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Prognosis and causes of death of patients with acute exacerbation of fibrosing interstitial lung diseases

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ABSTRACT

Background The aim of this study was to compare the clinical characteristics, causes of death and factors impacting on the prognosis of patients with idiopathic pulmonary fibrosis (IPF) and other fibrosing interstitial lung disease (FILD) with a history of acute exacerbation (AE) of IPF or FILD.

Methods Retrospective data of hospital treatment periods caused by AE-IPF and AE-FILD were collected from medical records. Clinical features and survival data of IPF and non-IPF cases were evaluated and compared. The underlying and immediate causes of death were gathered from death certificates.

Results A total of 128 patients fulfilled the criteria for inclusion. IPF (n=79/62%), rheumatoid arthritis-associated interstitial lung disease (RA-ILD; n=17/14%) and asbestosis (n=11/8.6%) were the most common FILD subgroups in the study. The median survival after hospitalisation in AE-IPF was 2.6 months compared with 21 months in other AE-FILDs (p<0.001). The survival difference was not explained by age, gender or pulmonary function test results at the time of hospitalisation. Patients with non-specific interstitial pneumonia and RA-ILD had the most favourable prognosis. ILD was the most common underlying cause of death in both patients with IPF and with other FILD accounting for 87% and 78% of deaths, respectively.

Conclusions We detected a significantly longer survival in AE of patients with non-IPF compared with that of AE-IPFs. The prognosis of patients was affected by the underlying lung disease since pulmonary fibrosis was the underlying cause of death in the majority of all patients with FILD having experienced an AE.

Key messages

Why read on?
- This is the first European study investigating comprehensive data on patients with acute exacerbation of fibrosing interstitial lung disease.

What is the key question?
- What are the prognoses and causes of death in patients with acute exacerbation of fibrosing interstitial lung disease?

What is the bottom line?
- The survival after acute exacerbation was dependent on the pulmonary fibrosis type of the patient.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) and other fibrosing interstitial lung diseases (FILD) are serious, often fatal disorders in individual patients.[1–4] The phenomenon of acute exacerbation (AE) has been associated with high mortality in IPF, and AEs also seem to cause significant mortality in other FILDs.[5–14] According to previous studies, every year about 5%–15% of patients with IPF will experience an AE.[5 13] Recently, it was shown that the incidence of AE or death in a study consisting of various types of patients with FILD was 7.8% per year.[15] The treatment of AEs is based on clinical practice in each hospital, although it mainly involves the administration of corticosteroids and antibiotics, while there is a lack of randomised, controlled studies investigating this subject.[5 16]

The first guidelines for diagnostic criteria of AE-IPF were issued in 2007 with the definition being revised in 2016.[5 17] It has been proposed that it would be beneficial to apply the definition of AE-IPF also to non-IPF FILDs.[16] Currently, AE-IPFs are divided into triggered and idiopathic exacerbations, and the exclusion of infection by bronchoalveolar lavage or endotracheal aspirate is no longer a requirement as was the case in the older recommendations. Thus, a significant number of cases that would fulfil the present criteria for triggered AEs have been excluded from earlier research materials.

AE-IPF mortality rates have tended to be lower in more recent studies when compared with values published prior to 2007. Recent data collected from several previous studies by Kondoh *et al*[17] including 995 patients indicates 1-month survival of 66% and a 3-month survival of 44 %, whereas in older studies, the mortality rates have tended to be much higher, 80%–100%.[17 18] Much less is known about survival after AEs in patients with

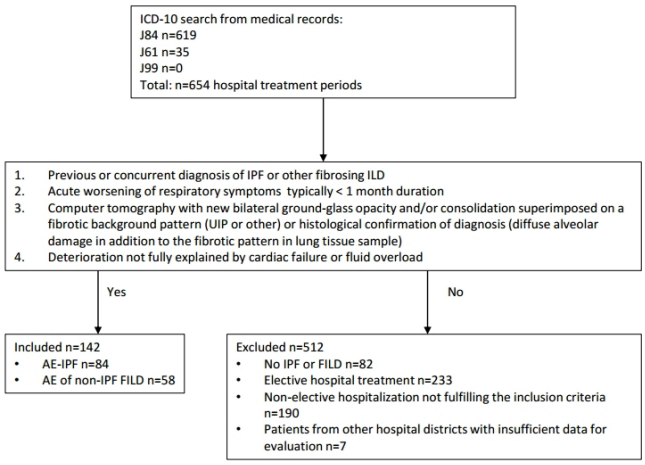

Figure 1 Flow chart of the study. FILD, fibrosing interstitial lung diseases; ICD-10, International Classification of Diseases version 10; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.

non-IPF FILDs. Most studies having investigated both patients with IPF and non-IPF with AE have revealed equally high mortality rates in both groups,[8 10–12 14] although a poorer survival of patients with AE-IPF has also been reported.[6 7 13]

The aim of this study was to investigate the prognosis and factors impacting on the outcome of patients with different types of FILDs, including both IPF and non-IPF patients treated non-electively due to AE in the respiratory wards or intensive care units (ICUs) in the hospitals of the Northern Ostrobothnia Hospital District, that is, Oulu University Hospital (OUH) and Oulaskangas Hospital (OH) during 2008–2017 in northern Finland. Both AE and the types of interstitial lung disease (ILD) were redefined by the current international criteria. Clinical features, including age, gender, radiological findings, pulmonary function test (PFT) results, smoking status, pharmacological therapy, survival data and causes of death, were evaluated and compared between IPF and non-IPF cases.

METHODS

Patient and public involvement

It was neither appropriate nor possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Patient and data collection

The study cohort consists of patients hospitalised due to an AE of IPF or non-IPF FILD in OUH and OH between 1 January 2008 and 31 December 2017. A flow chart of the study is presented in figure 1. The patients and their treatment periods were collected from the hospital's medical records according to the International Classification of Diseases version 10 (ICD-10) codes J84.1, J84.8 and J84.9. To find the hospitalisations related to asbestosis and rheumatoid arthritis-associated ILD (RA-ILD), another search was performed with ICD-10 codes J61, J99, J99.0* and J99*M05.1. The type of ILD was re-evaluated using the current international criteria.[19 20] A more detailed description of the diagnostic evaluation of the patients is presented in online supplementary material.

The data included date of birth, age at diagnosis and at hospitalisation, gender, smoking status at hospitalisation, date of FILD diagnosis, date of hospital admission, duration of hospital treatment, PFT, high-resolution CT (HRCT) reports and images, use of long-term oxygen treatment (LTOT) prior to hospital admission, pharmacological therapy for FILD prior to admission and during hospital treatment and the possible trigger for AE. The diagnosis date recorded was the first visit to the pulmonary clinic or the hospital admission date for those diagnosed with ILD during their hospital treatment. The date and causes of death for each study subject were collected from death certificates housed in the national registry of Statistics Finland. The histological diagnoses from surgical biopsies and autopsies were reviewed. Patients with a pattern of probable or consistent with usual interstitial pneumonia (UIP) in HRCT according to the present classification or histopathological finding of UIP were classified as UIP in statistical analysis. Patients with ILD with less than five pack years of smoking history were classified as non-smokers. Recorded PFT values at hospitalisation were measured maximally 6 months prior to or after the hospital admission date. Survival time was calculated from the hospital admission date to death, lung transplantation or last follow-up date (31 August 2019).

Readmissions after AE within 3 months were not regarded as new, separate AEs, if the clinical presentation of FILD had not been stabilised in that time frame and a new episode meeting the criteria of AE could not be ensured. In one patient without HRCT data, the diagnosis of AE was based on chest X-ray, typical clinical features and histological findings (diffuse alveolar damage (DAD) in addition to the UIP pattern in lung tissue sample). The causes for hospitalisations were classified into AEs and other reasons applying the novel criteria of AE-IPF to all FILDs.[5] The clinical information was collected systematically from electronic patient records dating back about 20 years in OUH and OH in a form specially designed for the present study. Complete case analysis was used to deal with variables with missing data.

Statistical analysis

IBM SPSS Statistics for Windows, V.25.0 (IBM Corp.) was used to perform statistical analysis and Origin(Pro), Version 2019b (OriginLab Corporation, Northampton, Massachusetts, USA) was utilised for graphs. Means and SD were calculated for continuing variables, which were normally distributed. Medians and IQR were used for continuing variables which were not normally distributed. Group differences of continuous variables were tested by using independent samples t-test and variance

Table 1 Data of the hospital treatment periods of the patients with acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) and other fibrosing interstitial lung diseases (FILD)

Variable	Total no of patients (n=128) Hospitalisations (n=142)	IPF (n=79) Hospitalisations (n=84)	Other FILD (n=49) Hospitalisations (n=58)	P value
LTOT preceding hospitalisation	27 (19)	16 (19)	11 (19)	0.990
Length of hospital treatment, days	9 (6–14)	8 (5–14)	11 (7–15)	0.197
Admission in winter or spring*	81 (57)	49 (58)	32 (55)	0.708
Treatment unit in hospital				
Respiratory ward	137 (97)	79 (94)	58 (100)	0.079
Respiratory ward only†	79 (56)	43 (51)	36 (62)	0.200
Intermediate care unit	61 (43)	41 (49)	20 (35)	0.090
Intensive care unit	24 (17)	16 (19)	8 (14)	0.411
Invasive mechanical ventilation	16 (11)	14 (17)	2 (3.4)	0.014
Trigger for AE-FILD				
No trigger	122 (86)	75 (89)	47 (81)	0.165
Infection‡	15 (11)	7 (8.3)	8 (14)	0.298
Drug	4 (2.8)	2 (2.4)	2 (3.4)	1.000
Postoperative§	1 (0.7)	0 (0)	1 (1.7)	0.408
Histological confirmation of AE-FILD¶	23 (16)	15 (18)	8 (14)	0.518

Data are presented as numbers of patients (%) and median (IQR).
Each hospital admission is treated as unique event.
*Hospital admissions between December and May.
†Patients treated in respiratory ward throughout the whole treatment period (no transfers to intensive or intermediate care unit).
‡Microbiologically or serologically confirmed respiratory infection.
§The patient had undergone minor surgery under larynx mask anaesthesia preceding the treatment period.
¶Diffuse alveolar damage could be observed either in autopsy (15 IPF, 7 other FILD) or in thoracoscopic surgical lung biopsy (1 other FILD) samples.
LTOT, long-term oxygen treatment.

analyses or Mann-Whitney U test. Differences in the categorised variables were calculated with χ^2 or Fisher's exact test. Survival was estimated by using Kaplan-Meier curves and the groups were compared with each other by using log rank tests. Log rank test with a linear trend for factor levels was used when the survival differences of five different FILD subgroups were evaluated. The effects of gender, age, PFT results, smoking status and corticosteroid treatment preceding hospitalisation on survival were assessed with Cox regression analysis. As this was a register-based retrospective study and the majority of study subjects were deceased, no patient consent forms were gathered in accordance with Finnish legislation.

RESULTS

Most patients with AE were men with either IPF or CTD-ILD

We investigated a total of 128 patients (79 with IPF and 49 with other FILD) with 142 non-elective hospital treatment periods due to AE (online supplementary E-Table 1 and E-Table 2). Table 1 shows each hospital admission analysed as a unique event. The majority of patients had IPF (62 %), while patients with CTD-ILD were the most common subgroup (16 %). Eleven patients (8.6 %) had an asbestosis-related AE accounting for 13 treatment periods. A slight majority of treatment periods (56%) took place in a respiratory ward, not in the ICU or intermediate care unit, without the need for non-invasive or invasive mechanical ventilation (IMV) support. Sixteen patients (13 %) required treatment with IMV; six of them survived the hospital treatment. In 86% of all treatment periods, there were no identifiable triggers for AE. The medical treatment of the patients is presented in online supplementary E-Table 3.

IPF was associated with shorter survival time and pulmonary fibrosis was the most common underlying and immediate cause of death

Median survival after hospitalisation in AE-IPF was 2.6 months, whereas patients with some other FILD had a much longer median survival, 21 months (p<0.001; figure 2(A)). The difference was clear even after adjustment for gender, age, smoking, forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO) determined at the time of hospitalisation (HR 2.39 (95% CI 1.41 to 4.05), p=0.001). When corticosteroid treatment preceding hospitalisation was included into the multivariate model, HR was even higher 2.86 (95% CI 1.65 to 4.96), with a p value<0.001. The

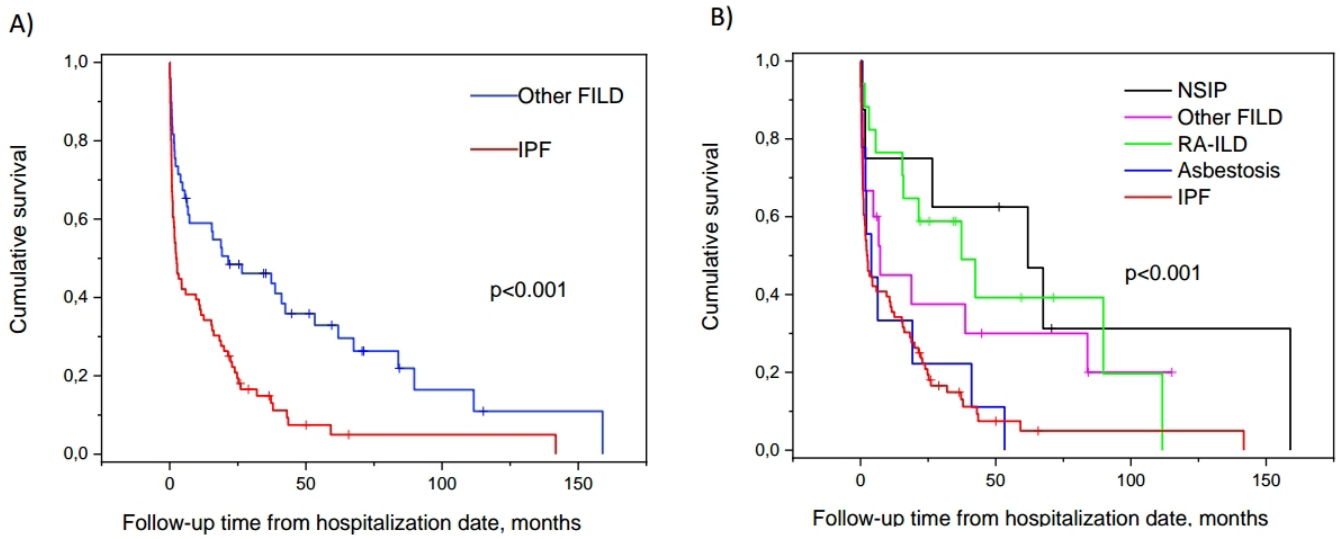

Figure 2 Survival time from the first hospitalisation caused by an acute exacerbation of a fibrosing interstitial lung disease (FILD). (A) Patients with idiopathic pulmonary fibrosis (IPF) versus non-IPF and (B) five different pulmonary fibrosis subgroups. NSIP, non-specific interstitial pneumonia; RA-ILD, rheumatoid arthritis-associated interstitial lung disease.

effect of corticosteroid treatment on survival time was significant in the above-mentioned adjustment model (p=0.006). When patients with FILD were divided into five subgroups, survival time was dependent on the FILD subtype (p<0.001; figure 2(B)). Patients with IPF or asbestosis seemed to have the shortest survival compared with other FILDs, and non-specific interstitial pneumonia (NSIP) was the subgroup with the most favourable prognosis. When possible risk factors for death were analysed separately for IPF and other FILD groups (online supplementary E-Table 4), it was revealed that age more than 80 years, UIP pattern and LTOT preceding hospitalisation seemed to elevate the risk for death in the non-IPF group, while this was not the case in patients with IPF. In contrast, treatment with corticosteroids preceding hospitalisation, treatment in an intermediate care unit or treatment with steroids (more than 150 mg/day) during AE were risk factors for death in IPF, but not in other FILDs. Pulmonary fibrosis was the most common underlying and immediate cause of death accounting for 84% and 45% of deaths, without statistically significant difference between patients with IPF and non-IPF (table 2).

DISCUSSION

We studied a cohort of 128 patients from northern Finland with AE-FILD, assessing their clinical characteristics and prognosis. As reported previously, the patients with AE-IPF had a poor prognosis.[5 17 18] We detected a longer posthospitalisation survival in patients with non-IPF in comparison with patients with IPF, a finding which has not been so explicit in previous studies restricted to AE of patients with IPF and non-IPF. Furthermore, we could discern survival differences between five subclasses of FILD, namely IPF, NSIP, RA-ILD, asbestosis and other FILD, which has not been shown in earlier studies. In addition, we could demonstrate that most patients with a history of AE-FILD also died due to their underlying lung disease, a finding that has not been identified earlier, because there are no previous studies on causes of death in study populations consisting of merely patients with AE-FILD.

AE-IPF and AE of CTD-ILD formed the largest groups in our cohort, a finding consistent with the previous studies on AE in patients with IPF and non-IPF.[6–8 10 21 22] In contrast to these publications, our study revealed that the patients with an AE of asbestosis were more common than those in whom the AE was related to NSIP, chronic hypersensitivity pneumonitis or scleroderma-associated ILD. To our knowledge, there are no previous publications examining patients with asbestosis with clinically confirmed AE, although a previous Japanese survey stated that histological DAD was observed in 35% of 40 autopsy cases of asbestosis,[23] which suggests that an AE might evoke significant mortality among patients with asbestosis, thus supporting the results of our study.

Most of the AE-IPFs found here occurred in winter or spring, which is consistent with previous investigations.[24 25] Patients with IPF experiencing an AE had a poor prognosis with a median survival of only 2.6 months, a result in line with earlier reports of median survival times ranging between 1 and 4 months after AE-IPF.[9 13 24 26 27] Unlike most of the published reports, we detected a clear difference in survival between patients with IPF and non-IPF after the AE. As presented in table 3, three studies from USA investigating cohorts with both patients with IPF and other FILD treated for acute respiratory failure, reported 1-year mortality rates of more than 50% for patients with non-IPF, that is, much higher than in our study where patients with non-IPF had a median survival of 21 months.[6–8] The studies mentioned above, however,

Table 2 Underlying and immediate causes for death in patients with idiopathic pulmonary fibrosis (IPF) and other fibrosing interstitial lung disease (FILD)

	Total n=107	IPF n=70	Other FILD n=37	P value
Underlying cause of death				
Interstitial lung disease	90 (84)	61 (87)	29 (78)	0.238
Cardiovascular disease	8 (7.5)	4 (5.7)	4 (11)	0.444
Lung cancer	2 (1.9)	2 (2.9)	0	0.543
Other cancer	4 (3.7)	2 (2.9)	2 (5.4)	0.608
Other reason*	3 (2.8)	1 (1.4)	2 (5.4)	0.274
Immediate cause of death				
Interstitial lung disease	48 (45)	34 (49)	14 (38)	0.288
Lower respiratory tract infection	31 (29)	21 (30)	10 (27)	0.747
Acute exacerbation of FILD or ARDS†	12 (11)	7 (10)	5 (14)	0.748
Ischaemic heart disease	7 (6.5)	4 (5.7)	3 (8.1)	0.691
Heart failure	1 (0.9)	0	1 (2.7)	0.346
Lung cancer	2 (1.9)	2 (2.9)	0	0.543
Other cancer	2 (1.9)	1 (1.4)	1 (2.7)	1.000
Other infection	1 (0.9)	0	1 (2.7)	0.346
Pulmonary embolism	1 (0.9)	0	1 (2.7)	0.346
Other‡	2 (1.9)	1 (1.4)	1 (2.7)	1.000

*Drowning (non-specific interstitial pneumonia (NSIP)), morbus Alzheimer (IPF), Parkinson's disease (unclassifiable FILD).
†While there is not a specific International Classification of Diseases version 10 code for acute exacerbation of fibrosing interstitial lung disease (AE-FILD), the immediate cause of death was classified as an AE-FILD, if this was clearly stated by the clinician who had signed the death certificate.
‡Morbus Alzheimer (IPF), acute renal failure (NSIP).
ARDS, acute respiratory distress syndrome.

did not use the current definition of AE-IPF in their inclusion criteria, and in addition, one study included patients treated in the ICU,[8] which is known to be a risk factor for death, at least in patients with IPF.[28] The other published studies concerning AE-FILD have been conducted in Japan,[9–14] of which only one demonstrated longer survival of patients with non-IPF compared with that of IPF[13]; in another study, the prognosis of AE-IPF compared with other FILDs was even better.[9] Altogether, it can be stated that the earlier publications focusing on acute respiratory worsening or AE of IPF or non-IPF FILDs have consisted of small and heterogenic study populations with variable inclusion criteria, which complicate making comparisons between the investigations. Our results showing a remarkable difference in survival time between patients with IPF and non-IPF after AE suggested that AE-FILD and AE-IPF cannot be considered as completely identical disease entities, and furthermore, even subtypes of non-IPF FILDs may have a variable prognosis after an AE.

It is noteworthy that all previously published studies using the current criteria of AE-IPF for inclusion and involving both patients with IPF and non-IPF have been implemented in Japan. Differences in genetic and environmental factors may, however, have some impact on the disease course after AE-FILD. For instance, it has been proposed that African Americans with IPF, who are less likely than Caucasians to develop IPF, nonetheless die younger than non-Hispanic Caucasians with pulmonary hypertension.[29] Environmental factors, such as air pollution, have been reported to be associated with AE-IPF.[30] In a previous study, the mortality of IPF was associated with an increased cumulative exposure to particulate matter.[31] However, further data are needed to establish convincing evidence of the effect of different genetic and environmental backgrounds on prognosis of AE-FILDs.

We observed no differences in age, gender, smoking history, FVC or DLCO between the IPF and non-IPF groups and furthermore, these factors did not explain the survival difference after AE between patients with IPF and other FILD. Clinical factors like gender, age, PFT and Gender-Age-Physiology (GAP) index have been demonstrated to be relevant in the prognosis in patients with IPF and non-IPF with or without a history of an AE.[28 32–35] There are also studies designating these clinical factors as risk factors for AE,[9–11 13 36–38] but their relevance in prognostic assessment of the patients who have already received an AE-FILD is less clear. A recent study described a risk assessment model for patients with AE-FILD including male sex, interstitial pulmonary fibrosis diagnosis, body mass index and some other parameters relevant to the circumstances behind their treatment in the ICU.[8] However, in our study, less than 20% of patients were treated in ICU with no statistically significant differences between IPF and non-IPF, that is, the above-mentioned risk score might not be applicable for the majority of patients with AE-FILD. Furthermore, since the prognostic significance of age, LTOT, treatment unit and corticosteroid treatment seemed to be different in patients with AE-IPF and non-IPF, it might prove difficult to plan a functional risk-predicting model for all types of patients with AE-FILD.

In our study, corticosteroid treatment preceding the hospitalisation was a risk factor for shortened survival in patients with IPF, a result which supported the previous guidelines according to which corticosteroids or other immunosuppressive medication is not recommended for IPF.[39] Since most hospital admissions were accomplished when no antifibrotic medication was available in Finland, rather few patients were administered nintedanib or pirfenidone in our study, even though current evidence

Table 3 Previous publications which have examined an acute respiratory worsening of idiopathic pulmonary fibrosis (IPF) and fibrosing interstitial lung diseases (FILD)

Publication	Criteria for inclusion	FILD type (n)	Survival
Huie *et al,* 2010, USA[6]	Hospitalisation caused by acute respiratory worsening (ARW)	IPF (13) CTD-ILD (11) Other ILD (4)	1-year survival: Total 14.8% IPF 0% Non-IPF 28.6% (p=0.045)
Moua *et al,* 2016, USA[7]	Hospitalisation caused by ARW	IPF (100) CTD-ILD (56) i-NSIP (15) CHP (11) Other ILD (38)	Mortality at 1 year after last hospitalisation: IPF 87% Non-IPF 71% (p=0.003)
Gannon *et al,* 2018, USA[8]	Treatment in intensive care unit due to acute respiratory failure	IPF (15) CTD-ILD (23) Other ILD (36) uIIP (52)	1-year mortality: IPF 87% CTD-ILD 52% other ILD 89% uIIP 85% (p=0.02 CTD-ILD vs uIIP)
Arai *et al*, 2016, Japan[9]	Patients with IIP undergone bronchoalveolar lavage (patients with AE-ILD)	IPF (29) Other IIP 'possible UIP' (12) Other IIP 'inconsistent with UIP' (5)	Median survival after AE-ILD or possible AE-ILD: IPF 68 days Possible UIP 13 days Inconsistent with UIP 39 days (p=0.028)
Suzuki *et al,* 2019, Japan[10]	Patients with AE-FILD (consecutive patients with ILD of one hospital)	IPF (124) NSIP (2) CHP (7) CTD-ILD (27) uIIP (33)	90-day mortality: IPF 38% Non-IPF 47% (p=0.345)
Murohashi *et al*, 2019, Japan[11]	Hospitalisation due to acute or subacute IIP or CTD-ILD treated with steroid pulse therapy	IPF (17) NSIP (18) AIP (6) COP (4) Other IIP (7) CTD-ILD (16)	3-month mortality: IPF 35.3% Other IIP 35.7% CTD-ILD 18.8% (p=0.460)
Usui *et al*, 2013, Japan[12]	Consecutive patients with AE of FILD	IPF (30) NSIP (18) FPF (2) Other (1)	Overall survival: 30% at 90 days No difference IPF versus non-IPF
Cao *et al*, 2019, Japan[13]	Patients with AE-IPF or AE-CTD-ILD admitted to a hospital	IPF (107) CTD-ILD (70)	Median survival: AE-CTD-ILD 35±4.2 days, better than AE-IPF (log rank, p=0.029).
Enomoto *et al*, 2019, Japan[14]	Patients with AE-IPF or AE-CTD-ILD treated in a hospital	IPF 37 CTD-ILD 15	3-month mortality rate 46.7% for AE-CTD-ILD. No statistically significant difference compared with AE-IPF.

AE-CTD-ILD, acute exacerbation of connective tissue disease-associated interstitial lung disease; AE-FILD, acute exacerbation of fibrosing interstitial lung disease; AE-ILD, acute exacerbation of interstitial lung disease; AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; AIP, acute interstitial pneumonia; CHP, chronic hypersensitivity pneumonitis; COP, cryptogenic organising pneumonia; CTD, connective tissue disease; FPF, familial pulmonary fibrosis; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; i-NSIP, idiopathic non-specific interstitial pneumonia; NSIP, non-specific interstitial pneumonia; uIIP, unclassified idiopathic interstitial pneumonia; UIP, usual interstitial pneumonia.

supports using antifibrotic treatment for patients with IPF.[40] However, we were not able to show any survival benefit of antifibrotic drugs in seven patients receiving pirfenidone or nintedanib.

The pharmacological therapy for AE was similar in both FILD-groups, being mostly corticosteroids and antibiotics. The mortality rates of our study were equal or even lower than in the investigations where pulse steroid treatment has been more common,[7 9 12 14] with

the exception of a study which estimated a 3 months' mortality rate of only about 35% for 17 patients with AE-IPF treated with pulse steroids.[11] We observed that pulse steroid treatment or treatment with a steroid dose more than 150 mg/day was risk factors for death in patients with IPF; however, this finding cannot be the explanation for higher mortality of patients with IPF, because only 17 patients (22 %) had been treated with high (more than 150 mg) corticosteroid dose. Possibly those patients suffering from more severe respiratory failure were selected to receive higher doses of steroids, and therefore it is difficult to draw any conclusions of the utility of this treatment.

As far as is known, this is the first time that the causes of death have been determined in a study population involving AE-IPF and AE of patients with other FILD. Pulmonary fibrosis was the underlying cause of death in 84% of patients, with no statistically significant difference between patients with IPF and other FILD. According to data from the USA, pulmonary fibrosis was the underlying cause of death in 60% of patients with IPF with a similar result (67.5 %) presented in a Finnish cohort of 117 patients with IPF .[1 3] Less is known about the causes of death in patients with other FILD, even though high mortality, though usually somewhat lower than in IPF, is known to be related to systemic sclerosis-associated ILD, RA-ILD, chronic hypersensitivity pneumonia, fibrotic NSIP and unclassifiable ILD.[2 41–47] It seems that an AE of FILD is a characteristic of a more progressive disease course, which is reflected in the relatively high proportion of pulmonary fibrosis deaths observed here. The immediate causes of death were mainly respiratory in both patients with IPF and non-IPF, with no statistically significant differences between the groups. The higher mortality rate of patients with AE-IPF compared with other AE-FILDs was not reflected in these rates, which is probably related to the fact that there is no specific ICD-10 code for an AE. The immediate causes of death in patients who died of AE were mostly recorded as 'pulmonary fibrosis' or 'pneumonia' diagnoses. It is possible that some AE-FILD deaths remain unrecognised, for example, because HRCT imaging is not expected to provide any benefits for an individual patient in the terminal phase of his/her pulmonary disease.

The retrospective study design, the study implementation being limited to two hospitals and the heterogeneity of the non-IPF study population can be considered as limitations of our study. Moreover, some AE-FILDs may have been excluded due to insufficient data for evaluation (eg, lack of HRCT) or faulty diagnosis codes in the medical records. Nevertheless, all non-elective hospitalisations of each study subject were assessed systematically, and we succeeded in gathering comprehensive data despite the retrospective study design.

Conclusions

To conclude, we have investigated a diverse group of patients with AE-FILD in a real-life setting; their prognosis varied depending on the underlying ILD. Pulmonary fibrosis represents a fatal condition and proved to be the underlying cause of death in the majority of all patients with FILD experiencing an AE. Further research is needed on this highly challenging disease group with such a poor prognosis.

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Contributors JS collected the study material, planned the data collection form, interpreted and analysed the data and prepared the draft of the manuscript. RB planned and participated in the statistical analyses. MP and RK participated in planning the data collection form, study design and the interpretation of the data. RK managed the study and contributed substantially to data interpretation by re-evaluating study patients and data from medical records. All authors participated in the preparation of the manuscript, read and approved the final manuscript.

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Competing interests JS reports congress fees and travel costs from Boehringer-Ingelheim, Novartis, Orion Pharma, Ratiopharm and Roche, and lecture fees from Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, Orion Pharma and Roche outside the submitted work. MP reports lecture fee from Boehringer-Ingelheim Finland and congress fee and travel costs from Roche, outside the submitted work. RB has nothing to disclose. RK reports consultant fees from GlaxoSmithKline and Boehringer-Ingelheim, lecture fees from Roche and Boehringer-Ingelheim, and a congress travel costs from Orion outside the submitted work.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District (statement 2/2015). Permission to use death certificates was given by Statistics Finland (Dnro: TK-53-515-15). The study was conducted in compliance with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets generated and analysed during the current study are not publicly available due to the relatively small population of Northern Finland since we could not guarantee individuals' anonymity as the data were collected in a detailed manner, but it is available from the corresponding author on reasonable request.

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