Supplementary material

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PROGNOSIS AND CAUSES OF DEATH OF PATIENTS WITH ACUTE EXACERBATION OF FIBROSING INTERSTITIAL LUNG DISEASES

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DIAGNOSTIC EVALUATION OF THE PATIENTS

The study material included the patients treated in Oulu University Hospital (OUH) and Oulaskangas Hospital (OH) between the years 2008 and 2017 during which time, there was adherence to the respective international guidelines on the diagnostics and treatment of idiopathic pulmonary fibrosis (IPF), idiopathic interstitial pneumonias and other ILDs in clinical practice. Most interstitial lung disease (ILD) patients have undergone a multidisciplinary diagnosis (MDD) evaluation, which has been the clinical practice in OUH and OH during the entire implementation period of this study. The physicians from OH are able to participate the multidisciplinary meetings via video connections.

For the present study, all available clinical, radiological and histological information from each patient was collected and evaluated. The most recent international guidelines were applied in the re-classification of cases. The radiological information after the hospitalization of survivors and autopsy findings were also utilized in the evaluation of the patients. If CTD was diagnosed after the ILD diagnosis, the primary idiopathic disease was changed to CTD-associated ILD

The histopathological diagnosis of FILD was obtained from surgical lung biopsy samples taken by video-assisted thoracic surgery (VATS) in 25 patients, of which 7 patients underwent also autopsy. In addition, histological investigation of lung tissue samples taken from autopsy was performed for 20 patients. When considering both surgical lung biopsies and autopsies, histological evaluation was performed in 45 patients (E-Table 1). In those cases in whom there was a discrepancy between the radiological pattern and the pathological pattern, the patients were evaluated in the multidisciplinary meetings by pulmonologists, thoracic radiologists and the lung pathologist. In this study, all clinical data and information from death certificates, pathologists' reports and the radiologists' reports were scrutinized.

E-TABLE 1. Characteristics of the patients hospitalized due to acute exacerbation of fibrosing interstitial lung disease (AE-FILD). Data is related to the first hospitalization date if not stated otherwise.

	Total n=128	IPF n=79	Other FILD n=49	p value
Age at diagnosis, years	68 (11)	69 (11)	66 (12)	0.124
Age at hospitalization, years	72 (10)	72 (10)	73 (9.5)	0.850
Time from diagnosis, years [A]	3.1 (1.1–8.5)	2.1 (0.9–5.4)	6.2 (2.9–13)	<0.001
No former ILD diagnosis	36 (28)	19 (24)	17 (35)	0.193
Male	90 (70)	58 (73)	32 (65)	0.329
One AE	116 (91)	75 (95)	41 (84)	0.057
Two AEs	11 (8.6)	4 (5.1)	7 (14)	0.103

Three AEs	1 (0.8)	0 (0)	1 (2.0)	0.383
Ever-smoker [B]	65 (51)	42 (53)	23 (47)	0.518
Current smoker	6 (4.7)	3 (3.8)	3 (6.1)	0.673
Pack-years of ever-smokers [C]	27 (15)	29 (16)	25 (14)	0.318
FVC% at diagnosis [D]	73 (17)	72 (16)	75 (18)	0.318
FEV1% at diagnosis	78 (18)	77 (17)	79 (19)	0.558
DLCO% at diagnosis [E]	53 (18)	50 (17)	57 (19)	0.082
FVC% at hospitalization [F]	63 (18)	62 (17)	64 (20)	0.503
FEV1% at hospitalization	67 (18)	66 (17)	69 (21)	0.466
DLCO% at hospitalization [G]	41 (15)	40 (15)	43 (15)	0.372
UIP [H]	101 (79)	79 (100)	22 (45)	<0.001
Histopathological UIP	32 (25)	25 (32)	7 (14)	0.027
Histopathology of FILD	45 (35)	27 (34)	18 (37)	0.768
Surgical lung biopsy	18 (14)	11 (14)	7 (14)	0.954
Autopsy	20 (16)	12 (15)	8 (16)	0.863
Surgical lung biopsy and autopsy	7 (5.5)	4 (5.1)	3 (6.1)	1.000
Survived the hospitalization	97 (76)	55 (70)	42 (86)	0.039
Cumulative mortality after hospitalization				
<15 days	19 (15)	16 (20)	3 (6.1)	0.029
<30 days	34 (27)	27 (34)	7 (14)	0.013
<60 days	48 (38)	36 (46)	12 (25)	0.017
<90 days	55 (43)	42 (53)	13 (27)	0.003
Deceased or transplanted	110 (86)	73 (92)	37 (76)	0.008
Transplanted during follow-up	5 (3.9)	3 (3.8)	2 (4.1)	1.000
Follow-up time from diagnosis, years	4.0 (1.7–8.3)	2.4 (1.0–5.5)	6.6 (3.8–11)	<0.001

Data is presented as either the number of patients (%), mean (standard deviation) or median (interquartile range).[A] The patients with former FILD diagnosis before acute exacerbation were included in this analysis. [B] Smoking data was missing from 2 patients with IPF and 1 patient with unclassifiable FILD. [C] Pack-year data of 8 ex-smokers was missing. [D] FVC and FEV1 data was missing from 10 IPF and 4 other FILD patients. [E] Data was missing from 14 IPF and 4 other FILD patients. [F] FVC and FEV1 data was missing from 16 IPF and 9 other FILD patients. [G] Data was missing from 26 IPF and 14 other FILD patients, of which 6 IPF and 5 other FILD patients were not able to perform the examination. [H] Either "probable UIP" or "consistent with UIP" in HRCT or/and histopathological diagnosis of UIP. AE, acute exacerbation of interstitial lung disease; DLCO, diffusion capacity for carbon monoxide; FEV1, forced expiratory volume in one second; FILD, fibrosing interstitial lung disease; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.

E-TABLE 2. Patients with fibrosing interstitial lung disease (FILD) hospitalized due to acute exacerbation.

Type of FILD	Total n=128 N (%)	Male/Female N/N
IPF[A]	79 (62)	58/21
NSIP	8 (6.4)	2/6
Asbestosis[B]	11 (8.6)	11/0
CHP	4 (3.2)	2/2
CTD-ILD	21 (16)	14/7
RA	17 (14)	12/5
Ssc	1 (0.8)	1/0

DLE	1 (0.8)	1/0
SSj	2 (1.6)	0/2
Unclassifiable ILD[C]	5 (4)	3/2

Data is presented as the number of patients (%). [A] Six IPF patients had a family history of pulmonary fibrosis. [B] One patient with asbestosis had also rheumatoid arthritis. [C] One unclassifiable ILD patient had a family history of pulmonary fibrosis. DLE, discoid lupus erythematosus; CHP, chronic hypersensitivity pneumonitis; CTD, connective tissue disease-associated; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; RA, rheumatoid arthritis; SSc, systemic scleroderma; SSj, Sjögren's syndrome.

E-TABLE 3. Pharmacological therapy for idiopathic pulmonary fibrosis (IPF) and other fibrosing interstitial lung diseases (FILD). Each hospital treatment period is analyzed as a unique event.

Pharmacological therapy	Total (n=128) Hospitalizations (n=142)	IPF (n=79) Hospitalizations (n=84)	Other FILD (n=49) Hospitalizations (n=58)	P-value
Prior to hospital admission due to AE-FILD				
Monotherapy for FILD				
Corticosteroid	34 (24)	15 (18)	19 (33)	0.041
Pirfenidone	5 (3.5)	5 (6.0)	0 (0)	0.079
Nintedanib	2 (1.4)	2 (2.4)	0	0.513
Corticosteroid, NAC and azathioprine	10 (7.0)	8 (9.5)	2 (3.4)	0.199
Combined with corticosteroid				
Azathioprine	3 (2.1)	1 (1.2)	2 (3.4)	0.567
NAC	1 (0.7)	1 (1.2)	0 (0)	1.000
Cyclophosphamide	1 (0.7)	0 (0)	1 (1.7)	0.408
Pirfenidone	1 (0.7)	1 (1.2)	0 (0)	1.000
Cs for some indication other than FILD	10 (7)	3 (3.6)	7 (12)	0.091
Corticosteroid (total)	60 (42)	29 (35)	31 (53)	0.025
No medical treatment for FILD	85 (60)	51 (61)	34 (59)	0.802
During treatment period				
Corticosteroid at least 20 mg per day[A]	103 (73)	64 (76)	39 (67)	0.240
Maximal dose of cs per day (mg) [B]	75 (40–160)	75 (40–150)	75 (40–180)	0.754
High-dose intravenous steroids [C]	24 (17)	14 (17)	10 (17)	0.928
Antibiotics	121 (85)	70 (83)	51 (88)	0.448
Cyclophosphamide	9 (6.3)	4 (4.8)	5 (8.6)	0.487
Antimycotics	22 (16)	14 (17)	8 (14)	0.642
Antiviral treatment	11 (7.7)	7 (8.3)	4 (6.9)	1.000

Data are presented as numbers of patients (%) or median (interquartile range). [A] Dose equivalent for prednisolone. Patients receiving high-dose steroids were excluded. [B] Dose equivalent for prednisolone. 2 IPF patients and 7 other FILD patients, each with one hospital treatment period, did not receive corticosteroid treatment at all and were excluded from analysis.[C]500–1000 mg per day for three days, dose equivalent for prednisolone. AE-FILD, acute exacerbation of fibrosing interstitial lung disease; cs, corticosteroid; FILD, fibrosing interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NAC, N-acetylcysteine.

E-TABLE 4. Univariate regression analysis of overall mortality for idiopathic pulmonary fibrosis (IPF) and other fibrosing interstitial lung disease (FILD) patients hospitalized due to acute exacerbation.

	IPF (n=79)			Other FILD (n=49)		
	N (%)/ Mean (SD)	HR (95 % CI)	P-value	N (%)/ Mean (SD)	HR (95 % CI)	P-value
Male	58 (73)	1.03 (0.61–1.76)	0.907	30 (61)	1.53 (0.76–3.07)	0.233
Age at hospitalization	72 (10)	1.00 (0.97–1.02)	0.724	73 (9.5)	1.05 (1.01–1.09)	0.020
Age group categories						
≤70 years	26 (33)	Reference		17 (35)	Reference	
71–80 years	34 (43)	0.84 (0.50–1.43)	0.528	23 (47)	1.16 (0.54–2.51)	0.707
>80 years	19 (24)	0.95 (0.51–1.80)	0.879	9 (18)	2.85 (1.14–7.16)	0.026
UIP pattern	79 (100)			22 (45)	2.33 (1.15–4.70)	0.019
FVC (%)[A]	62 (17)	0.99 (0.98–1.01)	0.355	64 (20)	1.00 (0.98–1.02)	0.990
FVC categories						
>75 %	13 (16)	Reference		10 (20)	Reference	
50 –75 %	32 (41)	0.94 (0.47–1.90)	0872	20 (41)	0.77 (0.31–1.93)	0.575
<50 %	18 (23)	1.53 (0.71–3.31)	0872	10 (20)	1.05 (0.37–3.00)	0.933
DLCO (%)[B]	40 (15)	1.00 (0.98–1.01)	0.578	43 (15)	1.00 (0.97–1.02)	0.751
DLCO categories						
>55 %	8 (10)	Reference		7 (14)	Reference	
36 – 55 %	19 (24)	1.38 (0.56–3.41)	0.488	17 (35)	1.72 (0.54–5.45)	0.358
≤35%	27 (34)	1.67 (0.72–3.86)	0.233	11 (22)	1.52 (0.46–5.06)	0.497
Could not perform	6 (7.6)	4.10 (1.32–12.71)	0.015	5 (10)	1.95 (0.48–7.90)	0.347
Long-term oxygen treatment	12 (15)	1.36 (0.73–2.55)	0.332	10 (20)	4.37 (1.85–10.35)	0.001
Smoking status						
Non-smoker	36 (46)	Reference		25 (51)	Reference	
Ex-smoker	39 (49)	1.53 (0.95–2.47)	0.084	20 (41)	0.72 (0.37–1.43)	0.349
Current smoker	3 (3.8)	0.67 (0.20–2.24)	0.511	3 (6.1)	0.44 (0.06–3.33)	0.429
Trigger for AE-FILD	9 (11)	1.43 (0.68–3.01)	0.350	11 (22)	1.05 (0.48–2.31)	0.905
Treatment unit						
Respiratory ward [C]	42 (53)	0.43 (0.26–0.69)	<0.001	30 (61)	0.83 (0.42–1.62)	0.581
Intermediate care unit	37 (47)	2.35 (1.46–3.80)	<0.001	17 (35)	1.62 (0.83–3.19)	0.159
ICU	16 (20)	1.31 (0.72–2.39)	0.370	7 (14)	0.64 (0.24–1.72)	0.379
Invasive mechanical ventilation	14 (18)	1.23 (0.67–2.37)	0.484	2 (4.1)	0.45 (0.06–3.5)	0.445
Pharmacotherapy preceding hospitalization						
Cs monotherapy for FILD	15 (19)	1.55 (0.87–2.77)	0.135	20 (41)	1.19 (0.61–2.31)	0.618
Cs, azathioprine and NAC	8 (10)	1.13 (0.54–2.37)	0.743	1 (2.0)	5.48 (0.69–43.9)	0.109
Cs for any indication	26 (33)	1.71 (1.05–2.78)	0.032	24 (49)	1.28 (0.66–2.50)	0.464
Antifibrotic drug [D]	7 (8.9)	0.94 (0.43–2.07)	0.877	0		
Pharmacotherapy during treatment period						
Cs at least 20 mg per day [E]	60 (76)	0.72 (0.41–1.24)	0.233	32 (65)	0.89 (0.45–1.77)	0.739
Cs > 150 mg per day [E]	17 (22)	2.20 (1.23–3.93)	0.008	11 (22)	2.11 (0.97–4.59)	0.060
High-dose steroid [F]	14 (18)	2.06 (1.10–3.83)	0.023	8 (16)	2.25 (0.97–5.23)	0.059
Antibiotics	66 (84)	1.51 (0.79–2.88)	0.215	42 (86)	1.68 (0.64–4.37)	0.291
Cyclophosphamide	4 (5.1)	2.40 (0.85–6.78)	0.100	4 (8.2)	0.74 (0.18–3.09)	0.674
Antimycotics	14 (18)	1.23 (0.65–2.31)	0.532	7 (14)	1.81 (0.69–4.72)	0.227

Antiviral treatment	7 (8.9)	1.07 (0.45–2.53)	0.877	4 (8.2)	0.87 (0.21–3.64)	0.848

[A] FVC data was missing from 16 IPF and 9 other FILD patients. [B] DLCO data was missing from 26 IPF and 14 other FILD patients, of which 6 IPF and 5 other FILD patients were not able to perform the examination.[C] Patients treated in the respiratory ward throughout the whole treatment period (no transmissions to ICU or intermediate care unit). [D]Five IPF patients had pirfenidone and 2 IPF patients had nintedanib as antifibrotic treatment.[E] Dose equivalent for prednisolone. Patients receiving high-dose steroids were excluded.[F] 500–1000 mg intravenous steroid per day for three days. Dose equivalent for prednisolone. AE-FILD, acute exacerbation of fibrosing interstitial lung disease; Cs, corticosteroid; DLCO, diffusion capacity for carbon monoxide; FILD, fibrosing interstitial lung disease; FVC, forced vital capacity; HR, hazard ratio; ICU, intensive care unit IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; NAC, N-acetylcysteine; SD, standard deviation; UIP, usual interstitial pneumonia.