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**Title**: Retrospective study on the role of quantitative chest computed tomography in predicting disease progression in mild scleroderma-related interstitial lung disease

**Objective(s)**: We aimed to explore the role of automated quantitative chest high-resolution computed tomography (HRCT) in predicting clinically meaningful progression of mild forms of interstitial lung disease (ILD) in systemic sclerosis (SSc).

**Method(s)**: In this nested case-control study, patients evaluated at the Centre hospitalier de l'Université de Montréal (CHUM) from 2010 to 2020 were included if they met ACR/EULAR classification for SSc and had ILD confirmed on HRCT, mild ILD defined as forced vital capacity (FVC) ≥80% predicted, non-contrast thin-section HRCT images, pulmonary function tests at time of HRCT and within two years thereafter, and absence of non-SSc-related pulmonary disease. Cases were patients who experienced clinically meaningful progression within two years (≥10% relative decline in FVC, or ≥5% to <10% relative decline in FVC with ≥15% relative decline in DLCO). Controls were matched 1:1 on age, sex and calendar year. Automated quantitative HRCT analysis of ILD extent and patterns was done using Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER). Exploratory statistical analyses included t-tests, Mann-Whitney U tests, Chi-square tests and conditional logistic regression.

**Result(s)**: Thirty-eight patients with mild SSc-ILD were included. Mean (SD) age was 58.2 (11.5) years, 68% were females and 37% had diffuse SSc. Anti-topoisomerase I, anti-Ro52 and nucleolar anti-nuclear antibodies were present in 8%, 38% and 49%, respectively. Median [IQR] SSc duration was 5.6 [1.2, 13.3] years and time from ILD diagnosis was 0.06 [0.00, 1.95] years. There were 19 progressors and 19 non-progressors. Mycophenolate and/or cyclophosphamide were given in 50% of progressors and 42% of non-progressors. Automated quantitative HRCT analysis showed that progressors had significantly more honeycombing (2.54% vs 0.94% of total lung volume, p=0.04) compared to non-progressors. Progressors also had numerically more total fibrosis (sum of reticulation and honeycombing) in the whole lung (6.8% vs 3.8%, p=0.08) and lower peripheral lung zones (15% vs 9%, p=0.07). Ground-glass opacities and pulmonary vessel volumes were not associated with disease progression. Conditional logistic regression analyses showed that honeycombing by percentage-involvement tended to be associated with an increased risk of disease progression (OR 1.82, 95%CI: 0.91-3.64).

**Conclusion(s)**: Using automated quantitative HRCT analyses, we found that a higher extent of honeycombing and fibrosis on HRCT may be associated with a higher risk of lung disease progression in patients with mild SSc-ILD. This study was limited by the small convenience sample and retrospective design. Larger and/or prospective studies would be helpful to determine the prognostic role of HRCT disease extent and patterns in mild SSc-ILD.