CHEST™

Outcomes After Hospitalization in Idiopathic Pulmonary Fibrosis

A Cohort Study

A. Whitney Brown, MD; Chelsea P. Fischer, BS; Oksana A. Shlobin, MD; Russell G. Buhr, MD; Shahzad Ahmad, MD; Nargues A. Weir, MD, FCCP; and Steven D. Nathan, MD, FCCP

OBJECTIVE: The outcomes of patients with idiopathic pulmonary fibrosis (IPF) who undergo hospitalization have not been well characterized. We sought to determine the frequency of all-cause and respiratory-related hospitalizations and to evaluate their impact on the subsequent course and survival of patients with IPF.

METHODS: The records of patients with IPF evaluated at a tertiary center were examined for the cause and duration of hospitalization. Data on subsequent patient outcomes were collated.

RESULTS: The IPF cohort consisted of 592 patients, 25.3% of whom were hospitalized subsequent to their IPF diagnosis. A respiratory-related cause accounted for 77.3% of these hospitalizations. The median transplant-free survival for all patients was 23.3 months (interquartile range [IQR], 7.6-63.6 months) from the time of consultation. Transplant-free survival after hospital admission was much lower for patients with a respiratory hospitalization compared with those with a nonrespiratory hospitalization (median survival, 2.8 months [IQR, 0.63-16.2 months] vs 27.7 months [IQR, 7.4-59.6 months]; $P = .0004$). Multivariate analyses demonstrated that both all-cause and respiratory-related hospitalizations were strongly associated with mortality after adjusting for baseline demographics. Among patients with a respiratory hospitalization, 22.4% died while in the hospital, whereas 16.4% eventually went on to lung transplantation.

CONCLUSIONS: Hospitalizations are common events in patients with IPF. Most hospitalizations are respiratory-related and are associated with high in-hospital mortality and limited survival beyond discharge. Both all-cause and respiratory hospitalizations are associated with mortality, and therefore, either could be used as an end point in IPF clinical trials.

CHEST 2015; 147(1):173-179

Manuscript received October 10, 2013; revision accepted August 10, 2014; originally published Online First September 4, 2014.

ABBREVIATIONS: GAP Index = Gender, Age, Physiology Index for Idiopathic Pulmonary Fibrosis; IPF = idiopathic pulmonary fibrosis; IQR = interquartile range

AFFILIATIONS: From the Advanced Lung Disease and Transplant Program (Drs Brown, Shlobin, Ahmad, Weir, and Nathan and Ms Fischer), Department of Medicine, Inova Fairfax Hospital, Falls Church, VA; and the Department of Medicine (Dr Buhr), University of California at Los Angeles, Los Angeles, CA.

FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

CORRESPONDENCE TO: Steven D. Nathan, MD, FCCP, Advanced Lung Disease and Transplant Program, Inova Heart and Vascular Institute, 3300 Gallows Rd, Falls Church, VA 22042; e-mail: steven.nathan@inova.org

DOI: 10.1378/chest.13-2424

Idiopathic pulmonary fibrosis (IPF) is a deadly disease with a median survival of only 2.5 to 4 years from diagnosis.[1-4] The disease tends to run an unpredictable course, which precludes assigning a precise prognosis and impacts referral for transplant and stratification of patients in clinical trials.[4,5]

Hospitalizations, specifically respiratory-related hospitalizations, have prognostic significance in COPD and cystic fibrosis.[6-8] As with patients with these diseases, many patients with IPF will require hospitalization.[9] The bleak course for patients with IPF admitted to an ICU has been the subject of a number of small studies, and hospitalization has been linked to short-term mortality in studies of highly select patients with IPF.[10-15] However, there is a paucity of data on the incidence and long-term outcomes after all-cause and respiratory-related admissions in a broad cohort of patients with IPF. Despite this, hospitalizations have been proposed and have been used as an end point in IPF clinical trials.[16-19]

We sought to analyze the frequency, duration, and subsequent mortality of all-cause and respiratory-related hospitalizations among a cohort of patients with IPF evaluated at a tertiary care center. We also explored whether hospitalization could be regarded as a meaningful end point in IPF clinical trials.

Materials and Methods

The records of all patients with IPF evaluated at a tertiary referral center were reviewed. Patients were diagnosed based on prior international consensus statements for the diagnosis of IPF.[20,21] Most of these same patients were included in a previous publication from our group that provides greater characterization of their diagnosis and treatment.[3,4] Hospitalizations of at least 24 h in duration subsequent to the IPF diagnosis were categorized as respiratory or nonrespiratory in nature and were analyzed for length of stay.

Elective hospitalizations for surgical lung biopsies were excluded. Lung allograft recipients were excluded from a subset of the survival analyses because of transplant-related survival bias, but were included in analyses of transplant-free survival and the competing risk analyses, with hospital admission for the transplant surgery itself excluded. The study was approved by the Inova Fairfax institutional review board (Study No. 12.1093).

Demographic and pulmonary function test data were collated, and vital status was ascertained from the clinic database and the Social Security Death Index. The Gender, Age, Physiology Index for IPF (GAP Index) was calculated for each patient.[22] Two authors reviewed all hospitalization events, with discordance in categorization adjudicated by a third.

The primary outcome was the association between hospitalization (all-cause and respiratory) and survival in patients with IPF. Other secondary outcomes included agreement on reason for hospitalization (respiratory vs nonrespiratory) between reviewers, relationship between length of hospitalization and subsequent survival, and association between baseline patient characteristics and hospitalization and survival.

Statistical Analysis

The association between patient characteristics and hospitalization type was investigated with bivariate analyses. Survival time was calculated from both the time of initial consultation and the time of initial hospitalization, and was analyzed by medians and interquartile ranges (IQRs). Kaplan-Meier survival curves from the time of hospitalization were generated and compared using the log-rank test, with patients categorized according to respiratory-related or nonrespiratory hospitalization.

Multivariate analyses using Cox proportional hazard modeling were performed to examine the relationship between all-cause and respiratory hospitalization adjusted for baseline patient characteristics. Hospitalization was modeled as a time-varying covariate. Although lung allograft recipients were excluded from the primary analysis, they were included in a competing risk analysis, with transplant as a competing event with death. In the multivariate analyses, a stepwise approach was used to select covariates, although race, BMI, and GAP Index were retained in the models because of their clinical significance. Multiple imputation was used for missing covariate data (BMI, GAP Index, and race).

All statistical analyses were performed using STATA version 12 (StataCorp LP). All tests were two tailed, and P values $< .05$ were considered significant.

Results

A total of 592 patients with IPF were evaluated between 1997 and 2012. Of these, 151 were listed and 128 underwent lung transplant. Twenty-three patients were listed and died without a transplant, and 441 patients were never listed (Fig 1). The median transplant-free survival for all patients was 23.3 months (IQR, 7.63-63.6 months) from the time of consultation. For those patients who did not receive lung allografts, the median survival was 35.3 months (IQR, 11.1-97.2 months). The demographics of the IPF cohort are shown in Table 1.

Hospitalization of at least 24 h in duration occurred in 25.3% of patients (n = 150). None of the admissions was purely for end-of-life care. Average hospital length of stay was 8.6 days (range, 1-56 days). ICU admission occurred in 56 of the 150 patients (37.3%) hospitalized. Noninvasive ventilation was required in 26 of the 150 hospitalized patients (17.3%), whereas 27 of the 138 (18%) required mechanical ventilation. The large majority of patients requiring mechanical ventilation (74.1%) died in the hospital. Five patients underwent a lung transplant while waiting in the hospital. Initial consultation from the advanced lung disease program was sought during the index admission in 44 cases. In the remaining 106 patients, hospitalization occurred a mean of 10.7 months after initial evaluation (range, 1 day-81.3 months).