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How does comorbidity influence survival in idiopathic pulmonary fibrosis?

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KEYWORDS
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Summary
Introduction: Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias. It is a serious and progressive lung disease with a median survival of three years. The role of comorbidities in the prognosis of IPF is not clear.
Objectives: To describe comorbidity and co-medication in a Danish IPF cohort and the association between clinically important comorbidities and survival.
Methods: The study cohort included all patients diagnosed with IPF at Aarhus University Hospital, Denmark between April 2003 and April 2009. Details on diagnostic examinations, pulmonary function, medication and comorbidities were registered based on medical records.
Results: A total of 121 patients were included. The most frequently observed comorbidities were cardiovascular disease (20%), arterial hypertension (15%) and diabetes mellitus (11%). Cardiovascular disease diagnosed during follow-up significantly increased mortality (HR 4.7, 95% CI 2.0–11.1). No difference was found based on cardiovascular disease already present at the time of IPF diagnosis. Diabetes (HR 2.5, 95% CI 1.04–5.9) and anticoagulant treatment (HR 3.3, 95% CI 1.5–7.2) were also factors associated with a significantly higher mortality in this population-based cohort.
Conclusion: These findings emphasize the need of careful diagnosis and treatment of comorbidities and their risk factors in patients with IPF. In the absence of efficient treatment options for the majority of patients diagnosed with IPF, this may play a role in the effort to optimize the survival of IPF patients. Further studies are needed to fully clarify the impact of comorbidities on prognosis in patients diagnosed with IPF.

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Background

Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias. It is a serious and progressive disease with a median survival of 2–3 years. In many cases, IPF is not diagnosed until pulmonary function is severely impaired. Comorbid diseases like lung cancer and cardiovascular disease may affect the prognosis of patients with IPF. However, the reported prevalence of comorbidity is variable and little is known about the impact of concomitant diseases on survival in patients with IPF. Corticosteroid therapy was widely used in IPF until recently, and may have had a negative influence on some comorbid diseases such as diabetes and osteoporosis. The aim of this study was to describe important comorbid conditions and to assess their impact on outcome in a well-characterized cohort of Danish IPF patients.

Methods

Study patients

IPF patients were identified in the Interstitial Lung Disease (ILD) Registry at Aarhus University Hospital, a retrospective cohort including all incident patients diagnosed with ILD at the Department of Respiratory Diseases, Aarhus University Hospital, between 1 April 2003 and 1 April 2009. ILD diagnoses in the International Classification of Diseases, version 10 (ICD-10) and lists of HRCT scans performed at the hospital were used to identify ILD patients in the hospital's administration system. All ILD diagnoses were re-evaluated according to standard diagnostic criteria by two ILD specialist pulmonologists. All available HRCT scans were re-evaluated by expert thoracic radiologists, and all biopsies had been evaluated by expert pathologists at our institution [1].

IPF was diagnosed according to the 2011 ATS/ERS/JRS/ALAT criteria [2]. Eligible patients were followed from the time of first hospital visit with suspected ILD to the last visit, death or transplantation. Follow-up ended 15 November 2009.

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

Data collection and assessments

All comorbidities were registered based on information from medical records. A diagnosis of diabetes was registered if the patient received antidiabetic therapy. Osteoporosis was registered in the presence of a DXA-scan with *T*-score below −2.5 or a history of fragility fracture. Cardiovascular disease was defined as one or more of the following: ischaemic heart disease, cerebral infarction or peripheral arterial disease based on patients' medical records.

Pulmonary hypertension (PH) was diagnosed in the presence of a tricuspid pressure regurgitation gradient ≥40 mmHg, a tricuspid annular plane systolic excursion <1.8 cm or right ventricular dilatation on echocardiography and/or mean pulmonary artery pressure ≥25 mmHg on right heart catheterization (RHC). Mild PH was defined as tricuspid regurgitation gradient ≤60 mmHg or mean pulmonary artery pressure ≤35 mmHg, and severe PH was defined as tricuspid regurgitation gradient >60 mmHg or mean pulmonary artery pressure >35 mmHg. PH was considered present at the time of diagnosis when the diagnosis was made within 90 days of the first visit to the department. When PH was diagnosed later than 90 days after first visit to the department it was considered as diagnosed during follow-up. Echocardiography was used as a screening tool for PH prior to referral for RHC.

Treatment for comorbid conditions was registered when the patient received the treatment at any time during the study period.

Severity of IPF was assessed on the basis of the GAP prognostic model [3] that incorporates gender, age, diffusion capacity of carbon monoxide (DLco) and forced vital capacity (FVC), and allows a separation of patients into disease categories with significantly different prognosis. Causes of death were registered based on the information from medical records. Follow-up with respect to mortality was based on information from the hospital's currently updated patient administration system and was complete.

Statistical analysis

Data are presented as means ± SD if continuous or as frequencies if categorical. Unless otherwise specified, the number of patients with available data (*n*) was used in the calculation of summary statistics. Survival was evaluated using the Kaplan–Meier method, and the log-rank test was used to determine statistical significance. Differences in hazard ratio (HR) for death were evaluated using Cox proportional hazards analysis. Unadjusted and adjusted Cox proportional hazards regression analyses were performed, and HR are presented along with 95% confidence intervals. Comorbidities diagnosed during follow-up were assessed as time dependent covariates.

Adjustment was performed using age and FVC as continuous variables and gender as categorical variable. Based on the number of events in the survival analysis, the number of variables in the adjusted analysis had to be limited to the clinically most important and robust parameters, but the inclusion of DLco in the model did not change the results. Differences in the use of antidepressants were assessed using a logistic regression model. All analyses were performed using STATA statistical software (version 12.1; StataCorp, College Station, Texas, USA).

Results

Comorbid conditions in IPF

A total of 121 IPF patients were included. IPF was the most frequent diagnosis in the 2003–2009 ILD cohort and constituted 28% of the diagnoses. Ninety-seven patients were diagnosed with definite IPF and one patient with possible IPF. Furthermore, 23 patients were classified as having IPF based on a probable UIP pattern on HRCT and clinical features typical of IPF, although no histopathological diagnosis was made because a surgical lung biopsy