. A p-value <0.05 was defined as statistically significant (173).

3.2. SSc-ILD study population

In our retrospective study we evaluated SSc-ILD patients (based on ICD10 J84 and M34 codes) discussed by the MDD of the Department of Pulmonology at Semmelweis University. Establishing a diagnosis of SSc and initiating treatment were determined by experts at immunological-rheumatological centers in central Hungary, guided by the EULAR-ACR criteria. (63). The prevalence of dcSSc (93%) was predominant in comparison to lcSSc which was only present in 4 cases. The treatment of patients with skin involvement was carried out by dermatology specialists and this research did not assess skin manifestations in detail. All patients were presented and discussed by the MDD. Thus, during the evaluation period between January 2017 and June 2019, 54 SSc-ILD patients were identified and out of these, 42 subjects had longitudinal functional and radiological data until June 2021. Study subgroups were formed based on the currently ongoing therapy of the participants. The subgroups were the following: patients without treatment (n = 12), patients undergoing ISU therapy (CYC or MMF with or without low-dose glucocorticoids), n = 21) and patients receiving biological therapy (RTX or tocilizumab) (n = 9). The patient enrollment is summarized in Figure 6.(187)

In our longitudinal investigation data were acquired from e-MedSolution informatic system. Medical history, including pulmonary symptoms, exposures, body mass index (BMI), comorbidities and medication were registered. Dyspnea was assessed by using the Borg dyspnea scale (188). Patients BMI were categorized based on World Health Organization (WHO) definition: underweight range - under 18.5 kg/m^2, healthy weight range - between 18.5 kg/m^2 and 24.9, overweight range – between 25.0 and 29.9 kg/m^2, and obese range between 30.0 and 39.9 kg/m^2. Physical examination, chest X-ray were performed and ILD was verified by HRCT examination. Processes of HRCT and PFT measurements match the technique described in the Methods part of CTD-ILD/IPAF(173, 187).

To predict mortality GAP score was calculated. Physical activity was measured by using the 6MWT. Arterialized capillary blood gases (ABGs), blood samples for serologic antibodies used in clinical routine were also performed(187).

The follow-up period and treatment time until June 2021 amounted to at least 31 months (in the longest case 53 months) included PFTs, DL_{CO}, KL_{CO} tests, radiological check-ups and therapy management. In our study we defined PF-ILD as an annual relative FVC decline ≥5% and a deterioration of clinical symptoms or a progression of features on HRCT, simultaneously. Rheumatological controls took place independently (170, 187).

3.2.1. Statistical analysis

For statistical analysis we used Graph Pad software (GraphPad Prism 5.0 Software, Inc., La Jolla, CA, USA) and Microsoft Excel (Microsoft Corporation, Redmond,DC, USA). Continuous variables are presented as mean and standard deviation. Testing for normality of the distribution was performed by Kolmogorov-Smirnow test. Differences between the groups were compared with Student's *t* test (for normally distributed continuous data), otherwise the Mann–Whitney U test was used. For investigation parametric variables between therapeutic subgroups Analysis of variance (ANOVA) and Tukey's post hoc analysis were applied. We used the chi-squared test and two-tailed Fisher's exact test for analyzing the non-parametric data. Predictors of the progression were calculated using the odds ratio and plot analysis. Correlation test between the BMI and FVC was performed by logarithmic transformation. All % values are expressed for the whole study population (all patients) or respective subgroups as indicated. A p-value < 0.05 was determined as statistically significant (187).

4. RESULTS

4.1. Determination of the patient characteristics, clinical symptoms and serological findings in the CTD-ILD and IPAF population in Hungary

In our first study 107 patients with autoimmune featured ILD or confirmed CTD fulfilled the inclusion criteria for enrollment, and they were divided into CTD-ILD (N=63) and IPAF (N=44) subgroups. The patient characteristics and clinical symptoms are summarized in Table 5.

Table 5. Patient characteristics (173).

Parameters	**All patients (*N* = 107)**	**CTD-ILD (*N* = 63)**	**IPAF (*N* = 44)**	***p*-value**
Age (years)	63.8 ± 13.9	59.7 ± 14.1	69.6 ± 11.5	**<0.001**
Sex (male/female) N	32:75	13:50	19:25	**0.018**
Ever smoker/Non-smoker N	44:63	22:41	22:22	0.118
Symptoms N (%)	–	–	–	–
Dyspnea	74 (69.2)	37 (58.7)	37 (84.1)	**0.006**
Cough	63 (58.6)	34 (54.0)	29 (65.9)	0.237
Dry cough	38 (35.5)	19 (30.2)	19 (43.2)	0.218
Sputum	25 (23.4)	15 (23.8)	10 (22.7)	1.000
Chest pain	20 (18.7)	10 (15.9)	10 (22.7)	0.452
Joint pain	57 (53.3)	36 (57.1)	21 (47.7)	0.431
Clubbing	12 (11.2)	4 (6.4)	8 (18.2)	0.068
Weight loss	16 (15.0)	3 (4.8)	13 (29.6)	**0.001**
Crackles	63 (58.9)	31 (49.2)	32 (72.7)	**0.017**
Raynaud's phenomenon	32 (29.9)	27 (42.9)	5 (11.4)	**<0.001**
CTD subtype N (%)	–	–	–	–
RA	–	13 (20.6)	–	–
SSc	–	32 (50.8)	–	–
SLE	–	6 (9.5)	–	–
Vasculitis	–	2 (3.2)	–	–
DM/PM	–	4 (6.4)	–	–
Others (MCTD, UCTD)	–	6 (9.5)	–	–

P-value indicates the comparison between CTD-ILD and IPAF groups. BMI: body mass index, CTD-ILD: connective tissue disease-associated interstitial lung disease, IPAF: interstitial pneumonia with autoimmune features, MCTD: mixed connective tissue disease, PM/DM: polymyositis/dermatomyositis, RA: rheumatoid arthritis, SSc: systemic sclerosis, SLE: systemic lupus erythematosus, UCTD: undifferentiated connective tissue disease. Statistically significant values were highlighted with bold in the tables.

The average age was 63.8 years and CTD subjects were notably younger compared to the IPAF subgroup (59.7 vs. 69.6, $p<0.001$). There was a female predominance in the whole study population, notably there was a significant difference in women between the 2 subgroups in favor of the CTD subgroup. There was a balanced smoking exposure in the IPAF subgroup, while two thirds of patients in the CTD subgroup considered themselves non-smokers. In the whole population the most common symptoms were in decreasing order of prevalence: dyspnea (69.1%), crackles (58.9%), cough (58.6%). More than half of the patients had articular involvement. In summary, significantly more patients suffered from dyspnea, weight loss, crackles in the IPAF group and Raynaud's phenomenon occurred more often in the CTD subgroup. GAP index points were remarkably better in the CTD-ILD subgroup in contrast to the IPAF population (1.8 vs. 2.5, $p=0.07$). In the serological testing ANA, anti-chromatin and RF antibodies were most frequently present. It has to be pointed out that no serological differences were detected between the two groups (Table 6) (173).

Table 6. Autoimmune serology (173).

Autoantibodies N (%)	All patients (*N*= 107)	CTD-ILD (*N* = 63)	IPAF (*N* = 44)	*p*-value
ANA	71 (66.4)	43 (68.3)	28 (63.6)	0.330
RF	22 (20.6)	11 (17.5)	11 (25.0)	0.466
Anti-CCP	10 (9.4)	5 (7.9)	5 (11.4)	0.738
Anti-RNA-polymerase	0	0	0	–
Anti-centromere	1 (0.9)	1 (1.6)	0	–
Anti-PCNA	2 (1.9)	1 (1.6)	1 (2.3)	1.000
Anti-Ku	0	0	0	0
Anti-P-ribosomal	0	0	0	0
Anti-cytoplasmatic	27 (25.2)	17 (27.0)	10 (22.7)	0.658
Anti-cytoskeleton	0	0	0	0
Anti-chromatin	32 (29.9)	19 (30.1)	13 (29.6)	1.000
Anti-Smith	4 (3.7)	2 (3.2)	2 (4.6)	1.000
Anti-myeloperoxidase	2 (1.9)	2 (3.2)	0	–
Anti-proteinase-3	1 (0.9)	1 (1.6)	0	–
Anti-Jo-1	3 (2.8)	2 (3.2)	1 (2.3)	1.000
Anti-SS-A	18 (16.8)	12 (19.1)	6 (13.6)	0.602
Anti-SS-B	5 (4.7)	3 (4.8)	2 (4.6)	1.000
Anti-SCL-70	17 (15.9)	17 (27.0)	0	–
Anti-RNP	10 (9.3)	8 (12.7)	2 (4.6)	0.192
ANCA	8 (7.5)	4 (6.4)	4 (9.1)	0.714

P-value indicates the comparison between CTD-ILD and IPAF groups. ANA: anti-nuclear antibodies, ANCA: anti-neutrophil cytoplasmic antibodies, Anti-CCP: anti-cyclic citrullinated peptide antibodies, Anti-SCL-70: anti-topoisomerase I antibodies, Anti-RNP: anti-ribonucleoprotein antibodies, APCNA: anti-proliferating cell nuclear antigen, CTD-ILD: connective tissue disease-associated interstitial lung disease, IPAF: interstitial pneumonia, RF: rheumatoid factor. Statistically significant values were highlighted with bold in the tables.

This section of the thesis does not cover the baseline functional and radiological characteristic of the subgroups (173).

4.2. Evaluating the decline in functional stability and estimating the prevalence of PF-ILD in the CTD-ILD and IPAF population

During the observation period an average of 24 months 34 CTD-ILD (23.5% males; mean age 58.4 ± 13.0 years) and 25 IPAF (48.0% males; mean age 69.0 ± 12.5 years) patients had longitudinal functional data. The annual FVC decline from baseline was more pronounced among IPAF cases in comparison to the CTD-ILD cases (-53.1 ± 0.3 ml vs. 16.7 ± 0.2 ml; p=0.294) (Figure 7). However, 68.0% (17/25 patients) were stable or did not worsen in the IPAF subgroup as compared to 82.4% (28/34 patients) in the CTD-ILD subgroup (p=0.200). According to the definition described in the Methods section during the follow-up period 14 patients fulfilled our PF-ILD criteria: 6 cases in the CTD-ILD subgroup (RA (N=3), SSc (N=2), other (N=1)) and 8 in the IPAF subgroup (173).

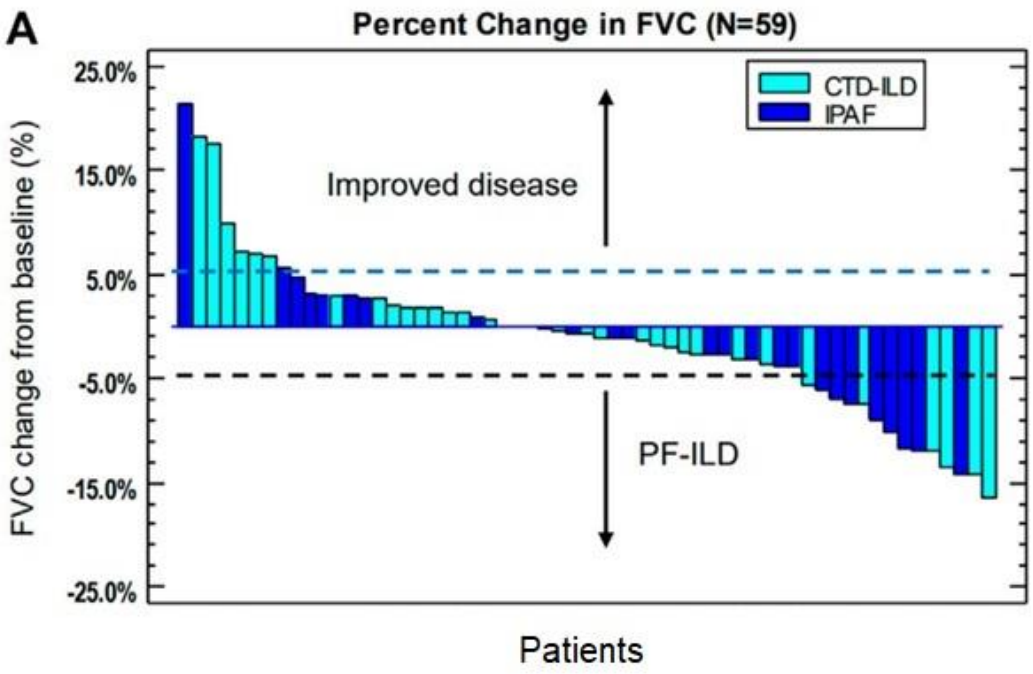


Figure 7. Longitudinal follow-up of CTD-ILD and IPAF patients: percent change in FVC. Each column represents an individual person. CTD-ILD: connective tissue disease-associated interstitial lung disease, FVC: forced vital capacity, IPAF: interstitial pneumonia with autoimmune features, PF-ILD: progressive fibrosing ILD (173).

4.3. Investigation of factors influencing progression of disease in CTD-ILD and IPAF

In our study, we detected possible prognostic factors for functional progression of disease (PF-ILD) in autoimmune mediated ILDs. These factors include malignancy as a comorbidity, anti-SS-A antibody positivity, and post-exercise pulse increase at the 6MWT (Table 7). Altogether 7 patients (2 males, 5 females) suffered from malignancies. The following cancerous diseases were present: chronic lymphocytic leukemia (N=1), lung (N=2), ovarian (N=1), breast (N=1), esophageal (N=1), and laryngeal cancer (N=1) (173).

Table 7. Factors influencing functional progression (173).

Factor	HR	95% CI	*p*-value
Patient comorbidities			
Hypertension	1.3	0.3 to 4.7	0.721
Thyroid disorder	11.9	0.8 to 182.8	0.076
Malignancy	8.2	1.3 to 50.8	**0.024**
PH	1.5	0.3 to 6.9	0.584
Smoking	1.1	0.3 to 4.7	0.891
BMI	0.9	0.8 to 1.1	0.21
ABG			
pH	21.8	0.0	0.936
pCO_2	0.1	0.8 to 1.2	0.990
pO_2	0.9	0.8 to 1.1	0.366
6MWT			
Distance (m)	1.0	1.0 to 1.0	0.309
SpO_2 baseline	1.7	0.8 to 3.6	0.173
SpO_2 post-exercise	0.9	0.6 to 1.3	0.474
Pulse baseline	1.0	0.9 to 1.1	0.783
Pulse post-exercise	1.1	1.0 to 1.3	**0.043**
Borg scale baseline	0.7	0.1 to 4.4	0.722
Borg scale post-exercise	0.6	0.2 to 1.8	0.403
HRCT pattern	1.2	0.6 to 2.5	0.632
Autoantibodies			
RF	3.3	0.2 to 46.0	0.380
Anti-CCP	1.6	0.1 to 18.2	0.730
Anti-PCNA	0.0	0.0	0.992
Anti-cytoplasmatic	5.4	0.6 to 48.1	0.134
Anti-chromatin	0.5	0.1 to 2.8	0.411
Anti-Jo-1	6.1	0.1 to 482.1	0.416
Anti-SS-A	13.1	1.7 to 100.5	**0.013**
Anti-SS-B	2.2	0.0 to 279.5	0.745
Anti-SCL-70	1.0	0.1 to 12.9	0.980
Anti-RNP N	2.1	0.2 to 27.6	0.579
ANCA	0.0	0.0	0.997

6MWT: 6-min walk test, ABG: arterialized capillary blood gases, ANCA: anti-neutrophil cytoplasmic antibodies, Anti-CCP: anti-cyclic citrullinated peptide antibodies, Anti-SCL-70: anti-topoisomerase I antibodies, APCNA: anti-proliferating cell nuclear antigen; BMI: body mass index, CI: confidence interval, HR: hazard ratio, HRCT: high- resolution computed tomography, PH: pulmonary hypertension, pH: potential of hydrogen, RF: rheumatoid factor. Statistically significant values were highlighted with bold in the tables.

4.4. Determining patient characteristics and clinical symptoms in the Hungarian SSc-ILD population

Patient characteristics and serological patterns are summarized in Table 8 and 9. The SSc-ILD population had a mean age of 58.7 years, nevertheless, this was higher in the no treatment subgroup (66.1 years). In the whole population a female predominance was present (87.0%) and 74.1% of the subjects were non-smokers. Most patients were in Stage I (0-3 points) in their GAP index, while only 2 of the followed patients were in Stage II (4-5 points). The average BMI was in physiological range in the no treatment subgroup (23.6 kg/m^2). On the other hand, overweight was noted in both the ISU (25.0 kg/m^2) and in the biological treatment subgroups (26.4 kg/m^2). Respiratory symptoms, like dyspnea and crackles were present in the largest proportion, followed by Raynaud's phenomenon, joint pain and finger clubbing. Among those who were on ISU therapy cough appeared significantly less in comparison to other subgroups. Gastrointestinal symptoms were present in 18.5% of cases, mainly in the no treatment subgroup (187).

Table 8. Patient characteristics (187).

Parameters	**All patients (N=54) #**	**No treatment (N=12)**	**ISU therapy (N=21)**	**Biological therapy (N=9)**
Age (year)	58.7±13.3	66.1±13.7	59.12±12.4	62.7±10.0
Sex (Male:Female) N		1:11	3:18	1:8
GAP score n (%)				
Stage I (0-3 points)	48 (88.9)	12 (100)	20 (95.2)	8 (88.9)
Stage II (4-5 points)	6 (11.1)	0	1 (5)	1 (1.1)
Stage III (6-8 points)	0	0	0	0
Ever smoker/Non-smoker N	14:40	4:8	5:16	2:7
BMI (kg/m2)	24.8±4.3	23.6±3.1	25.0±4.4	26.4±4.5
Overweight N (%)	21 (38.9)	3 (25.0)	8 (38.1)	5 (55.6)
PF-ILD N (%)	15 (27.8)	5 (41.7)	7 (33.3)	3 (33.3)
Symptoms N (%)				
Dyspnea	26 (48.2)	6 (50.0)	8 (38.1)	5 (55.6)
Cough	15 (27.8)	4 (33.3)	**1 (4.8)***	4 (44.4)
Chest pain	5 (9.3)	0	0	0
Joint pain	8 (14.81)	1 (8.3)	5 (23.8)	1 (11.1)
Clubbing	1 (1.91)	0	0	1 (11.1)
Weight loss	3 (5.6)	1 (8.3)	1 (4.86)	1 (11.1)
Crackles	15 (27.8)	5 (41.7)	6 (28.6)	2 (22.2)
Raynaud's phenomenon	38 (70.5)	8 (66.7)	13 (61.9)	5 (55.6)
GIT involvement	10 (18.5)	**5 (41.7)*** **	2 (9.5)	3 (33.3)
HRCT patter N (%)				
NSIP	34 (63.0)	11 (91.7)	15 (71.4)	**3 (33.3)** **
UIP/pUIP	8 (14.8)	1 (8.3)	2 (9.5)	**4 (44.4)*** **
Other or no data	10 (18.5)	0	4 (19.0)	2 (22.2)

total number of patients were 54, but out of these only 42 had follow-up data, * p<0.05 ISU vs. No treatment and biological therapy subgroup ** p<0.05 Biological therapy subgroup vs. No treatment subgroup, *** p<0.05 Biological therapy subgroup vs. ISU subgroup. BMI: body mass index, GIT: gastrointestinal, HRCT: high- resolution computed tomography, NSIP: nonspecific interstitial pneumonia, RF: rheumatoid factor, p(UIP): possible usual interstitial pneumonia. Statistically significant values were highlighted with bold in the tables

Table 9. Serological pattern (187) .

Parameters	All patients (N=54) #	No treatment (N=12)	ISU therapy (N=21)	Biological therapy (N=9)
Serological pattern N (%)				
ANA	23 (42.6)	8 (66.7)	12 (57.1)	3 (33.3)
ACA	1 (1.9)	1 (8.3)	0	0
RF	3 (5.6)	2 (1.7)	1 (4.8)	0
Anti-CCP	1 (1.9)	0	1 (4.8)	0
Anti-RNA-polymerase	2 (3.7)	1 (8.3)	1 (4.8)	0
Anti-cytoplasmatic	5 (9.3)	1 (8.3)	2 (9.5)	2 (22.2)
Anti-chromatin	12 (22.2)	5 (41.7)	6 (28.6)	1 (11.1)
Anti-Smith	1 (1.9)	1 (8.3)	0	0
Anti-Jo-1	1 (1.9)	0	1 (4.8)	0
Anti-SSA	2 (3.7)	0	2 (9.5)	0
Anti-SSB	1 (1.9)	1 (8.3)	0	0
Anti-SCL-70	18 (33.3)	8 (66.7)	**9 (42.9)****	1 (11.1)
Anti-RNP	4 (7.4)	3 (25)	1 (4.8)	0
Anti-dsDNS	3 (5.6)	1 (8.3)	1 (4.8)	1 (11.1)

total number of patients were 54, but out of these only 42 had follow-up data. Statistically significant values were highlighted with bold in the tables. ** $p<0.05$ ISU vs. No treatment subgroup. ACA: , anti-centromere antibodies, ANA: anti-nuclear antibodies, ANCA: anti-neutrophil cytoplasmic antibodies, Anti-CCP: anti-cyclic citrullinated peptide antibodies, Anti-RNP: anti-ribonucleoprotein antibodies, Anti-SCL-70: anti-topoisomerase I antibodies.

4.5. Analysis of HRCT pattern and involvement, lung function abnormalities and serological findings in SSc-ILD

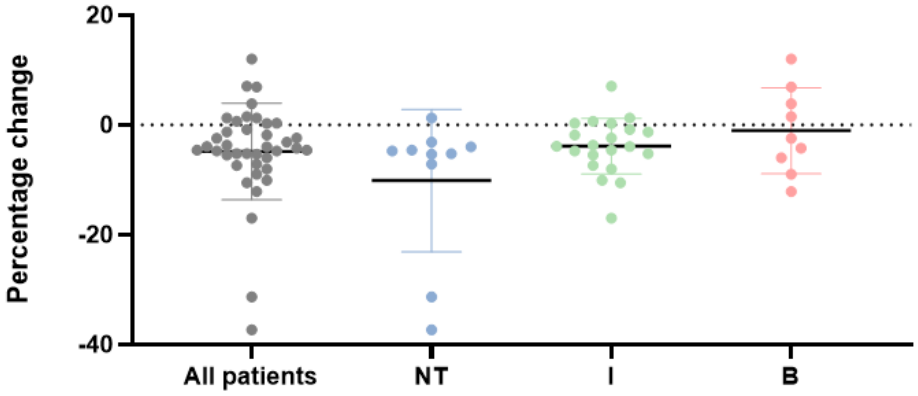
NSIP morphological pattern (principally less than 20% of lung involvement) was present in most cases on HRCT, proceeded by UIP and pUIP pattern (relatively equal involvement below and above 20%) (Table 8.). In the ISU and the no treatment subgroups patients were affected with NSIP much more frequently in contrast to the patients receiving biological treatment, where pUIP and UIP patterns were significantly more predominant (187).Analysis of lung function showed a mild restrictive functional decline. PFT data at baseline is summarized in Table 10.

Table 10. Lung function, ABG, 6MWT functional parameters (187).

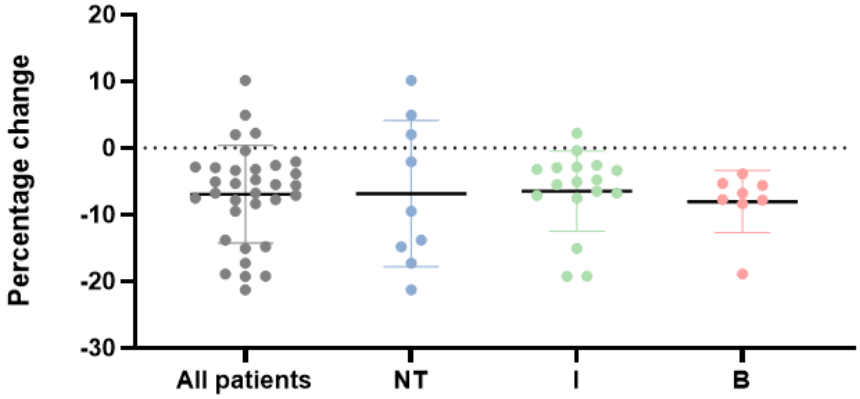
Parameters	All patients (N=54) #	No treatment (N=12)	ISU (N=21)	Biological therapy (N=9)
Lung function				
FVC (L)	2.5±0.8	2.5±0.8	2.8±0.8	2.2±0.6
FVC (%predicted)	89.8±23.2	97.6±21.7	92.4±26.6	82.2±17.2
FEV1(L)	2.2±0.6	2.1±0.6	2.3±0.7	2.0±0.6
FEV1(%predicted)	90.2±21.8	97.9±21.6	92.2±23.1	85.3±21.5
FEV1/FVC (%)	84.7±6.3	83.4±6.3	84.9±4.9	86.9±12.4
TLC (L)	3.9±1.1	4.0±1.0	4.1±1.4	3.8±1.0
TLC (%predicted)	78.4±21.00	81.4±16.2	81.1±23.0	79.2±23.4
Diffusion parameters				
DL_{CO} (mmol/min/kPa)	5.9±2.0	6.2±1.8	6.2±2.1	5.1±1.3
DL_{CO} (%predicted)	75.2±22.0	86.9±24.5	77.4±20.7	66.7±14.7
KL_{CO} (mmol/min/kPa/l)	1.4±0.4	1.3±0.3	1.4±0.4	1.3±0.3
KL_{CO} (%predicted)	70.0±18.12	66.0±15.6	70.5±18.9	67.0±16.7
ABG				
pH	7.4±0.0	7.4±0.0	7.4±0.0	7.4±0.1
pCO_2 (mmHg)	38.0±4.7	34.4±3.1	43.4±11.1	36.7±3.6
pO_2 (mmHg)	74.2±10.5	84.2±13.1	71.2±12.1	72.2±14.6
6MWT				
Distance (m)	444.2±119.8	365.3±233.9	468.8±108.0	342.0±106.6
SpO2 baseline (%)	94.9±2.8	96.7±3.2	97.3±2.1	93.9±4.4
SpO2 post-exercise (%)	89.9±10.0	82.7±19.9	95.3±2.4	87.6±8.1
Desaturation (%)	4.9±9.3	14.0±16.6	2.5±2.4	8.0±6.3
Pulse baseline (1/min)	84.8±14.6	78.7±11.9	82.9±9.6	86.4±11.6
Pulse post-exercise (1/min)	108.5±23.1	100.3±29.5	108.4±17.6	106.7±26.4
Borg scale baseline (0-10)	0.2±0.5	1.7±2.9	0.1±0.3	1.0±1.4
Borg scale post-exercise (0-10)	1.8±2.5	2.7±3.8	1.6±1.2	3.1±2.5

total number of patients were 54, but out of these only 42 had follow-up data. No statistically significant difference was detected. 6MWT: 6-min walk test, ABG: arterialized capillary blood gases, DL_{CO}: diffusing capacity for carbon monoxide, FEV1: forced expiratory volume in 1 s, FVC: forced vital capacity, KL_{CO}: transfer coefficient of the lung for carbon monoxide, TLC: total lung capacity.

Annual FVC decline was prominent in the no treatment subgroup (−10.2 ± 13.0%) in contrast to patients who were on ISU (−3.9 ± 5.1%) or biological treatment (−1.04 ± 7.8%). Patients receiving biological treatment showed the lowest degree of annual FVC decline, even showing functional improvement in 4 cases. There was no significant difference in lung function test results between the 3 observed subgroups. However, in the treated subgroups annual FVC declined only in a moderate rate compared to the no treatment subgroup. A slight deterioration in DL_{CO} was recognized in all 3 subgroups, especially in patients who received biological therapy (Figure 8) (187).



(a)



(b)

Figure 8. (a) Annual FVC changes in all SSc-ILD patients and in the specific treatment groups. Description of what is contained in the first panel; **(b)** Annual DL_{CO} changes in each specific treatment group. NT: No treatment, I: ISU therapy, B: Biological therapy (187).

Among the 13 antibodies tested in this study (Table 9)., more frequent occurring were- in growing order - the following: ANA, anti-SCL-70, anti-chromatin and anti-cytoplasmatic antibodies. Anti-SCL-70 was significantly more predominant in the ISU subgroup in comparison with the other 2 longitudinally followed subgroups (187).

4.6. Evaluating the distribution of PF-ILD according to treatment subgroups in SSc-ILD and factors of functional decline

In our study out of 42 patients who possessed longitudinal data, 15 patients fulfilled our PF-ILD criteria explained in Methods above. During-follow up the remaining 27 patients were stable and no traits of progressive functional decline were identified. PF-ILD was detected in the highest percentage in the no treatment subgroup (41.7%), while two thirds of subjects were stable or showed improvement during adjusted treatments (187).

Based on our plot analysis being overweight (BMI >= 25 kg/m^2, established by the definition of WHO) and absence of anti-SCL-70 antibodies proved to be a favoring factor for functional stability (Figure 9) (187).

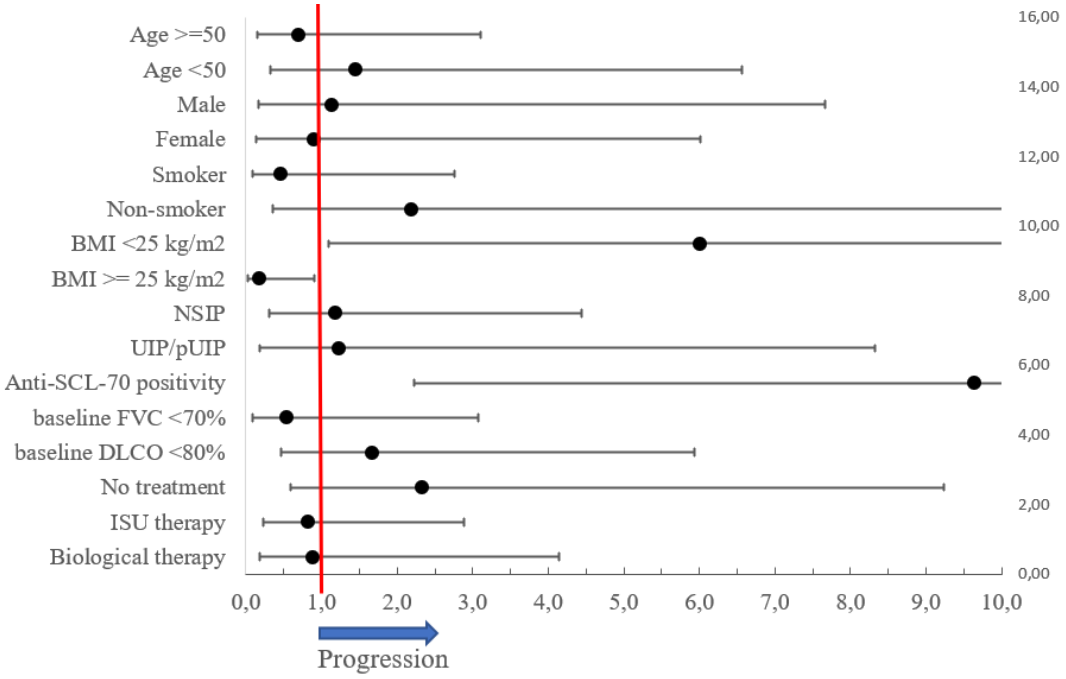


Figure 9. Risk factors of progression. Anti-SCL-70: anti-topoisomerase I antibodies, BMI: body mass index, DL_{CO}: capacity of the lungs for carbon monoxide, FVC: forced vital capacity, ISU: immunosuppression, NSIP: nonspecific interstitial pneumonia, (p)UIP: (possible) usual interstitial pneumonia (187).

More than the half of the patients (55.6%) receiving biological treatment were overweight, while patients in the no treatment subgroup were the least affected (25%). For stable SSc-ILD patients a significantly higher BMI was characteristic compared to PF-ILD cases (25.71 kg/m^2 vs. 22.9 kg/m^2; p=0.03). A clear negative correlation was explored between baseline BMI and annual FVC decline ($r = -0.97$, $r2 = 0.93$, $p < 0.001$) (Figure 10) (187).

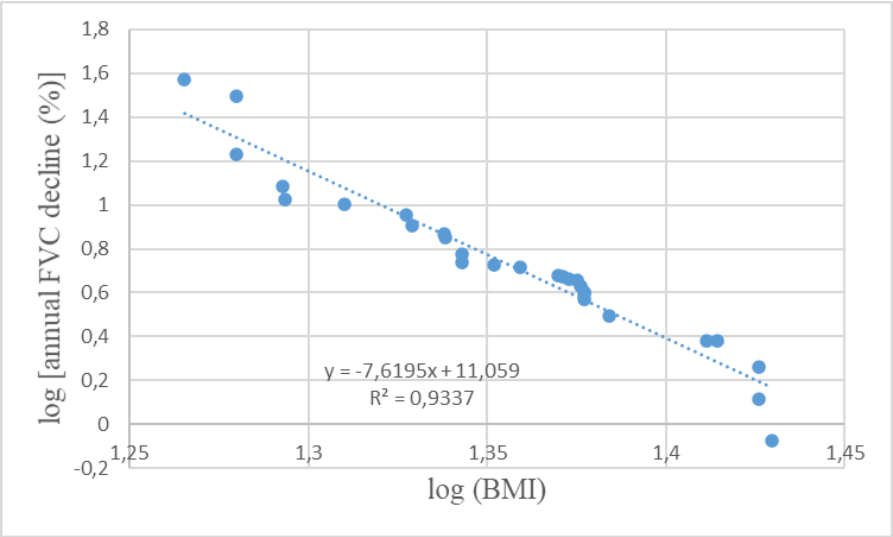


Figure 10. Negative correlation between BMI and annual FVC decline (%). BMI: body mass index, FVC: forced vital capacity (187).

Esophagus dysmotility and other gastrointestinal (GIT) involvements affected 10 patients, mainly patients with low or normal BMIs in comparison with overweight patients (p=0.019). However, GIT symptoms were equally represented in PF-ILD and non PF-ILD groups and no statistical association was found between GIT symptoms and PF-ILD (187).

5. DISCUSSION

Our studies represent CTD-ILD circumstances under real world conditions from an East-Central European country. Functional progression, its risk factors and also, characteristic of the new category of PPF in this special patient population was assessed.

5.1. Patient characteristics

Our two original single center studies are the first to summarize the patient characteristics of CTD-ILDs in Hungary. During the examined period out of 511 cases, 20.9% met the criteria of CTD-ILD or IPAF, they were discussed and defined by MDD, in line with international data (154, 158). In our second study, data of 54 SSc-ILD patients were processed. CTD-ILD patients are usually in their sixties, are non-smokers, women and present with cough, exercised induced dyspnea or basal crackles. The latter is the well-known symptomatic triad of the active disease (3, 6, 10, 59, 173, 189).

One of the uniqueness of our first study is the characterization of the IPAF group, which has been less studied so far. The disease prognosis falls somewhere between that of IPF and CTD-ILD, strongly influenced by their HRCT pattern (158, 190). The entire IPAF group is characterized by female dominance and half of the group had verifiable exposure to tobacco smoke. A significant number of patients had respiratory symptoms at baseline. According to our results IPAF patients are older, are more often smokers and are more symptomatic compared to CTD-ILD patients. Over the years, manifest CTD might evolve from IPAF cases. Thus, using the IPAF criteria in MDD might remark IIPs with autoimmune characteristics or “premature” CTD-ILDs, giving hope that patients will benefit from ISU treatment and the inflammatory process of the lungs may even be reversible, although the fibrotic remodeling is ongoing. However, the classification criteria of IPAF is a debated issue and in the future nailfold capillary microscopy might play a major role in the diagnostic procedure as microvascular malformations precede seropositivity, or Raynaud's phenomenon can be a warning sign for latent CTD (158).

5.2. Functional progression of pulmonary fibrosis

In the field to the new guideline appeared, the definition of PPF was a debated condition without international agreement in the field. Many have defined it in different ways based on the worsening of clinical symptoms, radiological appearance, lung function changes and quality of life. (39, 170, 191) Our functional progression criteria explained in the Method Section is up-to-date with latest PPF ATS/ERS/JRS/ALAT guideline (17).

In our research, we determined PF-ILD (this definition is accordance with PPF) incidence in autoimmune featured ILDs (CTD-ILD, especially in SSc-ILD and IPAF) looking at two domains: symptoms and functional decline.

In our first article the majority of patients were stable both in the IPAF (68.0%) and in the CTD-ILD subgroup (82.4%). Unfortunately, there was a significant progressive deterioration during follow-up in a small proportion (13.1%) of patients and more than half of them met the diagnosis of IPAF (N=8), while 6 patients had manifest CTD-ILD (RA (N=3), SSc (N=2), other (N=1)(173)).

In the SSc study 35.7% of patients fulfilled functional PPF criteria using the mentioned two domains, similarly to international data (87, 192). PPF prevalence was equal in the ISU and biological therapy subgroups, while it was frequenter in the treatment free group (33.3 to 41.7%). Patients who have preserved lung function and mild symptoms are at risk for developing PPF, as treatment initiation may be delayed by immunologists and respiratory specialists may overlook slight functional loss between control visits. SSc-ILD is heterogeneous disorder in which patients with mild symptoms, limited HRCT involvement and normal lung function should be monitored with more carefully. More detailed international guidelines about treatment initiation and SSc-ILD treatment are required in this field to prevent disease progression.

It is important to note that PPF is defined by very subtle changes regarding progression. However, our data were not focusing on the radiological progression, therefore the number of PPF might have been underestimated (17).

5.3. Risk factors of progression

Prior to the definition of PPF, various definitions existed for progressive fibrosing (PF) ILD, resulting in non-uniform classification criteria. According to literary data, the most significant predictive factors of progression in CTD-ILD are age, male sex, smoking history, UIP pattern and traction bronchiectasis on HRCT, reduced FVC and DL_{CO} at baseline (35, 69). In our studies, we detected other important prognostic factors that represent a risk for the development of clinical-functional PPF (PF-ILD) in autoimmune featured ILD. Our first research confirmed that possible prognostic factors for PPF are the presence anti-SS-A antibodies, post-exercise pulse increase at 6MWT, and malignancy (173). Our second study shows that the presence of anti-SCL-70 is possible factors worsening disease progression. Interestingly, overweight patients have lower risk for functional deterioration (187).

Anti-SS-A (Ro52 and Ro60) antibodies positivity have a useful role in clinical field. However, clinical associations are not completely established yet. It is included in the diagnostic criteria of SSc and is associated with more serious ILDs in anti-synthetase syndrome and IIMs and these patients react less for immunosuppression (193-195). Separated detection of Ro52 and Ro60 is not disease specific, although, in the clinical practice it is contributed to the correct diagnostic of CTDs, for example anti-SS-A/Ro60+ is associated with SLE, anti-SS-A/Ro52+ act as a marker of ILD in SSc and has diagnostic value in PM/DM (196-199). Ro52 and Ro60 should be separately examined in IPAF patients. (55).

Post-exercise pulse increase at the 6MWT is possibly another predictor of progression in CTD-ILD. In advanced disease, reduced diffusion capacity is associated with lower blood oxygen levels and hypoxemia. In the presence of an intact circulatory system, the body compensates for impaired lung function with a positive chronotropic response during exercise and in advanced ILD at rest, indicating a more severe lung involvement (200, 201). Secondary pulmonary hypertension (PH) frequently develops in ILD patients, such as in SSc-ILD, and is known to play a significant role in morbidity and mortality, indicating a worse prognosis. Secondary PH contributes to poorer hemodynamics and increased heart rate in this sense (202, 203). However, chronotropic response is influenced by comorbidities and the use of beta blockers.

It is known that patients, with concomitant malignancy and IPF have a poor survival (204). In our study, malignancy as a comorbidity proved to be a risk factor that favors disease progression.

It is a well-known fact, that the likelihood of progressive ILD is higher when anti–Scl-70 antibodies are present and anti-centromere antibodies are absent (69). And our data harmonize with this. Finally, the most surprising novelty of our SSc study is the determination of the role of BMI. There was a clear negative association between BMI and functional decline demonstrating that BMI is an essential clinical marker in SSc-ILD and it is easy to follow. This condition between functional stability and overweight is already known in plenty of respiratory disease. For example, the recognized role of the obesity paradox in COPD (205). In the INPULSIS, INBUILD and CAPACITY studies the post hoc analysis of low BMI and weight loss at baseline are associated with severe functional decline (206-208). Only limited data are available in extremely obese population. In our research, there was no significant difference in GIT involvement between PPF and the stable group, and more patients with normal BMI complained of GIT symptoms as compared to patients with decreased BMI. Therefore, lower BMI was not caused by GIT involvement. The lowest mean BMI was observed in the no treatment subgroup, where the annual FVC decline was the highest. In the ISU and in the biological subgroup the mean BMI showed overweight and parallelly, the majority of patients showed functional stability. Regular BMI monitoring has an impact on the timing of therapy initiation, especially in patients with normal lung function and mild symptoms.

5.4. Limitations and strengths

Our studies have several notable limitations, primarily due to their retrospective single-center design and the limited number of patients included. To address these limitations and obtain more comprehensive insights, it is crucial to conduct further prospective studies that specifically evaluate this particular subgroup of ILD patients. However, it is worth highlighting that our studies contribute valuable data by representing the distribution of ILD cases in an Eastern European country for the first time. Furthermore, our researches are unique in that it is based on a long-term longitudinal follow-up of ILD patients with autoimmune characteristics. The disease population covered the two primary rheumatology centers in the Central Hungary region.

6. CONCLUSIONS

1. In our study we determined patient characteristics, clinical symptoms and serological findings in the CTD-ILD and IPAF population in Hungary. The average age was 63.8 ± 13.9 years and there was a female predominance in sex. Smoking status was equally distributed in IPAF population, while CTD-ILD patients were more frequently non-smokers. Most observed symptoms were dyspnea (69.1%), crackles (58.9%), cough (58.6%) and more than half of the patients had joint involvement. ANA, anti-chromatin and RF antibodies were most frequently present, with no serological differences between the two groups.

2. During follow-up out of the 59 patients 14 (23.7%) fulfilled our PF-ILD criteria, while 68% of IPAF and 82.4% of CTD-ILD patients had stable disease.

3. Factors supporting functional progression in autoimmune featured ILDs (both CTD and IPAF) were malignancy, anti-SS-A antibody positivity and post-exercise pulse increase at the 6MWT.

4. Patient characteristics and clinical symptoms of the Hungarian SSc-ILD population were additionally described. Patients had a mean age of 58.7 ± 13.3 years and were mainly nonsmoking women. Patients on ISU and biological treatment had a slight over normal excess in BMI. Dyspnea, crackles, Raynaud's phenomenon, joint pain, and finger clubbing proved to be typical clinical signs and symptoms. GIT symptoms occurred in 18.5%, by and large in untreated patients.

5. Our study analyzed the HRCT pattern, lung function abnormalities and serological findings in SSc-ILD. NSIP with less than 20% was the most common radiological pattern, followed by UIP and pUIP. Baseline PFT data showed a mild restrictive

pattern. Functional decline appeared mainly in untreated patients, while those who received therapy were more stable during the follow-up.

6. Our study evaluated the distribution of PF-ILD according to treatment subgroups in SSc-ILD and factors predicting functional decline: out of 42 patients 15 fulfilled the PPF criteria of functional decline- with the highest proportion in untreated cases (41.7%). Total of 27 patients were stable during follow-up, mainly on adjusted treatment. Overweight (BMI >= 25 kg/m2) and the absence of anti-SCL-70 positivity have been confirmed as favoring factors of functional stability.

7. SUMMARY

This PhD thesis outlines the features of the CTD-ILD and IPAF patient population, highlighting the susceptibility of females and the importance of considering CTD-ILD in non-smoker ILD patients experiencing respiratory symptoms. A concomitant malignancy, anti-SS-A positivity, post-exercise pulse increase at the 6MWT might indicate worse disease prognosis in CTD-ILD. Thorough monitoring of BMI is recommended as low BMI or weight loss might be signs of functional decline and PPF. PPF is characterized by worsening of clinical symptoms, in many cases the rapid progression can lead to early death. With close monitoring, early recognition of progression, optimal treatment initiation may preserve stability of the lung function, this finding is especially important in symptomfree patients with physiological PFT. A multidisciplinary approach- based on the principle that four eyes see more than two -is recommended. Future studies are required in this field. BMI is an important prognostic factor in SSc-ILD progression and an initial low and normal BMI or weight loss should be followed closely by the clinical care team. The thorough monitoring of BMI in clinical practice is required and especially patients with normal BMI should be followed closely for deterioration. The timing of the introduction of ISU and biological therapy remains a major challenge for clinicians. A higher awareness and possibly lower threshold for therapy initiation is needed in patients with preserved lung function and a normal BMI. Although it is important to note that patients with a normal BMI were presented more often with GIT symptoms. However GIT involvement was not associated with the progressive form of ILD. Regular PFT and BMI follow ups should be performed in all SSc patients starting from the initial diagnosis, and anti-SCL-70 positivity is helpful when considering therapy introduction. Important further investigations should include detailed progression reports of the radiological changes, and new studies are needed to determine a follow-up protocol for imaging.

8. REFERENCES

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9.3. Presentations/abstracts related to the subjects of the thesis

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