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Possible UIP pattern on high-resolution computed tomography is associated with better survival than definite UIP in IPF patients

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ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing lung disease of unknown etiology. Inter-society consensus guidelines on IPF diagnosis and management outline radiologic patterns including definite usual interstitial pneumonia (UIP), possible UIP, and inconsistent with UIP. We evaluate these diagnostic categories as prognostic markers among patients with IPF.

Methods: Included subjects had biopsy-proven UIP, a multidisciplinary team diagnosis of IPF, and a baseline high-resolution computed tomography (HRCT). Thoracic radiologists assigned the radiologic pattern and documented the presence and extent of specific radiologic findings. The outcome of interest was lung transplant-free survival.

Results: IPF patients with a possible UIP pattern on HRCT had significantly longer Kaplan-Meier event-free survival compared to those with definite UIP pattern (5.21 and 3.57 years, respectively, $p = 0.002$). In a multivariable Cox proportional hazards model adjusted for baseline age, gender, %-predicted FVC, and %-predicted DLCO via the GAP Stage, extent of fibrosis (via the traction bronchiectasis score) and ever-smoker status, possible UIP pattern on HRCT (versus definite UIP) was associated with reduced hazard of death or lung transplant (HR = 0.42, CI 95% 0.23–0.78, $p = 0.006$).

Conclusions: Radiologic diagnosis categories outlined by inter-society consensus guidelines is a widely-reported and potentially useful prognostic marker in IPF patients, with possible UIP pattern on HRCT associated with a favorable prognosis compared to definite UIP pattern, after adjusting for relevant covariates.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a diffuse parenchymal lung disease of unknown cause characterized by progressive loss of lung function and a poor prognosis. Median survival is 2–3 years from the time of diagnosis [1]. IPF is defined histopathologically by the usual interstitial pneumonia (UIP) pattern, after exclusion of connective tissue disease, drug toxicity, and occupational/environmental exposure. Current guidelines outline clinical, high-resolution computed tomography (HRCT), and histopathologic criteria consistent with a diagnosis of IPF [1]. Diagnostic guidelines categorize HRCT findings as “definite UIP” pattern, “possible UIP” pattern, or “inconsistent with UIP” pattern. Definite UIP HRCT pattern in the correct clinical setting obviates the need for a lung

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Abbreviations list

DLCO	Diffusing Capacity of Lung for Carbon Monoxide
FVC	Forced Vital Capacity
HRCT	High Resolution Computed Tomography
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
SD	Standard deviation
UIP	Usual Interstitial Pneumonia

biopsy to diagnose IPF [1]. These radiologic patterns are further described in the "High Resolution Computed Tomography Evaluation" section under Methods.

Although IPF is invariably a progressive disease associated with a poor outcome, the individual disease course is heterogeneous. Older patients and those with greater physiologic impairment at baseline have a higher mortality risk [2]. More extensive fibrosis on HRCT is also associated with increased risk of death [2–5]. Knowledge of the HRCT pattern may add relevant prognostic information. Among patients with idiopathic interstitial pneumonias (including some with IPF), those with a UIP pattern on HRCT have shorter survival compared to those with alternative HRCT patterns [6,7]. Evaluation of variably-defined HRCT patterns as predictors of survival in IPF cohorts have not replicated these findings [4,8–11]. We sought to assess the prognostic value of the HRCT patterns defined in the 2011 ATS/ERS/JRS/ALAT guideline [1] on IPF diagnosis, as well as individual "inconsistent with UIP" HRCT features, in patients with biopsy-proven UIP and a clinical diagnosis of IPF.

2. Materials and methods

University of Michigan patients with UIP on a surgical lung biopsy (included biopsies were dated January 2001 to February 2013), a multidisciplinary team diagnosis of IPF, and a baseline HRCT, were retrospectively identified via the electronic medical record. Documentation of multidisciplinary case review was available for all subjects. Patient characteristics, forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) were documented at the time of the clinical evaluation. Transplant-free survival time is time from the HRCT to death or lung transplantation. Vital status (including date of death or lung transplantation) was confirmed via the electronic medical record and Social Security Death Master File, censored on November 17, 2014 (3 months prior to the registry search to account for reporting lag). This study was conducted in accordance with the amended Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/). The Institutional Review Board at the University of Michigan (HUM #00073617) approved this protocol, and need of written informed consent was waived by the IRB. Some of these results were previously presented as an abstract [12].

2.1. High resolution computed romography evaluation

HRCT data was collected with 1.0- or 1.5-mm-thick overlapping sections using a high-spatial-frequency reconstruction algorithm taken during a single breath hold on various CT scanners. One of four experienced thoracic radiologists (A.R.C., B.H.G., E.A.K., and B.S.) independently evaluated each HRCT prior to the scheduled multidisciplinary ILD conference. The presence of honeycombing, septal thickening, traction bronchiectasis, ground-glass opacities, mosaic attenuation, and air trapping was documented categorically, as previously defined [13]. The overall extent of each individual abnormality was documented as "Major" (one of the 2–3 most prominent features on the scan) or "Minor" (the feature is present but not one of the 2–3 most prominent). The craniocaudal distribution of the primary abnormality was documented as upper lung, lower lung, or diffuse, and axial distribution as central, peripheral, or diffuse. Finally, the radiologist rated the overall HRCT pattern as "definite UIP", "possible UIP", and "inconsistent with UIP" as outlined in the 2011 consensus guidelines on IPF [1]. Specifically, "definite UIP" is assigned when honeycombing is present in addition to subpleural, basal predominant reticular abnormality, with or without traction bronchiectasis, and without inconsistent features. "Possible UIP" pattern is defined by a subpleural, basal predominant reticular abnormality without inconsistent features, but radiologic honeycombing is absent. The "Inconsistent with UIP" pattern is assigned when any of the following HRCT features are present: upper lung, mid-lung, or peribronchovascular distribution of abnormality; extensive ground glass abnormality; profuse micronodules; discrete non-honeycomb cysts; diffuse mosaic attenuation/air-trapping; or consolidation. Fig. 1 shows examples of definite, possible, and inconsistent with UIP HRCT patterns seen in four patients with IPF included in this cohort, paired with the individual's histopathologic findings. The overall extent of fibrosis was measured by the traction bronchiectasis score, obtained by adding the number of lobes in which traction bronchiectasis is present (maximum of 5).

2.2. Statistical analysis

Demographic characteristics and summary of HRCT findings are displayed for the entire cohort and by HRCT pattern (definite, possible, or inconsistent with UIP), with means and standard deviations for continuous variables and percentages for categorical variables. Statistically significant differences between HRCT patterns for continuous and categorical variables are assessed using analysis of variance and Pearson's chi-squared (or Fisher's exact, when appropriate) methods, respectively. A combined endpoint of time to death or transplant was used in time-to-event analyses. The Kaplan-Meier method illustrates transplant-free-survival (combined endpoint of death or lung transplant) according to HRCT pattern, with statistically significant differences in event rates assessed via the log-rank and restricted means tests [14]. Univariable and multivariable Cox proportional hazards models [15] and pseudo-observation models [16] assess clinical and radiologic variables associated with lung-transplant-free survival. Pseudo-observation models do not rely on an assumption of proportional hazards. The DLCO was missing in n = 33 patients, and multiple imputation methods (with 5 imputations) were used to handle missing data in univariate and multivariate analyses involving DLCO [17], with complete case analysis (unimputed) results included in the e-appendix. For Cox models, index of concordance (c-statistic) gives model discrimination for various models [18], with higher values indicating improved prediction. Statistically significant differences/inferences are noted at the $P < 0.05$ level. All analysis was done using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 3.1.2 (The R Project, Vienna, Austria).

3. Results

One-hundred and thirty-three patients met inclusion criteria, of whom 41 (31%) had definite UIP pattern, 77 (58%) had possible UIP, and 15 (11%) had inconsistent with UIP pattern. As shown in Table 1, mean age at the time of the HRCT was 63.6 (SD 8.1) years, 63.2% (n = 84) were male, 62.1% (n = 82) were ever-smokers, and the mean baseline FVC %-predicted was 67.3 (SD 15.8). The mean age