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Predicting Mortality in Systemic Sclerosis-Associated Interstitial Lung Disease Using Risk Prediction Models Derived From Idiopathic Pulmonary Fibrosis

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BACKGROUND: Mortality risk prediction tools have been developed in idiopathic pulmonary fibrosis, however, it is unknown whether these models accurately estimate mortality in systemic sclerosis-associated interstitial lung disease (SSc-ILD).

METHODS: Four baseline risk prediction models—the Composite Physiologic Index, the Interstitial Lung Disease-Gender, Age, Physiology Index, the du Bois index, and the modified du Bois index—were calculated for patients recruited from a specialized SSc-ILD clinic. Each baseline model was assessed using logistic regression analysis with 1-year mortality as the outcome variable. Discrimination was quantified using the area under the receiver operating characteristic curve. Calibration was assessed using the goodness-of-fit test. The incremental prognostic ability of additional predictor variables was determined by adding prespecified variables to each baseline model.

RESULTS: The 156 patients with SSc-ILD completed 1,294 pulmonary function tests, 725 6-min walk tests, and 637 echocardiograms. Median survival was 15.0 years from the time of SSc-ILD diagnosis. All baseline models were significant predictors of 1-year mortality in SSc-ILD. The modified du Bois index had an area under the receiver operating characteristic curve of 0.84, compared with 0.77 to 0.81 in the other models. Calibration was acceptable for the modified du Bois index, but was poor for the other models. All baseline models include FVC and 6-min walk distance was identified as an additional independent predictor of 1-year mortality.

CONCLUSIONS: The modified du Bois index has good discrimination and calibration for the prediction of 1-year mortality in SSc-ILD. FVC and 6-min walk distance are important independent predictors of 1-year mortality in SSc-ILD. CHEST 2015; 148(5):1268-1275

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ABBREVIATIONS: 6MWD = 6-min walk distance; 6MWT = 6-min walk test; AUROC = area under the receiver operating characteristic; CPI = Composite Physiologic Index; CTD-ILD = connective tissue disease-associated interstitial lung disease; D_{LCO} = diffusion capacity of the lung for carbon monoxide; ILD = interstitial lung disease; ILD-GAP = Interstitial Lung Disease-Gender, Age, Physiology; IPF = idiopathic pulmonary fibrosis; PFT = pulmonary function test; RVSP = right ventricular systolic pressure; SSc = systemic sclerosis; SSc-ILD = systemic sclerosis-associated interstitial lung disease

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Fibrotic interstitial lung disease (ILD) is a common complication of systemic sclerosis (SSc),[1,2] with a reported prevalence of 25% to 90%.[3] ILD is the leading cause of mortality in SSc[4]; however, prognostication of SSc-associated ILD (SSc-ILD) remains challenging given the substantial variability in disease course. Previous studies have shown that mortality in SSc-ILD is influenced by a number of patient-specific, ILD-specific, and SSc-specific factors,[5] however, it is unknown how these variables should be used in combination to accurately estimate mortality risk in SSc-ILD.

SSc-ILD shares many clinical features and prognostic variables with idiopathic pulmonary fibrosis (IPF), a chronic progressive fibrotic ILD of uncertain etiology.[6] Previous studies have described mortality risk prediction tools in IPF,[7-10] including one model that has been validated in a large cohort of patients with a heterogeneous collection of connective tissue disease-associated ILD (CTD-ILD).[11] This study included a small number of patients with SSc-ILD, but did not report model performance in this population. SSc-ILD also has several distinct features compared with IPF, and it is, therefore, unknown whether risk prediction models derived in IPF can also be used to accurately estimate mortality risk in SSc-ILD.

We conducted a retrospective analysis using a large cohort of patients with SSc-ILD to determine whether previously validated IPF mortality risk prediction tools accurately estimate 1-year mortality in SSc-ILD. Our secondary goal was to compare previously derived IPF models to a similar novel model derived in SSc-ILD. We show that 1-year mortality in SSc-ILD can be predicted using previously derived risk prediction tools; however, calibration of most models was poor, and additional data are required to determine how these tools should be incorporated into clinical practice.

Materials and Methods

Study Population

Patients were identified from a specialized SSc-ILD clinic in which they were assessed by a multidisciplinary team consisting of a pulmonologist, rheumatologist, and specialized nurse. Patients were included if they fulfilled American College of Rheumatology (ACR) diagnostic criteria for SSc[12,13] and had fibrotic ILD with radiologic or pathologic findings consistent with nonspecific interstitial pneumonia or usual interstitial pneumonia.[6,14] There were no exclusion criteria. All patients provided written informed consent for inclusion in a prospective ILD database (University of British Columbia ethics No. H10-03435 and H14-02858).

Measurements

Patients underwent pulmonary function tests (PFTs) according to established criteria for measurement of spirometry, lung volumes, and diffusion.[15-17] Patients completed 6-min walk tests (6MWTs) following established procedures,[18] including use of a forehead oxygen saturation probe. PFTs and 6MWTs are typically performed at 6-month intervals at our center. Echocardiography was performed annually, including estimation of the right ventricular systolic pressure (RVSP) based on the velocity of the tricuspid regurgitant jet. Vital status was determined at the time of analysis for all patients, excluding one patient who had moved out of province who was censored at the date last known to be alive.

Mortality Risk Prediction Models

Four baseline risk prediction models were calculated, including the Composite Physiologic Index (CPI),[8] the ILD-Gender, Age, Physiology (ILD-GAP) Index,[11] the du Bois index,[9] and the modified du Bois index.[10] All four models were derived based on patients with IPF. The CPI was derived to predict the extent of fibrosis on CT scan[8] and is also associated with mortality in IPF. The CPI was calculated based on simultaneous measurements of FVC, FEV_1, and diffusion capacity of the lung for carbon monoxide (DLCO). The Gender, Age, Physiology Index was derived from a prospective cohort of patients with IPF,[7] and the ILD-GAP Index was subsequently validated in several other fibrotic ILD subtypes, including patients with a variety of CTD-ILDs.[11] The ILD-GAP Index is calculated based on the ILD diagnosis, patient sex, age at the time of assessment, FVC, and DLCO. The du Bois index was derived in the placebo arms from two randomized controlled trials of mild to moderate IPF,[19,20] with the purpose to estimate 1-year mortality. The du Bois index is calculated based on patient age, history of respiratory hospitalization in the preceding 24 weeks, FVC, and change in FVC in the preceding 24 weeks.[9] The modified du Bois index expanded the original du Bois index to also include 6-min walk distance (6MWD) and change in 6MWD in the preceding 24 weeks.[10] For the du Bois indexes, change in FVC and 6MWD were both calculated based on changes that occurred over intervals of 16 to 32 weeks (ie, 24 $\pm$ 8 weeks), allowing for the irregular follow-up intervals typical of clinical practice.

Statistical Analysis

Mortality risk prediction models were calculated as previously described.[8-11] For the primary analysis, each baseline model was included as a single predictor variable in a logistic regression analysis with 1-year mortality as the outcome variable. Discrimination was quantified using the area under the receiver operating characteristic (AUROC) curve for prediction of 1-year mortality. An AUROC curve ≥ 0.70 is generally considered acceptable for clinical use. Calibration (the extent to which observed event rates match expected event rates in population subgroups) was assessed using the Hosmer-Lemeshow goodness-of-fit test, in which a low *P* value indicates poor discrimination. The observed 1-year mortality rate in our SSc-ILD cohort was compared with the score-specific expected 1-year mortality provided in the original ILD-GAP Index and du Bois publications.[9,11] The performance of each model for the prediction of time to death was also assessed using a Cox proportional hazards analysis, reporting discrimination using the c-statistic. Individual patients could provide multiple data points for each model if repeated measurements were available.

The incremental prognostic ability of additional potential predictor variables was determined by adding these individual variables to each of the baseline models. These potential predictors of mortality were prespecified and included commonly measured variables that have been identified as possible prognostic variables in SSc-ILD or in other ILD populations. These variables included age, sex, smoking history and pack-years, BMI, measures of pulmonary physiology, 6MWD, and RVSP. A stepwise logistic regression analysis was performed to determine which additional variables provided independent prognostic information when added to the baseline models, retaining variables with a *P* value $< .05$.