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A cohort study of interstitial lung diseases in central Denmark

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KEYWORDS
Interstitial lung disease;
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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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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 only 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