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Original Research

DIFFUSE LUNG DISEASE

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Predicting Survival Across Chronic Interstitial Lung Disease

The ILD-GAP Model

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Background: **Risk prediction is challenging in chronic interstitial lung disease (ILD) because of heterogeneity in disease-specific and patient-specific variables. Our objective was to determine whether mortality is accurately predicted in patients with chronic ILD using the GAP model, a clinical prediction model based on sex, age, and lung physiology, that was previously validated in patients with idiopathic pulmonary fibrosis.**

Methods: **Patients with idiopathic pulmonary fibrosis (n = 307), chronic hypersensitivity pneumonitis (n = 206), connective tissue disease-associated ILD (n = 281), idiopathic nonspecific interstitial pneumonia (n = 45), or unclassifiable ILD (n = 173) were selected from an ongoing database (N = 1,012). Performance of the previously validated GAP model was compared with novel prediction models in each ILD subtype and the combined cohort. Patients with follow-up pulmonary function data were used for longitudinal model validation.**

Results: **The GAP model had good performance in all ILD subtypes (c-index, 74.6 in the combined cohort), which was maintained at all stages of disease severity and during follow-up evaluation. The GAP model had similar performance compared with alternative prediction models. A modified ILD-GAP Index was developed for application across all ILD subtypes to provide disease-specific survival estimates using a single risk prediction model. This was done by adding a disease subtype variable that accounted for better adjusted survival in connective tissue disease-associated ILD, chronic hypersensitivity pneumonitis, and idiopathic nonspecific interstitial pneumonia.**

Conclusion: **The GAP model accurately predicts risk of death in chronic ILD. The ILD-GAP model accurately predicts mortality in major chronic ILD subtypes and at all stages of disease.**

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Abbreviations: CTD-ILD = connective tissue disease-associated interstitial lung disease; DLCO = diffusion capacity of lung for carbon monoxide; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia; PFT = pulmonary function test; UCSF = University of California, San Francisco

Risk prediction in patients with chronic interstitial lung disease (ILD) is challenging because of heterogeneity in disease-specific and patient-specific variables. Idiopathic pulmonary fibrosis (IPF) is associated with a significantly worse median survival time than other forms of ILD, such as chronic hypersensitivity pneumonitis (HP), connective tissue disease-associated ILD (CTD-ILD), and idiopathic nonspecific interstitial pneumonia (NSIP).[1-3] Patient characteristics such as age, sex, and pulmonary physiology are associated

with survival in IPF.[4] No systematic approach to risk prediction in non-IPF chronic ILD has been conducted to date, and prognostication remains challenging for clinicians.

We recently derived and validated the GAP risk prediction model (which includes the GAP Score, Index, and Staging System) for patients with IPF.[4] The GAP model integrates patient-specific variables into a simple and clinically useful tool for clinicians.

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In this study, we extended this analysis to test the performance of the GAP model across other chronic ILDs (chronic HP, CTD-ILD, idiopathic NSIP, and unclassifiable ILD) and to derive a modified GAP model that optimizes mortality estimation by integrating patient-specific and disease-specific variables.

Materials and Methods

Study Patients

The study cohort included patients enrolled in the University of California, San Francisco (UCSF) ILD database between January 2001 and August 2012. Patients were included if they had chronic ILD of at least 3-months duration and pulmonary function tests (PFTs) available within 6 months of their initial clinic visit date. Chronic ILD was defined as IPF, idiopathic NSIP, CTD-ILD, chronic HP (all according to established criteria[5-7]), and unclassifiable ILD (defined as patients without a specific ILD diagnosis following multidisciplinary review of clinical, radiologic, and pathologic data).[8] A subcohort of patients with follow-up pulmonary function data were identified for longitudinal model validation. The UCSF Committee on Human Research approved this project, and all patients provided written informed consent (approval #10-01592).

Statistical Analysis

All data analysis was performed using STATA 12.0 (StataCorp LP). The primary outcome was all-cause mortality, verified using the United States Death Registry Index. Lung transplantation was treated as a competing risk. Derivation and validation of the original GAP model has been described previously.[4] This same methodology was used in the present study to test the performance of the GAP model and screen potential alternative prediction models for the chronic ILD cohort. Briefly, candidate models with four to seven predictors were screened using 20 repetitions of 10-fold cross-validation of Harrell's c-index, a measure of discrimination.[9] The following candidate predictor variables were considered: age, sex, diagnosis made by surgical lung biopsy, smoking status and number of pack-years, and baseline pulmonary physiology (FVC, total lung capacity, and diffusion capacity of lung for carbon monoxide [Dlco]).[10-12] We used the approach of Wolbers et al[13] to estimate the c-index in the presence of competing risks.[14] This analysis was repeated for each individual ILD, except for idiopathic NSIP, which was combined with CTD-ILD because of similar characteristics and small sample size.

Using this approach, a modified GAP score was developed that included a variable to adjust for differences in survival between chronic ILD subtypes, making it possible to calculate 1-, 2-, and 3-year risks using a simple modification of the original GAP Score formulas. In addition, the original GAP Score was previously simplified to the point-score GAP Index.[4] A modified ILD-GAP Index was developed using similar methodology. Further methodologic details are provided in e-Appendix 1.

Results

Patient Characteristics

A total of 1,208 patients were identified with chronic ILD, representing 71% of the entire parent cohort enrolled during the study period. The final study population included 1,012 patients (196 patients did not have baseline PFTs available) (Table 1). An additional 1,117 follow-up PFTs were available from 655 of the included patients for longitudinal validation. The final study population included 307 patients with IPF, 281 with CTD-ILD, 206 with chronic HP, 173 with unclassifiable ILD, and 45 with idiopathic NSIP. Most patients were included in previous cohort studies.[2,4,8,15] Approximately 40% of patients with HP had an identified antigen exposure.[2] Patients with IPF were older, more likely to be men, and had a greater number of pack-years compared with the patients with non-IPF chronic ILD ($P < .0005$ for all comparisons). There were no significant differences in FVC or Dlco comparing patients with and without a diagnosis of IPF ($P = .53$ and $P = .18$, respectively).

Survival Across ILD Category

Median follow-up was 3.0 years (range, 0-14.0 years). Two hundred eighty-one patients died, including 129 with IPF, 55 with CTD-ILD, 33 with chronic HP, 54 with unclassifiable ILD, and 10 with idiopathic NSIP. Forty-four patients had lung transplantation, including 25 with IPF, eight with CTD-ILD, eight with chronic HP, one with unclassifiable ILD, and two with idiopathic NSIP. Unadjusted mortality was similar in idiopathic CTD-ILD, chronic HP, and idiopathic

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