A cohort study of interstitial lung diseases in central Denmark

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Received 13 May 2013; accepted 3 September 2013
Available online 20 September 2013

KEYWORDS
Interstitial lung disease; Epidemiology; Idiopathic pulmonary fibrosis; Diagnosis; Classification

Summary
Introduction: Interstitial lung diseases (ILDs) form a heterogeneous group of diseases with varying degrees of inflammation and fibrosis. Epidemiological data based on the current diagnostic criteria are sparse.

Objectives: To characterize the incidence rate of ILDs and idiopathic pulmonary fibrosis (IPF) in Danish patients diagnosed at a referral hospital, to evaluate disease severity and survival in these ILD patients and to compare the use of the 2001 and 2011 guidelines to diagnosis of IPF.

Methods: Single-centre, retrospective, observational cohort study including incident patients diagnosed with ILD at Aarhus University Hospital between 2003 and 2009. All diagnoses were re-evaluated according to current diagnostic criteria. Disease severity in IPF was assessed using the GAP index.

Results: The ILD incidence was 4.1 per 100,000 inhabitants/year. IPF was the most common diagnosis (28%) followed by connective tissue disease-related ILD (14%), hypersensitivity pneumonitis (7%) and non-specific interstitial pneumonia (NSIP) (7%). The GAP index was a strong predictor of survival in IPF. Twenty-three patients who had IPF based on the 2001 criteria had a “possible UIP” HRCT pattern but no lung biopsy, and IPF could therefore not be diagnosed based on the 2011 criteria.

Conclusion: ILD and IPF incidence was 4.1 and 1.3 per 100,000 inhabitants/year. The diagnostic re-evaluation raised the number of IPF diagnoses, but a diagnostic “grey zone” was still evident in patients with UIP features not qualifying the patients to be diagnosed with IPF. The GAP index was valuable as a measure of IPF severity in this cohort.

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0954-6111/5 - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.rmed.2013.09.002
Background

Interstitial lung diseases (ILDs) form a heterogeneous group of rare diseases characterized by varying degrees of pulmonary inflammation and fibrosis. The majority of the cases are idiopathic, but ILDs may be caused by many exogenous factors, such as connective tissue diseases, organic dust and certain drugs.

Since 2001, the idiopathic interstitial pneumonias (IIPs) have been classified in seven different entities according to the American Thoracic Society/European Respiratory Society (ATS/ERS) Multidisciplinary International Consensus Classification of the IIPs [1]. This consensus has heightened the clinical relevance of disease classification and is of major importance in epidemiological studies of ILDs. In 2011, the ATS/ERS/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) guidelines of idiopathic pulmonary fibrosis (IPF) [2] redefined IPF and introduced a diagnostic algorithm that made surgical lung biopsy unnecessary in patients with a definite, usual interstitial pneumonia pattern (UIP) on high-resolution computed tomography (HRCT).

The true incidence of the ILDs is unknown, but previous European studies have reported incidences between 4.6 and 7.6 per 100,000 inhabitants/year [3–8]. A US study reported incidences of 31.5 per 100,000 among men and 26.1 per 100,000 among women [9]. In all studies, IPF and sarcoidosis were the most frequent diagnoses.

Focussing on IPF, the reported incidence in the USA has been estimated at 6.8–17.4 per 100,000 inhabitants/year depending on the criteria used [10,11]. In the UK, an IPF incidence of 4.6 per 100,000 inhabitants/year has been reported [12], and the incidence appears to be rising by 5% per year [13]. Incidence data on other IIPs are sparse. To the authors’ knowledge, only one previous study [8] reports incidences of non-IPF idiopathic ILDs according to the 2001 guidelines.

The aims of the present study are

1. to investigate the incidence of ILDs including IPF in the Central Denmark region
2. to describe the severity of IPF using the GAP index
3. to compare IPF diagnoses based on the 2001 ATS/ERS criteria and the 2011 ATS/ERS/JRS/ALAT criteria.

Additionally, this study describes the use of bronchoalveolar lavage (BAL) and video-assisted thoracoscopic surgery (VATS) in this cohort and how they contribute to ILD diagnostics.

Methods

Study design and patients

This was a single-centre, retrospective, observational cohort study including all incident patients who were diagnosed with ILDs other than sarcoidosis and who paid a first visit to the Department of Respiratory Diseases, Aarhus University Hospital, between 1 April 2003 and 1 April 2009. Patients were followed until 15 November 2009. The department is one of three specialized ILD referral centres in Denmark. The patients included were identified from ILD diagnoses (ICD-10) in the hospital registry and from lists of performed HRCT scans. We did not include sarcoidosis, since most sarcoidosis patients in Denmark are diagnosed and treated at local hospitals without referral to a specialized centre. Eligible patients were retrospectively followed from the time of their first visit on suspicion of an ILD until their last visit to the centre, death, transplantation, or loss to follow-up. Cause-of-death information was obtained from medical records.

The study was approved by the Danish Data Protection Agency and The Danish National Board of Health.

Data collection and assessments

Details of all diagnostic examinations and pulmonary function tests at enrolment and throughout the follow-up period were retrospectively registered from medical charts.

All available HRCT scans, patient histories and pathological specimens used for disease evaluation were re-evaluated according to the ATS/ERS Multidisciplinary International Consensus Classification of the IIPs and the 2011 ATS/ERS/JRS/ALAT criteria for IPF and other standard diagnostic criteria when available [1,2,14,15] Three radiologists and two pulmonologists specialized in the evaluation of ILDs were involved in the re-evaluation.

The 2011 ATS/ERS/JRS/ALAT criteria emphasize a multidisciplinary approach that involves pulmonologists, radiologists and pathologists to establish a confident diagnosis. With regards to these 2011 criteria, an IPF diagnosis requires exclusion of known causes of ILD, as well as the presence of a UIP pattern on the HRCT and a histopathological pattern of UIP. In the process of re-evaluation, the terms "end-stage fibrosis" or "unclassifiable ILD" were used in cases where the diagnostic examinations and the re-evaluation failed to meet the 2011 criteria for IPF or any other specified subtype of ILD. A diagnosis of "end-stage fibrosis" was used in the presence of extensive, severe reticulation and/or honeycombing on HRCT that did not satisfy the HRCT UIP criteria. Furthermore, BAL differential counts, VATS (performed in 19% of these patients) or other findings suggested no alternative diagnosis. In other indeterminate cases, the term "unclassifiable ILD" was used.

The primary disease evaluation using the 2001 ATS/ERS criteria was also recorded in the study database. Incidence estimates are based on the 344 patients referred from Aarhus Hospital’s main geographic coverage, which is the Central Denmark Region with 1.2 million inhabitants [16]. Patients referred from other areas (n = 87) were not included in the incidence calculations.

In the absence of agreed criteria for classifying mild, moderate and severe disease in IPF, we used the GAP model [17] to assess outcome based on disease severity. The model includes gender, age and physiology (forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLco)). BAL was performed according to ATS guidelines [18].

Statistical analysis

Data are presented as mean ± standard deviation (SD) or median (range) if continuous or as frequencies if categorical. Survival was evaluated using the Kaplan–Meier method and differences in survival curves were evaluated using the
log-rank test. Cox proportional hazard regression was used to examine the association between BAL cell counts and time to death in IPF. Proportionality of hazards was evaluated by visual inspection of log–log plots. All analyses were performed using STATA statistical software (version 12.1; StataCorp, College Station, Texas, USA).

Results

Demographics and disease incidence

A total of 431 incident ILD patients were included in the study, and the median observational period was 19 months (interquartile range (IQR) 10–36 months). The median duration of patient reported symptoms before the first visit to the referral centre was 13 months (IQR 6–36 months) and the median time from the first visit until the final diagnosis was 2 months (IQR 0.6–4 months).

The observed incidence rate of ILD was 4.1 per 100,000 inhabitants/year in the Central Denmark Region. The incidence rose from 3.8 to 6.6 per 100,000/year during the six-year observation period (2003–2009).

The estimated 2009 incidence of 6.6 per 100,000 inhabitants/year in the Central Denmark Region corresponds to 368 new cases/year in Denmark (5,580,000 inhabitants).

IPF was the most common diagnosis (n = 121/431, 28%). In IPF patients, the median duration of symptoms before the first visit to the referral centre was 28 months (IQR 12–60 months), and the median time from the first visit until the final diagnosis was 1.7 months (IQR 0.7–3.3 months). The incidence of IPF was 1.3 per 100,000/year based on the findings in this cohort. Two thirds of the IPF patients (81/121) were referred from pulmonologists at 12 different regional hospitals and one third (40/121) of the IPF patients were referred directly to the ILD centre from GPs and non-pulmonary hospital departments in the geographical area served by Aarhus University Hospital. There was no statistically significant difference between the group referred directly to the ILD centre and the group referred from pulmonologists at regional hospitals in terms of age, gender, pulmonary function and survival (age p = 0.14, gender p = 0.42, DLco p = 0.76, FVC p = 0.26, survival p = 0.71). The estimated incidence of NSIP was 3.0 per million/year and the incidence of DIP was 2.5 per million/year. Demographics and diagnoses are presented in Table 1.

Bronchoalveolar lavage (BAL)

71% of the patients (306/431) had a bronchoscopy with BAL as part of their baseline examination. In 55% (169/306) of these cases, BAL cytological analysis, differential count and flow cytometry results were available. A specific differential cell count was made a standard part of the BAL evaluation in 2007. In specimens analysed before 2007, the cytological analysis was descriptive and contained no specific cell counts. Positive BAL culture was found in 14% (43/306). Streptococcus pneumoniae (n = 15) and Haemophilus influenzae (n = 14) were the predominant pathogens.

Transbronchial biopsy (TBB) was performed in 25% of the patients. The TBB contributed positively to the diagnosis in four cases of hypersensitivity pneumonitis.

In IPF, a BAL differential count was available in 54 patients. There was no difference in survival between IPF patients who had a BAL differential count and those who did not (p = 0.34). The median eosinophil percentage in IPF was 6%, the median lymphocyte percentage was 3% and the median neutrophil percentage was 7%. We found no association between BAL cell counts and survival in IPF using median values of eosinophil percentage, lymphocyte percentage and neutrophil percentage as thresholds (p = 0.26, p = 0.89, p = 0.53, respectively; 22 deaths occurred among the 54 patients). Median lymphocyte percentages were 7% (IQR 2–22) in NSIP and 59% (IQR 36–72) in HP.

Video-assisted thoracoscopic surgery (VATS)

VATS was performed in 40% (173/431) of the patients in the cohort. The highest biopsy rates were seen in NSIP (87%) and DIP (75%). In IPF, 43% (52/121) were biopsied.

The percentage of biopsy-confirmed IPF diagnoses declined markedly from more than 90% of the patients in 2003 to less than 20% in 2009 concomitantly with the implementation of the ATS/ERS 2001 recommendations.

The reasons for refraining from VATS were recorded in all 268 non-biopsied patients. In half of them (n = 136), the overall risk of the biopsy procedure was considered too high. The 30-day mortality after VATS was 1% (n = 2) and the 60-day mortality was 3% (n = 5). Two deaths occurred within the first 30 days; one sudden and unexpected death after two days, and one death from respiratory insufficiency after 25 days. The three deaths seen in the following 30 days occurred due to acute exacerbation (n = 1), persisting pneumothorax with subsequent infection (n = 1), and sepsis with possible fungal infection and cerebral embolism (n = 1).

Survival

There were 115 deaths during the observation period. The majority (n = 82, 71%) were respiratory deaths, and IPF accounted for 53% (n = 61) of all deaths in the cohort.

Mortality was markedly higher for IPF and end-stage fibrosis than for any other diagnosis, and the survival difference between the two groups was not statistically significant (p = 0.9). The median survival in IPF was three years (range 1 day–6.4 years) and in end-stage fibrosis 2.5 years (range 30 days–3.7 years) (Fig. 1).

Survival at five years was 93.0% in HP, 73.6% in NSIP, and 48.2% in CTD-ILD. When IPF patients were stratified into three groups based on their gender, age, FVC and DLco according to the GAP model, a highly statistically significant survival difference was found (p < 0.0001). One-year survival in GAP stage I was 95% and in GAP stage III 46%. Five-year survival was 46% in GAP stage I and 9% in GAP stage III. The results are shown in Fig. 2.

Diagnostic criteria in IPF

Comparison of 2001 ATS/ERS criteria and 2011 ATS/ERS/JRS/ALAT criteria

Following a systematic re-evaluation based on the 2011 criteria, 121 patients were diagnosed with IPF. In 82 of these patients, the re-evaluation confirmed the primary
diagnosis entered into the medical record. The re-evaluation identified 39 additional patients who met the criteria for IPF. Other causes of ILD were excluded based on medical history and clinical examination. Serological testing was available in 60% of the patients; primarily antinuclear antibodies (ANA), immunoglobulin M rheumatoid factor (IgM-RF) and antineutrophil cytoplasmic antibodies (ANCA). All patients met the major and minor criteria for IPF when diagnoses were reassessed based on the 2001 ATS/ERS criteria (Table 2). No patients diagnosed as having IPF developed features of connective tissue disease within the longitudinal follow-up period. The median survival was the same ($p = 0.44$) in patients who were diagnosed with IPF primarily ($n = 82$) and patients who were diagnosed at the reassessment ($n = 39$).

### Table 1 Patient characteristics at time of inclusion.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n (%)</th>
<th>Gender %</th>
<th>Mean age at first visit (SD)</th>
<th>Smoking %, Biopsy (%)</th>
<th>BAL (%)</th>
<th>Mean FVC % (SD)</th>
<th>Mean DLco % (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>431 (100)</td>
<td>55 (236:195)</td>
<td>61.0 (14.1)</td>
<td>68</td>
<td>173 (40)</td>
<td>306 (71)</td>
<td>71.3 (22.2)</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>121 (28)</td>
<td>77 (93:28)</td>
<td>67.4 (8.4)</td>
<td>81</td>
<td>52 (43)</td>
<td>93 (77)</td>
<td>72.0 (20.7)</td>
</tr>
<tr>
<td>Unclassifiable ILD</td>
<td>62 (14)</td>
<td>45 (29:33)</td>
<td>59.3 (14.5)</td>
<td>73</td>
<td>21 (34)</td>
<td>38 (61)</td>
<td>73.7 (22.8)</td>
</tr>
<tr>
<td>Connective tissue disease-related ILD</td>
<td>54 (13)</td>
<td>41 (22:32)</td>
<td>58.4 (11.9)</td>
<td>59</td>
<td>13 (24)</td>
<td>38 (70)</td>
<td>76.5 (24.5)</td>
</tr>
<tr>
<td>End-stage fibrosis</td>
<td>43 (11)</td>
<td>63 (27:16)</td>
<td>71.5 (8.0)</td>
<td>70</td>
<td>8 (19)</td>
<td>28 (65)</td>
<td>67.8 (20.7)</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis $n = 32$</td>
<td>32 (7)</td>
<td>63 (20:12)</td>
<td>48.6 (14.6)</td>
<td>34</td>
<td>15 (47)</td>
<td>29 (94)</td>
<td>68.4 (18.7)</td>
</tr>
<tr>
<td>Non-specific interstitial pneumonia $n = 30$</td>
<td>30 (7)</td>
<td>47 (14:16)</td>
<td>53.8 (16.0)</td>
<td>60</td>
<td>26 (87)</td>
<td>26 (87)</td>
<td>60.7 (22.5)</td>
</tr>
<tr>
<td>Desquamative interstitial pneumonia $n = 20$</td>
<td>20 (5)</td>
<td>55 (11:9)</td>
<td>45.6 (13.4)</td>
<td>80</td>
<td>15 (75)</td>
<td>13 (65)</td>
<td>70.1 (19.8)</td>
</tr>
<tr>
<td>Drug-induced ILD $^b$</td>
<td>20 (5)</td>
<td>50 (10:10)</td>
<td>68.0 (11.9)</td>
<td>70</td>
<td>1 (5)</td>
<td>8 (40)</td>
<td>64.2 (25.5)</td>
</tr>
<tr>
<td>Cryptojenic organizing pneumonia</td>
<td>10 (3)</td>
<td>50 (5:5)</td>
<td>65.7 (14.1)</td>
<td>60</td>
<td>5 (50)</td>
<td>6 (60)</td>
<td>77.6 (25.6)</td>
</tr>
<tr>
<td>Histiocytosis</td>
<td>8 (2)</td>
<td>38 (3:5)</td>
<td>48.9 (17.4)</td>
<td>100</td>
<td>4 (50)</td>
<td>6 (75)</td>
<td>84.1 (17.5)</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis</td>
<td>4 (1)</td>
<td>0 (0:4)</td>
<td>57.4 (14.5)</td>
<td>25</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>74.5 (10.9)</td>
</tr>
<tr>
<td>Eosinophilic pneumonia</td>
<td>4 (1)</td>
<td>0 (0:4)</td>
<td>55.1 (5.5)</td>
<td>50</td>
<td>1 (25)</td>
<td>3 (75)</td>
<td>68.3 (15.8)</td>
</tr>
<tr>
<td>Respiratory bronchiolitis ILD</td>
<td>2 (0.5)</td>
<td>100 (2:0)</td>
<td>43.0 (--)</td>
<td>100</td>
<td>0 (0)</td>
<td>1 (50)</td>
<td>97.5 (--)</td>
</tr>
<tr>
<td>Lymphocytic interstitial pneumonia</td>
<td>2 (0.5)</td>
<td>100 (2:0)</td>
<td>80.0 (--)</td>
<td>100</td>
<td>0 (0)</td>
<td>2 (100)</td>
<td>88.0 (--)</td>
</tr>
</tbody>
</table>

ILD: interstitial lung disease; BAL: bronchoalveolar lavage; FVC: forced vital capacity; DLco: diffusing capacity of the lung for carbon monoxide.

$^a$ UIP pattern $n = 22$; NSIP pattern $n = 14$; unspecific pattern $n = 18$.

$^b$ Nitrofurantoin-induced ILD in 12 cases.

**Figure 1** Survival analysis (Kaplan–Meier estimates) comparing idiopathic pulmonary fibrosis (IPF) ($n = 121$), end-stage fibrosis ($n = 43$), non-specific interstitial pneumonia (NSIP) ($n = 30$), hypersensitivity pneumonitis ($n = 32$) and connective tissue-related ILD ($n = 54$).

**Figure 2** Survival in IPF based on the GAP model. GAP stage I $n = 37$, GAP stage II $n = 55$, GAP stage III $n = 23$. 
All 121 patients underwent an HRCT scan. In 60 cases (50%), HRCT showed a definite UIP pattern according to the 2011 criteria. Fourteen of the 60 patients with a definite UIP pattern on HRCT were biopsied. All biopsies showed UIP patterns consistent with an IPF diagnosis. Sixty-one patients had possible UIP patterns on HRCT with subpleural, basal predominance, reticular abnormality and no inconsistent findings, but absence of honeycombing.

Of the 61 patients with a possible UIP pattern on HRCT, 38 had a biopsy: 30 had a definite UIP pattern on histopathology, seven had probable UIP and one patient had a possible UIP pattern. The remaining 23 patients with a possible UIP pattern on HRCT had no biopsy, but their clinical course made IPF a likely diagnosis (Table 3).

**Discussion**

**Main results**

This study showed that IPF was the most common of the ILDs in the Danish cohort, and the incidence of ILDs of 4.1 per 100,000 inhabitants in the Danish cohort was comparable to findings in previous European studies [3–8]. The incidence of IPF was low in this study where all IPF diagnoses were based on re-evaluation according to the 2011 criteria.

We found that the GAP index was useful as a measure of disease severity in IPF and was a strong predictor of mortality. Although the GAP model is previously validated in a separate cohort, this study shows that it is useful in IPF in a different clinical setting.

### Table 2 IPF diagnosis by 2001 criteria.

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Total n = 121</th>
<th>Biopsy n = 52</th>
<th>No biopsy n = 69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposures excluded</td>
<td>121 (100%)</td>
<td>52 (100%)</td>
<td>69 (100%)</td>
</tr>
<tr>
<td>Abnormal PFT</td>
<td>121 (100%)</td>
<td>52 (100%)</td>
<td>69 (100%)</td>
</tr>
<tr>
<td>HRCT reticulation</td>
<td>121 (100%)</td>
<td>52 (100%)</td>
<td>69 (100%)</td>
</tr>
<tr>
<td>BAL or TBB with no features to support other diagnosis</td>
<td>BAL 93 (77%)</td>
<td>BAL 45 (87%)</td>
<td>BAL 47 (68%)</td>
</tr>
<tr>
<td></td>
<td>BAL + TBB 13 (11%)</td>
<td>BAL + TBB 7 (13%)</td>
<td>6 (9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor criteria</th>
<th>Total n = 121</th>
<th>Biopsy n = 52</th>
<th>No biopsy n = 69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;50</td>
<td>118 (97%)</td>
<td>49/52 (94%)</td>
<td>69/69</td>
</tr>
<tr>
<td>Gradual onset of symptoms</td>
<td>121 (100%)</td>
<td>52/52 (100%)</td>
<td>69/69</td>
</tr>
<tr>
<td>Symptoms &gt;3 months</td>
<td>121 (100%)</td>
<td>52/52 (100%)</td>
<td>69/69</td>
</tr>
<tr>
<td>Crackles</td>
<td>97 (80%)</td>
<td>41/52 (79%)</td>
<td>56/69</td>
</tr>
</tbody>
</table>

**Incidence**

**ILD**

The Danish Board of Health recommends that all patients requiring diagnosis and treatment of ILD be referred to specialized centres, and the centralization at a few public hospitals provides excellent conditions for observational studies. The incidence of ILD might be underestimated in our study due to referral bias. However, we found no difference in age, gender, pulmonary function and survival between patients referred directly from GPs or non-respiratory departments in the geographical area served by the Aarhus University Hospital and patients referred from pulmonologists at regional hospitals. These findings argue against an under-representation of older and severely ill patients in the study.

The number of referrals to our centre rose during the study period. In addition to the secular trend observed by Navaratnam et al. [13], it is likely that other factors contributed to the observed rise. Thus, access to CT scans improved during the past decade owing to increased focus on early detection of lung cancer. Furthermore, the period saw a stronger GP focus on the diagnosis of chronic obstructive pulmonary disease (COPD) and correct interpretation of spirometry. These factors are likely to have contributed to referral and diagnosis of ILD patients who would otherwise have remained undiagnosed or misdiagnosed with COPD.

**IPF**

The observed IPF frequency of 28% is low, considering that sarcoidosis is not included in the study. In previous studies, IPF accounted for 40–49% of ILD patients after exclusion of sarcoidosis [3–9], but these studies were published before the introduction of the more specific 2011 criteria.

It has also been argued that IPF is over-diagnosed outside the specialized centres. One study observed that community physicians were more likely to assign a final diagnosis of IPF than academic physicians [19]; and a population-based study [11] found that only 10% of cases identified by the use of diagnostic codes proved to be IPF. In our cohort, 10% of the patients are diagnosed with end-stage fibrosis. The majority of these patients did not undergo a lung biopsy due to frailty and impaired lung function. Our study shows that survival in this group is indistinguishable from survival in IPF, and it is likely that many of these patients would have been diagnosed with IPF if a full diagnostic work-up had been possible.

**IPF diagnostic criteria**

The systematic diagnostic re-evaluation increased the number of IPF diagnoses in this cohort and lowered the number of patients with unclassified ILD. However, 23 patients presented a ‘possible UIP’ HRCT pattern, although no definite IPF diagnosis could be made, because no biopsy had been performed. These patients fulfilled the previously used 2001 IPF criteria, but were in a diagnostic grey zone when evaluated by the 2011 criteria. Based on careful exclusion of differential diagnoses and evaluation of the disease course, we chose to include these patients in the...
The mean age in this group was significantly higher than in the group of patients from whom a biopsy was drawn (70.3 years vs. 63.3 years). In patients older than 70 years with a possible UIP pattern on HRCT scan, Fell et al. [20] reported a positive predictive value of 95% of a UIP pattern on lung biopsy. These findings strongly support the IPF diagnosis in this group of patients, and the study by Fell et al. may be helpful in the management of patients in the diagnostic “grey zone” that presents a considerable challenge in clinical practice.

The fibrotic ILDs, including end-stage fibrosis and the fibrosing idiopathic pneumonias (definite, probable and possible IPF and fibrotic NSIP) may be seen as part of the same disease entity. Future revisions of the diagnostic criteria may be able to reflect this, as our understanding of the disease process and the prognostic determinants increases.

BAL and VATS in ILD and IPF

We found that the use of biopsies in IPF diagnostics declined over the years following the introduction of the 2001 ATS/ERS recommendations. The biopsy complication rate remained low with a 30-days mortality of 1% and non-fatal complications in 13% of the cases, all of which is comparable to current standards [21,22]. Our findings also corroborate the recommendation against the use of TBB in IPF diagnostics, since TBB contributed positively to diagnosis in HP only, and not in IPF. The role of BAL in IPF diagnostics remains an issue for debate. We found that characteristic patterns of BAL inflammation contributed to the multidisciplinary assessment in many ILD cases, and BAL cell counts were comparable to findings in previous studies [23,24]. Furthermore, BAL cultivation revealed bacterial infection in 14% of the cases.

In the IPF population, we investigated the correlation between BAL cell counts and survival. We found that no difference in survival was present based on median cell counts of eosinophils, lymphocytes or neutrophils. Cell counts were available in 55% of the patients who underwent BAL. The results corroborate a previous study [25] that showed no predictive role of eosinophil and lymphocyte counts with respect to survival. We did not find a correlation between neutrophil levels and mortality that has been shown in the study by Kinder et al. These findings were unchanged when we used the same cell count thresholds as in Kinder’s study.

Severity and survival

This study illustrates the differences in prognosis among the ILDs. It confirms that especially IPF is diagnosed at late stages of the disease when symptoms have been present for years and pulmonary function is severely impaired. IPF survival in this cohort is similar to other IPF populations. Survival in end-stage fibrosis has not been reported previously, and is indistinguishable from survival in IPF in this cohort. We found that the combination of gender, age and physiological parameters in the GAP index, separated the patients with IPF into three groups with significantly different mortality and served as a useful predictor of survival in IPF.

Conclusion

The study of this well-characterized, population-based cohort of Danish ILD patients presents a standardized re-evaluation of diagnoses for all ILD subtypes and a reliable picture of the relative distribution of ILD diagnoses. IPF is the most frequent diagnosis and the demographic

### Table 3 2011 diagnostic criteria for IPF.

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>Definite UIP</th>
<th>Probable UIP</th>
<th>Possible UIP</th>
<th>Non-classifiable fibrosis</th>
<th>No biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UIP 60</td>
<td>IPF 8</td>
<td>IPF 5</td>
<td>IPF 1</td>
<td>IPF 0</td>
<td>IPF 46</td>
</tr>
<tr>
<td>Possible UIP 30</td>
<td>IPF 7</td>
<td>Probable IPF 1</td>
<td>Probable IPF 0</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Not UIP</td>
<td>Possible IPF 0</td>
<td>Not IPF 0</td>
<td>Not IPF 0</td>
<td>Not IPF 0</td>
<td>Not IPF 0</td>
</tr>
</tbody>
</table>

IPF: Idiopathic pulmonary fibrosis; UIP: usual interstitial pneumonia; HRCT: high-resolution computed tomography
characteristics of the IPF cohort are typical. The GAP index was a valuable prognostic tool that could be used in a clinical setting different from its derivation and primary validation. The re-evaluation of ILD diagnoses led to fewer unclassified cases, but the comparison of the current and previous IPF criteria revealed a group of patients diagnosed with IPF by the 2001 criteria who were in a grey zone when evaluated by the 2011 criteria.

Conflict of interest statement

The development of the ILD Registry at Aarhus University Hospital was supported by Actelion Pharmaceuticals. AM is a full-time employee of Actelion Pharmaceuticals Ltd. CH, OH and EB report no conflict of interest.

Acknowledgements

The authors thank the following participating physicians who performed the radiology review: Hanne Nellemann, Finn Rasmussen and Henrik Torp Madsen, Department of Radiology, Aarhus University Hospital; and Janne Møller, MD, for assistance in the data collection process.

Statistical support was provided by Berthold Schaan, PhD, at Factum GmbH, Germany, sponsored by Actelion Pharmaceuticals Ltd.

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