



# Recent Advances in Predicting Mortality and Progression of Systemic Sclerosis–Associated Interstitial Lung Disease

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Predicting mortality and progression in patients with connective tissue disease-associated interstitial lung disease (CTD-ILD) is challenging because no accurate biomarker is existed and heterogeneity in disease and patient variables are extensive<sup>1</sup>. Idiopathic pulmonary fibrosis (IPF) is a poor prognostic and chronic fibrosing interstitial lung disease (ILD) of uncertain etiology. Previous studies have showed mortality risk prediction models in IPF including age, sex, and pulmonary physiology scoring (GAP scoring system), and composite physiologic index (CPI) which are associated with mortality of IPF<sup>2-5</sup>. A prediction model in patients with CTD-ILD (ILD-GAP) has been validated<sup>6</sup>. The Korean ILD Study Group in the Korean Academy of Tuberculosis and Respiratory Disease (KATRD) has created two IPF registries from 2003 to 2007 as the 2008 group, and from 2013 to 2017 as the 2018 group. The Korean ILD study group has already showed that CPI and GAP models were associated with survival of IPF patients in a nationwide cohort study<sup>7-9</sup>.

Systemic sclerosis–associated interstitial lung disease (SSc-ILD) is similar with IPF in many clinical features and prognostic variables. Recently systematic approach to risk prediction in non-IPF chronic ILD (ILD-GAP)<sup>6</sup> and CTD-ILD such as SSc-ILD<sup>10-13</sup>, rheumatoid arthritis (RA)-ILD<sup>14-16</sup>, and myositis-

associated (MA)-ILD<sup>17</sup>, and ILD with non-small cell lung cancer (NSCLC)<sup>18</sup> has been conducted to date, and prognostication remains challenging for clinicians. These studies derived and validated the GAP and CPI models for risk prediction of the patients with IPF<sup>2</sup>. CPI, GAP, or ILD-GAP are applicable for evaluating the risk prediction of mortality and progression of patients with SSc-ILD, RA-ILD, and ILD-NSCLC in a similar manner as in those with IPF but the ILD-GAP risk prediction model is a poor predictor of mortality among individuals with MA-ILD<sup>17</sup>.

There are no valid biomarkers to predict the progression of SSc-ILD, although Anti-topoisomerase I and several inflammatory markers are candidate biomarkers that need further evaluation<sup>12</sup>. Despite the established relationship between SSc-ILD and morbidity and mortality, patients' clinical courses are variable and difficult to predict. There is still no consensus on screening for ILD, nor on monitoring for disease progression. Currently chest computed tomography (CT) scans remain the gold standard to screen for and diagnose SSc-ILD<sup>12</sup>.

In clinical practice, the severity of SSc-ILD may be staged based on the "Goh criteria," whereby patients have "limited" or "extensive" disease based on chest high-resolution CT scans with extent of ILD clearly less or more than 20% of involving pulmonary area, and with the use of an forced vital capacity (FVC) threshold of 70% in indeterminate cases<sup>19</sup>. A recent analysis showed that a decline in FVC or diffusing capacity for carbon monoxide (DL<sub>CO</sub>) over 2 years was a better predictor of mortality than baseline FVC and DL<sub>CO</sub><sup>20</sup>.

The progression of SSc-ILD is variable and it is important that patients are appropriately monitored after a diagnosis of ILD in SSc. Serial measurements of symptoms, physical examination, and pulmonary function tests (PFTs) are important to assess disease progression at regular clinic visits, and recent studies highlight the impact of change in PFT on mortality<sup>13,20,21</sup>. Kaenmuang and Navasakulpong<sup>13</sup> reported that short-term lung function had declined during the 12-month follow-up in 78 patients with progressive or stable SSc-ILD. The predictive factors in progressive SSc-ILD were male sex and no previous aspirin treatment in a single Thailand univer-

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sity hospital of seventy-eight SSc-ILD.

In the recently published SENSIS trial, patients with SSc-ILD treated with nintedanib had a lower rate of annual FVC decline than those receiving placebo with difference of 41 mL<sup>22</sup>. However, there is currently no consensus regarding treatment initiation or escalation. Most SSc experts make a decision on when to initiate therapy on a case-by-case basis according to their clinical experience and consideration of the risk factors for SSc-ILD progression. Better identification of which patients are at risk of progression will help to identify those who can benefit the most from early treatment<sup>23</sup>.

ILD is a major complication of SSc, and early and systematic screening of progression or deterioration is required and potentially enable treatment prior to deterioration of lung function in patients with SSc-ILD at high risk of disease progression is mandatory. Chest CT scans and serial PFTs remain important diagnostic tools, but may need to be performed regularly following SSc diagnosis to detect changes suggesting ILD<sup>12</sup>. In future, new imaging techniques and diagnostic and predictive biomarkers will play an important role in predicting mortality and progression of SSc-ILD.

## Conflicts of Interest

No potential conflict of interest relevant to this article was not reported.

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