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### **Predicting progression of mild interstitial lung disease in systemic sclerosis: an international retrospective cohort study.**

Our aim was to explore demographic, clinical, and serological predictors of progression in mild interstitial lung disease (ILD) associated with systemic sclerosis (SSc).

We conducted an international retrospective cohort study using data from the Canadian Scleroderma Research Group (CSRG), Australian Scleroderma Cohort Study (ASCS), Centre hospitalier de l'Université de Montréal (CHUM), and Stanford University SSc cohorts. Patients were included if they had ILD, forced vital capacity (FVC)  $\geq 80\%$  predicted, and available follow-up pulmonary function test data. ILD progression was defined as a relative decrease of at least 10% in FVC, or a relative decrease of 5 to 10% in FVC with a relative decline of at least 15% in DLCO. Multivariable Cox regression analyses were used to analyze the association between each predictor variable and time to ILD progression, adjusting for age, sex, ethnicity, smoking, and disease duration from first non-Raynaud symptoms, and using fixed effects meta-analysis for pooled data.

A total of 591 patients were analyzed, including 280 CSRG, 232 ASCS, 56 CHUM and 23 Stanford patients. Mean age was  $58.8 \pm 11.8$  years, 84% were female, 87% were White, 44% had diffuse SSc, and median disease duration was 10.4 years. Of these, 304 patients progressed over a mean follow-up of 3.6 years. Factors associated with a shorter time to ILD progression included age (pooled HR: 1.06, 95% CI: 1.01, 1.12 per 5-year increase), diffuse subtype (pooled HR: 1.34, 95% CI: 1.04, 1.73), and higher modified Rodnan skin score (mRSS, pooled HR: 1.07, 95% CI: 1.00, 1.14 per 5-unit increase). In the CHUM cohort, lower % predicted DLCO was also associated with a higher risk of progression (HR: 0.87, 95% CI: 0.78, 0.98 per 5%-predicted increase). Anti-topoisomerase I antibodies were associated with progression in the first 2 years of follow-up (HR: 1.71, 95% CI: 1.08, 2.70).

In this international cohort, we identified risk factors associated with a shorter time to ILD progression in mild forms of SSc-ILD. These features warrant closer monitoring and earlier treatment in this population and can inform enrichment strategies for interventional trials.