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Review

The clinical impact of major comorbidities on idiopathic pulmonary fibrosis

*Atsushi Suzuki, Yasuhiro Kondoh**

Department of Respiratory Medicine and Allergy, Tosei General Hospital, 160 Nishioiwake-cho, Seto, Aichi 489-8642, Japan

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a progressive and devastating disease with a median survival time of 2–3 years after diagnosis. Patients with IPF exhibit distinct patterns of disease progression, and some patients display a more rapidly progressive clinical course. The clinical course of IPF may also include periods of acute deterioration, which are termed acute exacerbations.

Patients with IPF frequently experience various comorbidities, such as pulmonary infection, emphysema, pulmonary hypertension, lung cancer, gastroesophageal reflux, cardiovascular disease, diabetes mellitus, and obstructive sleep apnea. A previous age- and sex-matched study showed that IPF itself was an independent risk factor for these comorbidities. Other studies have demonstrated that these comorbidities are associated with disease progression and mortality in IPF.

These variations in the clinical course and comorbidities have affected the researchers' and physicians' understanding of IPF. Therefore, better identification and understanding of these variations may be helpful when making decisions regarding therapeutic interventions. Furthermore, the identification and treatment of comorbidities may have a clinically significant impact on patient survival. Future studies should use well-established definitions for distinct progression patterns and comorbid conditions to obtain greater insights into the pathogenesis and treatment of IPF.

Abbreviations: ACS, acute coronary syndrome; AE, acute exacerbations; AHI, apnea-hypopnea index; BAL, bronchoalveolar lavage; CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CPFE, combined pulmonary fibrosis and emphysema; CTD, connective tissue disease; DLI, drug-induced lung injury; DVT, deep-vein thrombosis; FVC, forced vital capacity; GER, gastroesophageal reflux; HR, hazard ratio; HRCT, high-resolution computed tomography; IIPs, idiopathic interstitial pneumonias; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis; LC, lung cancer; LD-CTD, lung-dominant CTD; MPAP, mean pulmonary artery pressure; NSCLC, non-small cell lung cancer; NSIP, nonspecific interstitial pneumonia; OR, odds ratio; OSA, obstructive sleep apnea; PH, pulmonary hypertension; PPFE, pleuroparenchymal fibroelastosis; RHC, right heart catheterization; RR, rate ratio; UCTD, undifferentiated CTD; UIP, usual interstitial pneumonia; VC, vital capacity.

**Corresponding author*. Fax: +81 561 82 9139.
E-mail addresses: atsushi-suzuki@tosei.or.jp (A. Suzuki), kondoh@tosei.or.jp (Y. Kondoh).

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Contents

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic and progressive fibrosing interstitial pneumonia of unknown cause, which corresponds to the histopathological and radiological pattern of usual interstitial pneumonia (UIP). It is a fatal disease with a median survival time of 2–3 years after diagnosis; however, its natural history is variable and unpredictable. Although a majority of patients with IPF demonstrates a gradual worsening to chronic respiratory failure over years, a minority remains stable or shows a rapid decline. In addition, a significant minority of patients may experience episodes of acute respiratory worsening despite previous stability. These episodes are termed acute exacerbations (AEs) when a cause cannot be identified [1].

Patients with IPF frequently experience various comorbidities, such as pulmonary infection [2–6], emphysema [7–11], pulmonary hypertension (PH) [12–17], lung cancer (LC) [18–32], gastroesophageal reflux (GER) [33–39], cardiovascular disease [40–44], diabetes mellitus [45–47], and obstructive sleep apnea (OSA) [48–53]. A previous age- and sex-matched study showed that IPF itself was an independent risk factor for these comorbidities [2]. The presence of these comorbidities may also be associated with a higher risk of AEs and may affect mortality [54,55].

These variations in the clinical course and comorbidities have affected researchers' and physicians' understanding of IPF. In this review, we discuss and summarize the current state of evidence on the variations in the clinical course of and comorbidities in patients with IPF.

2. Variations in the clinical course

The natural history of IPF is unpredictable at the time of diagnosis [1]. Although a majority of patients demonstrates a slow progression over time, a significant minority may experience episodes of acute respiratory worsening [1,56]. Moreover, it remains unknown whether these different natural histories represent distinct phenotypes of IPF or if the natural history is influenced by geographic, ethnic, cultural, racial, or other factors or comorbid conditions [1].

2.1. *Acute exacerbation*

Recent evidence suggests that some patients with IPF may experience acute respiratory deteriorations [1]. Many of these acute declines are idiopathic and are termed AEs. An AE-IPF can occur at any time during the disease course and often results in a fatal outcome [1,57,58].

Clinical, radiological, and surgical lung biopsy findings of AE-IPF were first described in the English literature in 1993 [57], and several reports regarding AE-IPF have been published thereafter. In 2007, Collard et al. summarized the state of AE-IPF and proposed a definition describing AE-IPF as "an unexplained worsening or development of dyspnea within 30 days, along with new lung infiltrates and exclusion of any recognizable etiology causing lung injury" [58]. In 2016, they revised the definition and diagnostic criteria for AE-IPF to include any acute respiratory event characterized by new bilateral ground-glass opacification/consolidation not fully explained by cardiac failure or fluid overload [59]. The reported incidence of AE-IPF varies widely among studies, but data from the placebo arms of large clinical trials show an incidence of AE-IPF of 5–15% over a period of 1 year [60–65]. Nevertheless, because the participants in clinical trials are a selected population, these results may be biased and differ from those of the general IPF population. However, several retrospective studies have reported similar incidences of AE-IPF [66–68].

Several risk factors for AE-IPF have been identified. Low forced vital capacity (FVC) is the most consistent risk factor

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