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Respiratory comorbidities and risk of mortality in hospitalized patients with idiopathic pulmonary fibrosis

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ABSTRACT

Background: Respiratory comorbidities are frequently associated with idiopathic pulmonary fibrosis (IPF). However, little is known about their prognostic impact in hospitalized patients with IPF. We examined the impact of respiratory comorbidities on the mortality rates of hospitalized patients with IPF using a Japanese nationwide database.
Methods: We identified 5665 hospitalized patients diagnosed with IPF between April 2010 and March 2013. The primary outcome was defined as the in-hospital mortality at 30 days after admission. The impact of respiratory comorbidities was assessed using a Cox proportional hazards model that incorporated clinically relevant factors.
Results: In hospitalized patients with IPF, the prevalence of bacterial pneumonia, pulmonary hypertension, and lung cancer were 9.5%, 4.6%, and 3.7%, respectively. Among patients with bacterial pneumonia, the four most common pathogens were *Streptococcus pneumoniae* (31.6%), methicillin-resistant *Streptococcus aureus* (18.4%), *Klebsiella pneumoniae* (9.2%), and *Pseudomonas aeruginosa* (9.2%). Lung cancer was more commonly found in the lower lobes (60.1%) than in other lobes. The survival at 30 days from admission was 78.4% in all patients and significantly lower in IPF patients with bacterial pneumonia (adjusted hazard

Abbreviations: IPF, idiopathic pulmonary fibrosis; GAP score, gender, age, and physiology variables score; JRS, Japanese Respiratory Society; DPC/PDPS, diagnosis procedure combination/per-diem payment system; ICD-10, International Classification of Diseases and Related Health Problems, 10th Revision; IIP, idiopathic interstitial pneumonia; AIP, acute interstitial pneumonia; COP, cryptogenic organizing pneumonia; NSIP, nonspecific interstitial pneumonia; LIP, lymphocytic interstitial pneumonia; DIP, desquamative interstitial pneumonia; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease

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ratio [HR], 1.30; 95% confidence interval [CI], 1.04–1.63; $p < 0.023$) and patients with lung cancer (adjusted HR, 1.99; 95% CI, 1.47–2.69; $p < 0.001$) than in others. Pulmonary hypertension was not associated with mortality. IPF patients with one or more of these three respiratory comorbidities had a poorer survival than others ($p < 0.05$).

Conclusions: Respiratory comorbidities, especially bacterial pneumonia and lung cancer, influence mortality in hospitalized patients with IPF.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive fibrosing interstitial pneumonia of unknown cause. Lung cancer, pulmonary infection, and pulmonary hypertension, which are respiratory comorbidities of IPF, have been reported as the causes of mortality in cohort studies and clinical trials [1,2]. However, only a few studies have investigated the influence of these respiratory comorbidities on the disease outcome in hospitalized patients with IPF.

The risk of mortality in patients with IPF has been determined using multidimensional indices, such as the gender, age, and physiology variables (GAP) score [3] and the Japanese Respiratory Society (JRS) classification (PaO_2 at rest and SpO_2 during a 6-minute walk test) [4]. However, respiratory comorbidities such as lung cancer, bacterial pneumonia, and pulmonary hypertension are not included in those indices.

The Japanese government established the Diagnosis Procedure Combination/Per-Diem Payment System (DPC/PDPS), a case-mix payment system according to the diagnosis and procedures for acute hospitalized patients in Japan [5]. The DPC/PDPS covers about 45% of acute care hospitals and includes the data of 5 million hospital admissions in 2011. We previously analyzed several respiratory diseases using this database [6,7].

In the present study, we hypothesized that respiratory comorbid illnesses were associated with the mortality risk in hospitalized patients with IPF. Thus, we examined the prevalence of individual comorbidities and the strength of the association between the nature and number of respiratory comorbidities and the risk of mortality in hospitalized patients with IPF using the DPC/PDPS.

2. Patients and methods

2.1. Data source

We used the DPC/PDPS to collect patient data from April 2010 to March 2013. The details of the DPC/PDPS have been described previously [6,7]. This database includes the main diagnoses, comorbidities present at admission as defined in the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes, and Japanese text data. The database also includes the following data: patient age, sex, height, body weight, Brinkman Index, dyspnea classification [8], the unique identifiers (specialties) of the hospitals, date of admission, length of stay, and status at discharge. All of the data were anonymously collected in the database, so the requirement for informed consent was waived. This study was approved by the Ethics Committee of Tokyo Medical and Dental University, Tokyo, Japan (April 27, 2010; approval number 788).

2.2. Inclusion and exclusion criteria

In this study, idiopathic interstitial pneumonia (IIP) was defined as having both the relevant ICD-10 code (J841) and a diagnosis of IIP in the text data. We identified patients with IIP hospitalized between April 2010 and March 2013. We excluded inpatients who were hospitalized for examination and treatment for lung cancer, such as bronchoscopy, surgical lung biopsy, or chemotherapy. The study population included 16,322 IIP patients. We also divided these patients into 7 groups according to the international consensus classification of the American Thoracic Society/European Respiratory Society [9]: idiopathic pulmonary fibrosis (IPF), acute interstitial pneumonia (AIP), cryptogenic organizing pneumonia (COP), nonspecific interstitial pneumonia (NSIP), lymphocytic interstitial pneumonia (LIP), desquamative interstitial pneumonia (DIP), and respiratory bronchiolitis-associated interstitial lung disease (RB-ILD). For the baseline variables, we extracted the following data: age, sex, comorbidities present at admission (applicable to at least 2.5% of IPF patients), body mass index (BMI), Brinkman index, dyspnea classification, and the unique identifiers of the hospitals. Comorbidities included "temporal" comorbidities that might be a cause of admission such as bacterial pneumonia recorded at the time of hospital admission. Respiratory comorbidities were defined as bacterial pneumonia, pulmonary hypertension, and lung cancer with reference to relevant previous reports [1,10–12]. The institution criteria used by the JRS were used to define a special hospital.

2.3. Statistical analyses

All values are expressed as the mean. The Kaplan-Meier method was used to produce estimates and plots for the patient survival stratified according to the IIP classifications and the number of respiratory comorbidities. The survival time was calculated as the number of days from admission until the patient's death. The log-rank test was used to compare the survival time between groups. The age-adjusted and sex-adjusted hazard ratios were estimated using the Cox proportional hazard model. We calculated the hazard ratio (HR) with 95% confidence intervals (CIs). *P* values < 0.05 were considered to be statistically significant. All calculations were